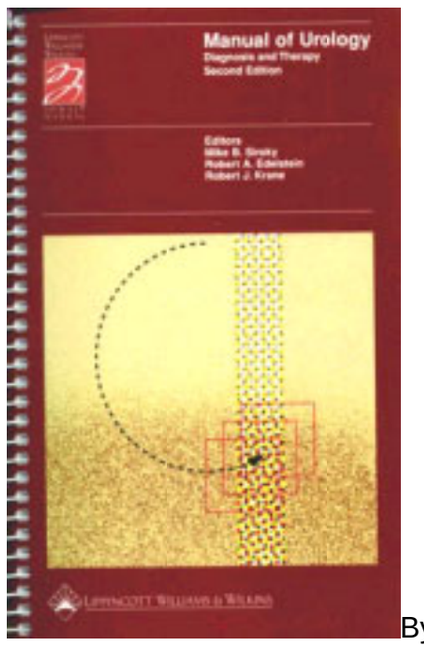
Manual of Urology: Diagnosis and Therapy 2nd edition: By Mike B Siroky MD, Robert D Oates MD, Richard K Babayan MD By Lippincott, Williams & Wilkins



By OkDoKey

Manual of Urology

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To the memory of

Max K. Willscher, M.D.
November 13, 1944–July 31, 1995

A graduate of
the Boston University Training Program in Urology,
a colleague, and
a friend

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Preface

The *Manual of Urology, Second Edition* represents a complete revision of the first edition of this manual, published in 1989. Although there are approximately the same number of chapters, the amount of information has been expanded considerably, arranged in an easily accessible outline format. Furthermore, while the number of radiologic and other photographs has been reduced, the number of tables, charts, and drawings has increased substantially.

Since the first edition 9 years ago, major changes in urologic practice have occurred, and the new material reflects this “mini-revolution.” For example, the chapter on genitourinary radiology is a thoroughly modern treatment of this subject, emphasizing ultrasound and cross-sectional imaging. Updated chapters detail the new endoscopic instruments developed in the last decade, as well as innovative techniques in detecting urinary calculi. The diagnosis and treatment of bladder outlet obstruction, urinary incontinence, male erectile dysfunction, male infertility, and neurogenic bladder dysfunction have become varied and sophisticated, and this is reflected in the new chapters on these areas. The chapter on radiation therapy has been entirely rewritten to emphasize the many new treatment modalities that now exist, and the discussion of infectious diseases includes data regarding newer antibiotic agents.

At the same time, the purpose and orientation of the first edition have been maintained by presenting problems and therapeutic principles. The purpose also remains one of serving as a companion to the house officer and medical student responsible for urology patients, and to provide up-to-date, detailed and handy information, instruction, and advice. Open operative procedures are not depicted in great detail, but endoscopic, medical, and diagnostic procedures are well described. Most chapters were written by current and past residents and trainees associated with the Boston University training program in urology, with input from the faculty.

The first edition was well received in this country and was translated into Japanese as well. We hope that medical students, residents, and fellows find this manual useful in the day-to-day care of urologic patients. Of course, we are grateful for the efforts of our contributing authors. We also wish to thank everyone associated with Lippincott Williams & Wilkins for their support during the long process of producing this work, in particular R. Craig Percy and Michelle M. LaPlante.

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Chapter 1 Imaging of the Genitourinary Tract

Charles Hyde and Rebecca K. Schwartz

An extensive array of modalities and procedures is available for imaging of the genitourinary tract. Selection of the appropriate modality depends on the clinical question at hand in addition to considerations of patient safety, patient comfort, and cost. To make a good choice, one needs a thorough understanding of the utility of the various imaging modalities (see Table 1-1). In our discussion, we focus mainly on the technique and indications for urologic imaging. Interpretation of these studies is beyond the scope of this chapter.

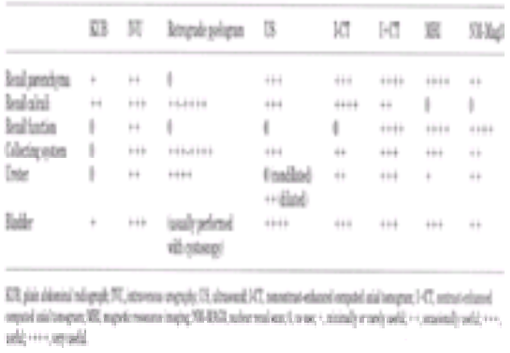

Table 1-1. Utility of various imaging modalities

I. Plain Abdominal Radiograph

A. **Technique.** No preparation is needed. A single supine view is usually adequate; “upright” views, useful in evaluating the bowel, are rarely useful in evaluating the genitourinary system.
B. **Indications.** The frequently used acronym KUB (kidneys, ureters, and bladder) is a misnomer, as the plain abdominal radiograph does not demonstrate the ureters and only rarely demonstrates the bladder. It is only moderately useful to demonstrate the renal contours. These can be assessed on technically optimal films, which hint at abnormalities such as renal masses and abnormalities of renal size or position. However, the greatest utility of the abdominal radiograph in urology is to evaluate for calculi, check the presence and position of catheters and stents, and obtain a preliminary view before performing other examinations.
C. **Common findings**
   1. **Bony abnormalities** may include the following types:
      a. Congenital, such as spina bifida and sacral agenesis
      b. Posttraumatic, such as fractures of the spine or pelvis
      c. Postsurgical, such as surgically resected ribs or the presence of vascular clips
      d. Associated with other diseases, such as osteoblastic metastases (typical of prostate carcinoma), osteolytic metastases (the majority of solid tumors), or manifestations of hematologic disorders (sickle cell anemia, myeloma) or Paget's disease
   2. **Abnormal gas collections** include the following:
      a. Gas in the renal parenchyma or collecting system as a result of recent instrumentation or emphysematous pyelonephritis
      b. Gas in the bladder lumen as a result of recent instrumentation, emphysematous cystitis, colovesical or enterovesical fistula, urinary tract infection
      c. Gas in the bladder wall, as seen in emphysematous cystitis

II. Ultrasound

Ultrasound (US) is very useful in evaluating the urinary tract. Widely available, relatively inexpensive, and entailing no use of radiation, US provides generally excellent visualization of the kidneys, intrarenal collecting systems, and bladder. US is used as an initial screening examination of the urinary tract and has assumed much of the role once played by intravenous urography (IVU) in this regard. One significant drawback of US in comparison with other modalities, such as computed axial tomography (CT), magnetic resonance imaging (MRI), and IVU, is that no information other than inferential is obtained about renal function. US can also be of limited use in obese patients or in patients with a very large amount of bowel gas.

US plays a lesser role in ureteral evaluation. Although US can sometimes visualize a dilated proximal or distal ureter, most of the ureter will be obscured by overlying bowel gas, and a nondilated ureter generally cannot be seen at all. The prostate is moderately well seen on transabdominal US and is very well visualized on transrectal US (TRUS). Another US examination frequently of interest to the urologist is scrotal US.

A. **Technique.** No special preparation is required. Because the kidneys are situated posteriorly and away from gas-containing structures, renal US, unlike general abdominal US, does not require the patient to be fasting. Whenever possible, imaging of the patient is performed with a urine-distended bladder to improve visualization of the bladder and prostate. We then have the patient void and scan the bladder again, to calculate a postvoid residuum.
   Because US examination is performed in real time, it is particularly useful for imaging children or patients who are uncooperative. With a portable machine, US examinations can be performed at the patient's bedside.
B. **Indications.** US is useful for general screening of the urinary tract. It is the examination of choice in defining renal cysts. It is particularly useful for detecting renal masses, diagnosing and following hydronephrosis, and evaluating the bladder. It is a useful adjunct in demonstrating renal calculi. It is less useful in evaluating lesions of the intrarenal collecting system, perirenal spaces, adrenals, and ureters, and in the setting of trauma.
C. **Renal transplant.** US of renal transplants is a special case. Because of the superficial location of a transplant and the lack of interposition of bowel gas, visualization of the transplant is usually excellent. Doppler tracings of the iliac artery, main renal artery, and intralobar and arcuate arteries give excellent insight into the evaluation of transplant failure and rejection (see Chapter 22).
D. **Scrotal US** is the single best radiologic method for evaluating the scrotal contents, including the testicles and extratesticular structures, and it is an invaluable part of the evaluation of scrotal pathology. Testicular pathology (including masses and inflammation), extratesticular pathology (including hydroceles), and epididymal pathology (including spermatoceles, epididymal masses, and inflammatory conditions) are all routinely imaged. In terms of technique, no preparation is needed. A high-frequency (5- to 10-MHz) linear transducer is used to image the scrotum directly.
E. **TRUS.** Transabdominal ultrasound of the prostate is generally limited to quantifying prostate size. To obtain a detailed image of the prostate and periprostatic structures, TRUS, in which a high-frequency transducer is placed in the rectum, must be performed. The prostatic zones are usually well seen, and the prostate is accurately measured.
   1. **Indications for TRUS** include an abnormality on digital rectal examination, elevated prostate-specific antigen (PSA), or previously abnormal results of a prostate biopsy. It must be emphasized that TRUS is neither sensitive nor specific; a normal result on TRUS examination does not exclude prostate carcinoma, and an abnormal examination result can be seen with benign prostatic hypertrophy (BPH), focal prostatitis, and other conditions. One of the major indications for TRUS is to guide a needle biopsy of the prostate. Important but less frequently applied indications for TRUS are examination of the seminal

vesicles and ejaculatory ducts in the evaluation of infertility, and imaging of the prostate for abscess. TRUS can also be used to diagnose or drain a prostatic abscess.

2. **Technique.** The patient is given a Fleet enema and is asked to void before the examination. We currently give 400 mg of ofloxacin orally 1 hour before the biopsy and twice daily for five additional doses after the procedure. We perform the biopsies with the patient in the left lateral position, although many advocate the lithotomy position for equally good results. We obtain six segmental biopsy specimens with an 18-gauge spring-loaded needle. If a focal abnormality is present, we typically obtain one to three additional biopsy specimens. Some bleeding—usually self-limited—from the rectum or urethra is common following the procedure. We have a 1% incidence of bleeding significant enough to require observation and a 1% incidence of postbiopsy infection.

III. Computed Axial Tomography

CT, like US, has revolutionized the radiologic evaluation of the genitourinary tract. CT allows the radiologist to assess directly the morphology and function of the kidneys, the appearance of the surrounding retroperitoneal soft tissues (lymph nodes, adrenals, aorta, inferior vena cava), and the patency of vascular structures (renal veins and arteries). In the pelvis, CT can evaluate the bladder, prostate, and surrounding soft tissues and lymph nodes, as well as the ureters. CT is limited for the evaluation of the penis and scrotum, and these structures are generally better assessed by US or MRI.

A. **Technique.** CT examinations can be performed with or without oral contrast, and with or without IV contrast. It is important that the specific indications—the specific question to be answered—be discussed with the radiologist before a CT is performed, as the technique used will vary significantly.

The technique used must also vary with the capabilities of the CT scanner. Until recently, most scanning was performed with conventional axial CT, with stepped table movement between tomographic slices. This imaging process is relatively slow, with a scanning time of approximately 2 seconds and an interscan delay of 2 to 8 seconds. At least a minute is required to scan through the kidneys. Problems with this method include motion artifacts, gaps in scanning, and limited ability to evaluate the entire kidney in a uniform phase of enhancement. **Partial volume artifacts**, a particular problem when small peripheral masses are evaluated, occur if the lesion being studied is not in the center of the slice. The CT number (Fig. 1-1) calculated for any tissue slice will be an average of the different types of tissue included (Fig. 1-2).

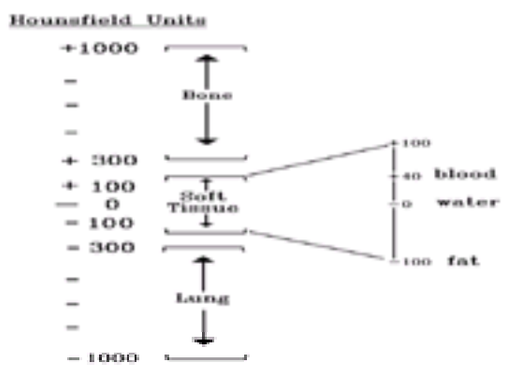

FIG. 1-1. The Hounsfield scale for computed axial tomographic (CT) density.

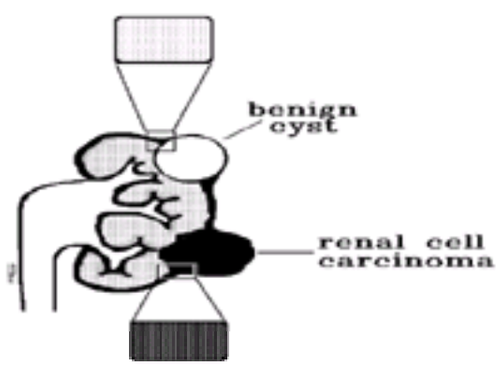

FIG. 1-2. “Partial voluming” occurs when various tissue densities are imaged.

More recently, helical (spiral) scanning has replaced axial scanning as the preferred method for many indications, including the genitourinary tract. In helical scanning, the CT table moves continuously, and images are continuously obtained. Thus, an entire sequence is obtained in a single breath hold. The pitch is the ratio of table speed to collimation. At a pitch of 1:1, an average kidney can typically be scanned at 5-mm collimation in fewer than 30 seconds. Neither motion artifact nor gaps are a problem when patients are able to cooperate and hold their breath. “Partial voluming” is minimized with images reconstructed in the center of a lesion.

IV contrast is routinely used for most indications (Table 1-2 and Table 1-3). It is important that patients be kept fasting for 4 hours before administration of IV contrast to reduce the risk of emesis and aspiration. After adequate IV access has been obtained, approximately 100 mL of contrast material is given at the rate of 1.5 to 4.0 mL/s, depending on the specific indication. After contrast material is given, several phases of renal enhancement occur. Knowledge of these different phases allows one to optimize the scanning protocols and interpret the findings intelligently.

Children:	0–12 kg	3.0 mL/kg
	12–23 kg	2.0 mL/kg
	24–45 kg	50 mL
	>45 kg	1.0 mL/kg
Adults		1.0 mL/kg

Table 1-2. Dosage for iodinated contrast media

Generic name	Trade name	% Weight	Osmolality (mosmol/kg)	Ionic
Sodium diatrizoate 50	Hypaque 50	50	1,550	Yes
Meglumine diatrizoate 60	Hypaque 60 Reno-M-60 Conray 60	60	1,400–1,500	Yes
Iohexol 300	Omnipaque 30	65	700	No
Iopromide 240	Ultravist 240	50	500	No
Meglumine diatrizoate	Cystografin	30	600	Yes
Meglumine iothalamate	Cysto-Conray	43	1,000	Yes
Iohexol 180	Omnipaque 180	39	450	No
Iopamidol 128	Isovue 128	26	300	No

Table 1-3. Characteristics of commonly used radiographic contrast media

1. The **angiographic phase** occurs 15 to 40 seconds after contrast injection begins. The number, location, and patency of the renal arteries and the location and patency of the renal veins can be assessed.
2. The **cortical phase** of renal enhancement normally occurs between 25 and 80 seconds after the initial exposure to contrast material. The renal cortex is maximally enhanced, and the corticomedullary differences are greatest. Enhancement of the cortex is often uneven, and both the sensitivity and specificity for detecting renal lesions are diminished.
3. The **nephrographic phase** usually begins 90 to 120 seconds after the injection of contrast medium and is characterized by the homogeneous enhancement of the entire renal parenchyma as a consequence of enhancement of the medulla. It is in this phase that detection of renal lesions, particularly smaller lesions, is greatest.
4. The **excretory** or **urographic phase** begins when contrast material is visualized in the collecting system, including calyces, infundibula, and renal pelvis. This typically begins 3 to 5 minutes after injection and persists for several minutes. A nephrogram can be seen through much of the excretory phase.

B. Protocols

We use the following CT protocols in our institution. Modified protocols will be used in different institutions.

1. **Renal/ureteral calculi.** In our institution, helical CT scanning has replaced IVU as the primary imaging modality for the evaluation of renal colic. Helical scanning with 5-mm collimation, reconstructed at 4-mm intervals, without IV or oral contrast is used to search for renal and ureteral densities that represent calculi. Oral contrast should not be used, as it may lead to difficulties in defining bowel diverticula and distinguishing the appendix from calculi. If scanning without IV contrast fails to demonstrate a calculus, or if a comparison of relative renal function is important for clinical decision making in a patient who has been identified as having a renal stone, repeated scanning with IV contrast and delayed images (10 minutes after injection) can be performed.
2. **Renal masses.** CT scanning to search for renal masses or to evaluate suspected renal masses identified by other imaging modalities should be performed without and with IV contrast (see Chapter 8). Initially, a scan without IV contrast is performed. Following contrast administration, scanning should commence within a minute to visualize the kidney in the nephrographic phase, and scanning should be repeated 10 minutes after contrast administration, as some tumors are better seen in the urographic phase. With helical scanners that allow for rapid, repetitive sequential imaging, postcontrast imaging is also performed in the angiographic phase to obtain more information about the renal vasculature. With this protocol, invasion of the renal vein and inferior vena cava can be assessed, and the number and location of renal arteries can be shown. Additional imaging of the abdomen and pelvis facilitates staging by determining lymph node spread and the presence of metastatic disease. If a renal mass is identified, a chest CT is also recommended.
3. **CT angiography of the kidneys.** CT angiography is a new technique developed to image the renal arteries and veins without catheter angiography. Contrast is injected through an antecubital vein, as in a routine enhanced CT scan, but at a more rapid rate, typically 3 mL/s or more. Scanning commences within 20 to 25 seconds. Delayed scanning may be performed to obtain anatomic images of the kidneys. Two- and three-dimensional reconstructed images of the renal vasculature demonstrate anomalies such as accessory renal arteries and retroaortic or circumaortic renal veins, and pathologic entities such as renal artery stenoses, occlusions, and aneurysms.
4. **Renal infection.** Generally, pyelonephritis is a clinical diagnosis, and CT is used to define complications or response to treatment in complex cases. Routine scanning of the kidneys without IV contrast can demonstrate renal enlargement; diffuse, focal, or multifocal areas of low attenuation (abscess or focal pyelonephritis); and perinephric inflammation or fluid collections. CT following IV administration of contrast also depicts all these abnormalities and can be used if questions remain. Most findings are nonspecific, however, and routine administration of IV contrast is not warranted.
5. **Bladder and ureters.** Scanning of these structures must be performed 5 to 10 minutes after contrast injection and can be supplemented by prone positioning and the Valsalva maneuver. Depiction of the ureters is improved by scanning without oral contrast. Helical scanning with 5-mm collimation, reconstructed at 4-mm intervals, allows for two-dimensional reconstructions. Ureteral obstruction and periureteric inflammation and masses can be demonstrated. US is the preferred modality for evaluating the bladder, although CT is preferred for visualizing the perivesicle fat and pelvic lymph nodes.

IV. Excretory Urogram, Intravenous Urogram, Intravenous Pyelogram

The above three terms are used interchangeably, although we prefer intravenous urogram (IVU). The first edition of this manual noted that “the IVU is still the initial examination in most instances for the evaluation of the genitourinary tract,” but we no longer can make this statement. Although there remains a role for IVU, we no longer consider the IVU to be the cornerstone of urologic imaging. The IVU is able to evaluate, to some degree, all aspects of the urinary tract—kidney parenchyma, renal function, intrarenal collecting system, ureters, and bladder; however, it is not the best means of evaluating any of these (see Table 1-1).

A. **Technique.** The patient should preferably be fasting to minimize emesis. Some radiologists routinely give a laxative. The patient should not be excessively hydrated, particularly by IV hydration. The patient should void immediately before the examination.

There are many acceptable protocols for obtaining images in an IVU. In fact, as emphasized for many years, it is important to “tailor” the urogram to attempt to answer the clinical questions raised. Nevertheless, the following is the “standard” set of films obtained at our institution, with the understanding that departures from this protocol are common:

1. Scout abdomen and tomogram
2. Injection of contrast material by bolus IV injection
3. Tomograms at consecutive levels through the middle of the kidney at 1, 2, and 3 minutes after injection
4. A 5-minute abdominal radiograph
5. Placement of abdominal compression
6. Ten-minute coned views of the kidney, anteroposterior (AP) and both 30° posterior obliques
7. Abdominal film after compression device released ("release film")
8. AP and oblique views of the bladder
9. Postvoid AP bladder

An initial plain radiograph, called a scout film, is used to check for excessive bowel gas and internal or external radiodense objects, including contrast material in the gastrointestinal tract (barium or contrast from recent CT), and to check radiographic technique.

The discussion of bolus versus drip infusion for performing an IVU was important in the past. A bolus injection gives superior images and is preferred. Drip infusion is used only when a bolus is impossible. Contrast is given according to the guidelines in Table 1-2.

Tomograms, which we routinely perform, increase the radiation exposure but also improve the visualization of the renal parenchyma and collecting system, predominately by “separating” the kidneys from adjacent bowel gas.

Abdominal compression is performed by inflating a rubber balloon over each side of the sacrum or at the pelvic brim, causing partial obstruction of the ureters. When properly performed, it can significantly improve visualization of the intrarenal collecting system and ureters, largely by removing minimal external compression on the collecting system by normal crossing blood vessels. When improperly performed, it is uncomfortable for the patient and worthless.

Contraindications include recent abdominal surgery, aortic aneurysm, and an acutely obstructed urinary tract. A release abdominal film obtained after the compression device has been removed offers the best opportunity to visualize the ureters by IVU. A prone view can occasionally be helpful, as can a film with the patient upright.

Views of the bladder must be tailored depending on the indication for the IVU, and some can be eliminated if further evaluation of the bladder (e.g., by cystoscopy or US) is planned or has already been performed. A complete evaluation on IVU includes AP and oblique views of the bladder and a postvoid image.

B. **Indications.** The current indications for IVU are for evaluation of the calyces and ureters, especially in cases of known or suspected urothelial malignancy, for postoperative evaluation of the ureter, or for detailed evaluation of the calyces, ureteropelvic junction, and ureterovesical junction. Although IVU can be used in the evaluation of calculi and hydronephrosis, it is no longer the initial test of choice for either of these indications. Further, it no longer has a primary role in the evaluation of trauma, noncalculous hematuria, suspected renal malignancy, infections, renal failure, polycystic kidney disease, hypertension, and prostate disorders. An absolute contra-indication to performing an IVU would be the inability of the patient to tolerate contrast material because of renal insufficiency or allergy history.

V. Iodinated Contrast Material

The use of iodinated contrast material is so important to the practice of urologic imaging that a more detailed discussion of contrast agents, including their pharmacology, complications, and the treatment and prevention of complications, seems appropriate (Table 1-3).

Radiographic contrast material is classified as LOCM (low-osmolarity contrast material) and HOCM (high-osmolarity contrast material). These differ somewhat in complication rates. Contrast material is excreted by glomerular filtration, without significant tubular excretion or reabsorption. Because of the tubular reabsorption of water, the contrast material becomes concentrated in the collecting system and readily visible on radiographs.

A. **Systemic reactions to contrast material.** Contrast reactions are frequently described as mild, severe, and fatal. Reactions can be ascribed to (1) osmolality (e.g., nausea, vomiting, flushing, heat); (2) allergic phenomena (e.g., itching, facial edema, urticaria, laryngeal edema, bronchospasm); or (3) toxic effects (e.g., cardiac arrhythmias, seizures, nephrotoxicity). Most adverse reactions develop within 5 minutes, and certainly within 1 hour. Urticaria, facial edema, laryngeal edema, bronchospasm, and seizures are considered severe reactions. The incidence of each of these reactions is about one-third to one-half as great with LOCM as with HOCM. Fatal reactions do occur. The incidence is sufficiently low that an estimate of frequency is not definitely known. Nevertheless, the best data currently available indicate the rate of fatal reactions to be 0.00043% or 1/232,500 for HOCM and 0.00029% or 1/344,800 for LOCM. It a consistent finding that systemic contrast reactions are considerably more common following IV injections than intraarterial injections.
   1. **Treatment of contrast reactions.** Pruritus or a scant urticaria is usually self-limited. More severe reactions can be treated with 50 mg of diphenhydramine IV, intramuscularly (IM), or orally (PO). As urticaria can be part of a generalized anaphylactoid reaction, close observation is mandatory. If laryngeal edema is present, 0.1 to 0.3 mL of 1:1,000 epinephrine should be given subcutaneously (SC) every 15 minutes to a total of 1 mg. Hydration and oxygen should be provided, and administration of diphenhydramine and histamine $_2$ (H_2) blockers considered. If bronchospasm is present, a b-adrenergic agonist inhaler may provide symptomatic relief. If persistent, parenteral b-adrenergic agonists or aminophylline should be considered.

      Hypotension may be seen as an isolated symptom or associated with sneezing, urticaria, watery eyes, or any other symptoms of an anaphylactoid syndrome. Rapid fluid replacement, frequently several liters, is the most important treatment. A vasovagal reaction may present with hypotension and bradycardia and may be accompanied by diaphoresis, abdominal cramps, and generalized anxiety. Besides rapid fluid resuscitation (aided by Trendelenburg's position), 0.5 to 1.0 mg of atropine may be given IV.
   2. **Prophylaxis.** Pretreatment with corticosteroids 12 hours before contrast administration reduces the frequency of almost all reactions. No protective effect was seen when steroids were given only 1 hour before contrast administration, and no additional protective effect is seen with pretreatment for more than 24 hours. Common pretreatment protocols are 20 mg of prednisone PO or 100 mg of hydrocortisone PO every 6 hours for three or four doses preceding contrast administration. Pretreatment with antihistamines probably reduces the chance of urticaria and respiratory symptoms and is usually also given; pretreatment with H_2 blockers is logical, if unproven. It is difficult to weigh the relatively small risk of low doses of steroids versus the small risk of a contrast reaction. In patients who have had a previous contrast reaction, the balance might be in favor of pretreatment.
   3. **Nephrotoxicity.** There is a direct nephrotoxic effect of contrast material on the renal tubules. The incidence is small in patients with normal baseline renal function. Elevation of serum creatinine more than 50% over baseline is seen in 1.6% of patients, and elevation of serum creatinine 150% is seen in 0.15% of patients. Nephrotoxic effects are usually seen within 24 to 36 hours, usually peaking within 48 to 72 hours. There is a gradual recovery, and baseline renal function is seen within a week in the great majority of patients. Patients at increased risk are diabetics, those with renal insufficiency (serum creatinine levels > 1.2 mg/dL), those with cardiac disease (low cardiac output), the elderly, infants, and dehydrated patients, particularly those taking furosemide. These effects can be additive, and those at greatest risk are diabetics with preexisting renal insufficiency. The risk for contrast-induced nephropathy is the same for LOCM and HOCM. There is no known benefit in using nonionic contrast material. Prophylaxis is with adequate hydration before, during, and after exposure to radiocontrast agents.

VI. Magnetic Resonance Imaging

MRI (Fig. 1-3) has many uses in the genitourinary system, particularly in patients who because of renal insufficiency or allergy history cannot safely tolerate IV contrast administration. The outstanding soft-tissue resolution offered by MRI makes it well suited for evaluating renal masses, and its potential for noninvasive vascular imaging has revolutionized the radiologic evaluation of vascular anatomy. Tissue contrast in MRI depends on the relaxation properties of protons in varying magnetic fields, rather than on ionizing radiation, which makes MRI a comparatively risk-free examination. Imaging protocols vary significantly, however, based on the indication for the examination; hence, MRI nearly always has a more restricted field of view and scope than CT for answering general questions about the status of other structures, and it is imperative to define the goal of MRI before the examination begins.

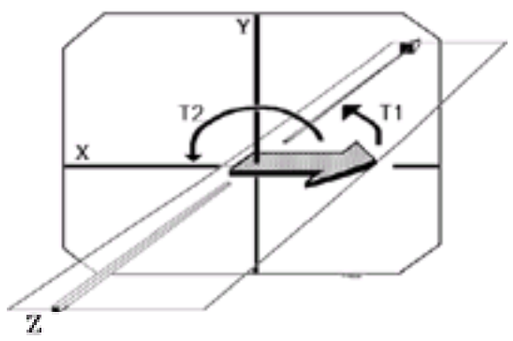

FIG. 1-3. Basic principles of magnetic resonance imaging (MRI). Induced by a strong magnetic field, basic alignment of nuclei is along the z-axis. Short pulses of radiofrequency waves are used to disturb the basic alignment into the x-y plane, after which “relaxation” toward the z-axis alignment occurs. The time constant for relaxation toward the z-axis is called T_1; the time constant for relaxation within the x-y plane is called T_2.

The nuclear magnetic resonance (NMR) signal contains at least three independent parameters: (1) spin density, (2) T_1 relaxation time, and (3) T_2 relaxation time. The spin density is proportional to the number of nuclei present in the tissue and is thus a rough indicator of hydrogen density. Water has a higher spin density than bone. The T_1 relaxation time is a measure of the time it takes nuclei to realign themselves with the basic magnetic field of the scanner (Fig. 1-3). The T_2 relaxation is a measure of signal decay resulting from intermolecular interaction. T_2 is generally much less than T_1.

MRI of the kidneys is performed with a variety of pulse sequences, depending on the indication for the examination. In general, T_1-weighted images are best for defining anatomy and are often performed in multiple planes, usually axial and coronal. If appropriate for optimal depiction of a mass or other pathology of interest, sagittal or oblique imaging may also be useful. T_1-weighted images with a fat saturation pulse will null the signal from fat and help to identify lesions such as angiomyolipomas, which often have a significant macroscopic fat content. Microscopic fat, as seen in adrenal adenomas, can be detected with gradient echo

“in-phase” and “out-of-phase” techniques.

T_2-weighted images are better for demonstrating pathology and help to differentiate between cysts, which are very bright, and solid masses, which are only somewhat bright. Imaging after administration of gadolinium is crucial to discriminate between solid, enhancing lesions and cystic, nonenhancing lesions. As in CT scanning, serial MR sequences after gadolinium administration can help define masses seen in different phases of enhancement (cortical, nephrographic, and urographic). Image quality is enhanced in high magnetic field strength systems with improved gradients that allow for rapid imaging during breath holding. It is often useful to obtain rapid sequential series of images during the angiographic, nephrographic, and urographic phases following gadolinium administration.

MR angiography makes possible a detailed evaluation of the renal vasculature. Flowing blood has different signal characteristics than thrombus or tumor within a vessel. Both black-blood and bright-blood techniques have been developed to evaluate vascular patency and morphology. In addition, gadolinium-enhanced scans offer better contrast and spatial resolution of vascular abnormalities, especially when performed as rapid, breath-hold sequences.

A. **Indications.** Indications for MRI of the genitourinary system include evaluation of renal masses, renal vasculature, prostate cancer, and adrenal masses. Experimental uses include MR urography.
B. **MRI of renal masses.** Renal masses can be characterized by MRI as solid or cystic. Postgadolinium images, performed in a dynamic fashion, are an essential component of the MRI protocol. Visualization of small masses is enhanced by high-resolution imaging in multiple phases of enhancement. Urographic-phase imaging can help exclude the diagnosis of a calyceal diverticulum, which can on occasion be confused with a renal mass on earlier images. As with CT, anatomic imaging of the remainder of the abdomen can reveal lymph node and adrenal metastases. MRI is readily suited to the determination of vascular (renal vein, inferior vena cava) patency with either gadolinium-enhanced or nonenhanced techniques, and of the number and origin of renal arteries, which may be useful in surgical planning.
C. **MR angiography of the renal vasculature.** Both the status and number of the renal arteries and the position of the renal veins can readily be assessed with MRI. Many scanners allow for breath-hold, high-resolution, gadolinium-enhanced MR arteriography, which has proved to be nearly as accurate as conventional angiography for the assessment of renal artery number and morphology, without the associated risks of femoral artery puncture and complications of iodinated contrast administration. Renal vein and inferior vena cava patency can generally be assessed without the use of gadolinium, with either black-blood (spin echo) or bright-blood (gradient echo) techniques.
D. **MRI of prostate cancer.** With the use of endorectal MR coils, high-resolution imaging of the prostate can be obtained. Foci of suspected neoplasm can be demonstrated, as well as extracapsular spread and involvement of the neurovascular bundle. During the same examination, an additional set of anatomic images of the pelvis can be obtained with the body coil to assess for pelvic adenopathy and metastatic disease to bone.
E. **MRI of adrenal masses.** Adrenal masses can be readily characterized with MRI. In-phase and out-of-phase imaging can be performed, without gadolinium administration, to assess for the presence of microscopic amounts of fat in an adrenal mass noted on CT or US. The presence of microscopic fat in a lesion strongly favors the diagnosis of adrenal adenoma rather than metastatic disease, and such lesions can potentially be followed with a biopsy being performed. An additional use for MRI of the adrenal glands is the evaluation of possible pheochromocytoma, which has an extremely bright appearance on T_2-weighted images.
F. **MR urography.** An experimental procedure, MR urography relies on the presence of urine-filled ureters. T_2-weighted sequences with very long echo times are best for accentuating the urine-filled ureters against the background of other abdominal-pelvic structures. Challenges to the development of this technique include artifacts caused by bowel motion and breathing, which can be reduced by injecting 0.5 mg of IM glucagon before the examination and by obtaining rapid, breath-hold images.
G. **Contraindications to MRI** include the presence of ferromagnetic intracranial vascular clips, cardiac pacemakers, and certain prosthetic cardiac valves. Relative contraindications, sometimes amenable to pharmacologic intervention, include severe claustrophobia and the patient's inability to lie still for 30 to 45 minutes of imaging.

Suggested Reading

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Chapter 2 Radionuclide Imaging

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Nuclear imaging of the genitourinary tract has the advantage of being essentially noninvasive, providing physiologic as well as anatomic information and subjecting the patient to minimal radiation exposure. Allergic reactions are virtually unknown following the injection of radiopharmaceuticals. The ability to provide functional and quantitative information is fundamentally unique to nuclear imaging and can be extremely useful in the assessment of renal function, renal blood flow, and obstructive uropathy.

I. Renal Imaging

A. Evaluation of flow and function

1. **Radiopharmaceuticals** are generally composed of a radioisotope bound to a carrier with physiologic properties.
   a. **Technetium-based radiopharmaceuticals.** The radioisotope most commonly used in renal imaging is metastable technetium 99 (^{99m}Tc), which is a readily available, low-cost isotope that is extracted from a molybdenum 99 generator. Radiopharmaceuticals based on ^{99m}Tc that are used to assess flow and function are as follows:
      1. ^{99m}Tc-DTPA (diethylene triamine pentaacetic acid) is handled primarily by glomerular filtration (80%), and the remainder is subject to tubular secretion.
      2. ^{99m}Tc-MAG3 (mercaptoacetyltriglycine) is handled by tubular secretion (approximately 90%). As a result, it has a higher rate of extraction than DTPA.
      3. ^{99m}Tc-glucoheptonate is handled by a combination of glomerular filtration and tubular secretion (approximately 40% within 1 hour) and peritubular cell deposition (12% of the dose is present in the kidneys at 1 hour).
   b. **^{131}-OIH (orthoiodohippurate).** Iodine 131 is produced in a cyclotron. Because it has some undesirable characteristics for an imaging agent (high-energy g photons and b emissions), images of poorer quality are produced. Like ^{99m}Tc-MAG3, ^{131}I-OIH is largely secreted by the proximal tubules. The tubular secretory capacity for OIH is greater than that for MAG3.
2. **Imaging and analysis.** After injection of any of the above radiopharmaceuticals, sequential images (frames) are obtained every 1 to 2 seconds for 60 seconds, then every 10 to 60 seconds for 20 to 30 minutes. These digital images are compressed into longer frames for interpretation (Fig. 2-1). Images from the first minute reflect renal blood flow; images from the subsequent 30 minutes reflect parenchymal and excretory function. Counts derived from these images are plotted over time; the plot is called a renogram. The renogram is commonly divided into three phases (Fig. 2-2A):

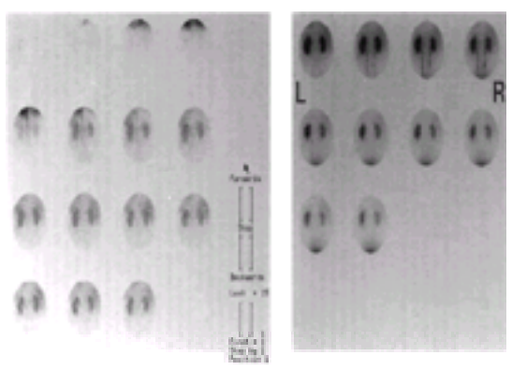

FIG. 2-1. Normal ^{99m}Tc-MAG3 study. **Left:** Flow images (4 seconds per frame) obtained for the first 60 seconds following injection. **Right:** The subsequent 30 minutes of information displayed in sequential 3-minute frames.

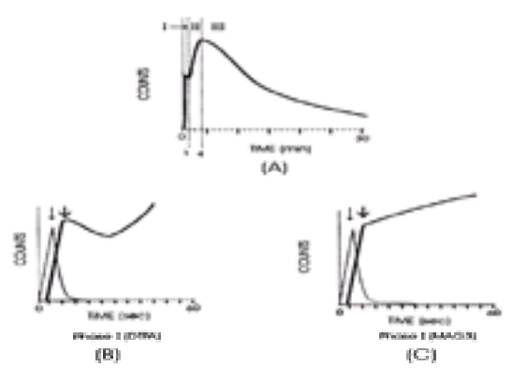

FIG. 2-2. Normal renogram. **A:** A plot of counts in the kidney over 31 minutes. The three phases (I, II, III) are marked. **B:** Phase I ^{99m}Tc-DTPA blood flow curve. Renal and aortic counts for the first minute are plotted. The *thinner arrow* indicates the peak counts in the aortic curve, and the *thicker arrow* indicates the peak counts in the renal curve. The time difference between these peaks should be 6 seconds. **C:** Phase I ^{99m}Tc-MAG3 blood flow curve. Because of the more rapid extraction of ^{99m}Tc-MAG3 from the blood pool, there is no clear peak in this curve, only an inflection point (*arrow*).

   a. **Phase I:** evaluation of renal blood flow. The plot of the first minute of data reflects renal blood flow (Fig. 2-2B and Fig. 2-2C). The aortic flow is plotted as well. Attention is given to the time delay between peak counts in the aorta and peak counts in the kidney. Because of rapid extraction, the ^{99m}Tc-MAG3 flow curve does not have a clearly defined peak, but rather an inflection point (Fig. 2-2C). Radiopharmaceuticals best suited for a bolus of good quality are ^{99m}Tc-DTPA, ^{99m}Tc-MAG3, and ^{99m}Tc-glucoheptonate. The time delay between peak aortic flow and peak renal flow should be less than 6 seconds.
   b. **Phase II:** parenchymal function (extraction and transit of nuclide). After the initial flow of nuclide into the kidney, renal uptake depends on parenchymal function. In a normally functioning kidney, counts will at first steadily increase within the kidney secondary to extraction of nuclide from the blood pool. Nuclide will traverse the parenchyma and begin to enter the collecting system. Within 5 minutes, excretion of nuclide into the renal collecting system will exceed the uptake of nuclide from the steadily diminishing blood pool, and the curve will enter phase III downslope. Peak uptake (the time of reversal of upslope to downslope) on a normal renogram should occur within 5 minutes after injection.
   c. **Phase III:** excretion. This phase in the normal kidney is characterized by a rapid component of emptying (when the parenchymal and blood pool supply of nuclide is greater), followed by a more gradual downslope as the supply of nuclide available for excretion decreases. A normal DTPA renogram will demonstrate 50% emptying of nuclide from the kidney within 20 minutes (Fig. 2-3).

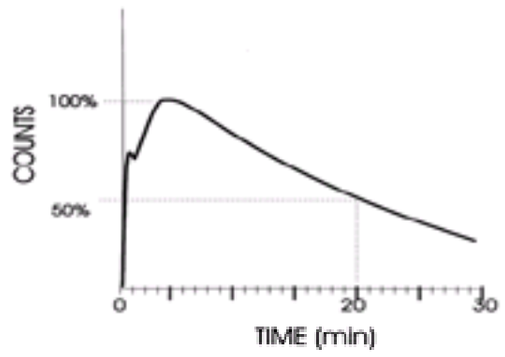

FIG. 2-3. Normal ^{99m}Tc-DTPA renogram demonstrating 50% excretion in 20 minutes.

B. Evaluation of focal and relative renal function with cortical agents
   1. Substances that are taken up and retained within the renal tubular cells may be used for static renal imaging, to evaluate relative renal function and function of renal masses. Typical agents available for this use are as follows:
      a. During the first 30 minutes, **^{99m}Tc-glucoheptonate** is used as a flow and function agent, as described above. After excretion is complete at 1 hour, 12% of the injected dose is retained in the tubular cells.
      b. **^{99m}Tc-DMSA** (dimercaptosuccinic acid) is commonly used for evaluation of renal morphology. It is extracted from the peritubular extracellular fluid and deposited in the tubular cells; 50% of the injected dose is present in the kidneys at 1 hour.
   2. **Acquisition and analysis.** Patients receive an intravenous injection of one of the above nuclides. Images of renal parenchymal retention are obtained after excretion of the agent is mostly complete. Images following the administration of glucoheptonate are obtained 1 to 2 hours after injection, whereas ^{99m}Tc-DMSA images are obtained 3 to 4 hours after injection. Normal ^{99m}Tc-DMSA images are shown in Fig. 2-4.

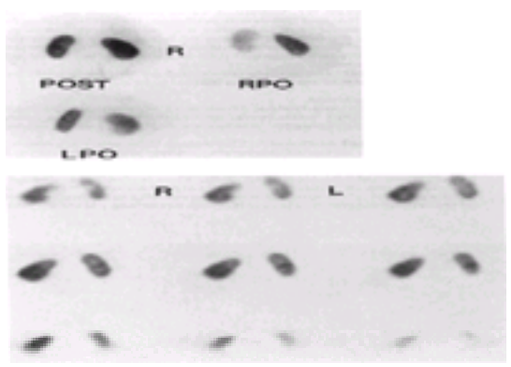

FIG. 2-4. Normal ^{99m}Tc-DMSA images. The upper images are planar posterior, left posterior oblique, and right posterior oblique. The lower images are coronal tomographic views of the same kidney.

C. **Imaging of renal infection.** Agents used specifically to image infectious or inflammatory processes include the following:
   1. **White blood cells labeled with ^{111}In.** Indium 111 is a moderately expensive radionuclide produced by cyclotron. A very careful technique is used to separate white blood cells from a 30- to 60-mL aliquot of whole blood drawn from the patient with a 16-gauge needle. These white blood cells are labeled with ^{111}In, resuspended in the patient's plasma, and reinjected into the patient through another large-bore access. Imaging is performed 24 hours later. The white cells retain their function and localize at sites of infection. White blood cells labeled with ^{99m}Tc are not recommended for imaging the genitourinary system, as the ^{99m}Tc that dissociates is excreted through the renal system.
   2. **Gallium citrate Ga 67.** Gallium 67 is produced by cyclotron. It is an iron analog and attaches to serum proteins, including lactoferrin and ferritin. It localizes at sites of infection and inflammation (e.g., interstitial nephritis) and in a limited number of tumor types. Gallium 67 is normally seen in renal parenchyma up to 72 hours after injection. After this time, accumulation is abnormal and suggestive of infection, inflammation, or certain tumors.
   3. **^{99m}Tc-DMSA** is currently recommended as the agent of choice for diagnosis and follow-up of pyelonephritis.

D. Clinical applications
   1. Vascular abnormalities
      a. **Renal arterial embolus.** Nonvisualization of a kidney on the flow scan is consistent with renal arterial embolus. Segmental embolus presents on scintigraphic study as a regional peripheral perfusion defect (Fig. 2-5).

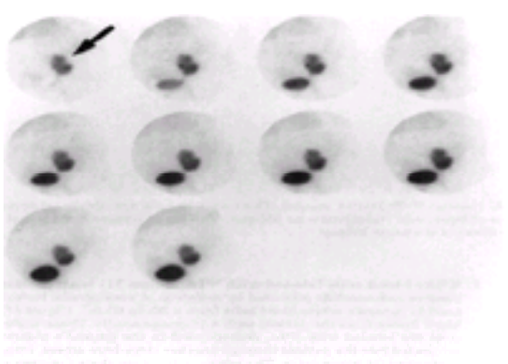

FIG. 2-5. Renal artery embolism. A peripheral wedge-shaped defect consistent with an infarct following embolism is marked by an *arrow* on this ^{99m}Tc-MAG3 transplant scan.

      b. **Renal arterial stenosis.** The renal flow scan by itself is relatively insensitive to arterial stenosis. Standard evaluation involves the comparison of renal function following the administration of an angiotensin-converting enzyme inhibitor, such as captopril, with baseline renal function (Fig. 2-6). This technique is very sensitive for the detection of clinically significant stenoses (>65%). After the administration of an angiotensin-converting enzyme inhibitor, the postglomerular compensatory efferent arteriole stenosis will dilate. The subsequent drop in the glomerular filtration pressure will be seen as a prolonged phase II of the renogram during a ^{99m}Tc-MAG3 study, and as reduced accumulation in phase II of a renogram performed with ^{99m}Tc-DTPA. This test is less useful within poorly functioning kidneys.

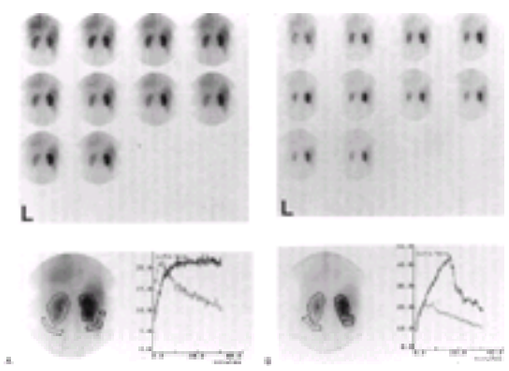

FIG. 2-6. Renal captopril study. **A:** Thirty-minute ^{99m}Tc-MAG3 functional images (the left kidney is on the left, the right kidney on the right) and a renogram of both kidneys following captopril ingestion. The images and renogram curve for the right kidney (*darker curve*) demonstrate steadily increasing counts in the kidney. **B:** Baseline images and curves obtained without captopril. The function of the right kidney is improved because of restoration of the compensatory efferent arteriolar stenosis.

c. **Renal vein thrombosis.** Although renal vein thrombosis is generally characterized as reduced perfusion and delayed accumulation, nuclear imaging is not the procedure of choice for this entity.

2. Parenchymal abnormalities
   a. **Malformations and anatomic variants.** Static imaging of the kidneys with ^{99m}Tc-DMSA or ^{99m}Tc-glucoheptonate is an excellent means of determining the size and configuration of functioning renal parenchyma. Polycystic kidneys usually demonstrate multiple bilateral photopenic defects ("cold spots"). Normal renal tissue in aberrant locations (horseshoe kidney, fetal location, hypertrophied column of Bertin) may also be defined by this method. Size and position of even the most atrophic and ectopic renal parenchyma may be assessed if there is a significant amount of functioning tubular mass. With renal duplication, ^{99m}Tc-DMSA or ^{99m}Tc-DTPA scintigraphy can assess regional parenchymal function before corrective surgery. Before nephrectomy, relative renal function can be assessed in the same manner (split function renography).
   b. **Transplant evaluation: acute tubular necrosis versus rejection.** Many transplanted kidneys demonstrate some evidence of acute tubular necrosis postoperatively. Renal scanning with ^{99m}Tc-DTPA demonstrates normal renal perfusion but little or no accumulation or excretion of the tracer. Renal scanning with ^{99m}Tc-MAG3 demonstrates normal renal perfusion and steadily increasing counts in the kidney with reduced excretion. Generally, one can expect gradual improvement in cases of acute tubular necrosis within about 3 weeks (Fig. 2-7), but resolution may take several months. Acute rejection is characterized by markedly decreased renal perfusion on scanning with both ^{99m}Tc-DTPA and ^{99m}Tc-MAG3. This is one of the earliest signs of rejection, and it can occur as early as 48 hours before clinical symptoms become apparent. In contrast to the images in acute tubular necrosis, images of parenchymal function are relatively better than the perfusion images. Rejection and acute tubular necrosis may occur simultaneously, however, and differentiation may not be possible. For this reason, many surgeons advocate baseline renal scans at 24 to 48 hours after transplantation, which can be compared with subsequent studies (Fig. 2-8).

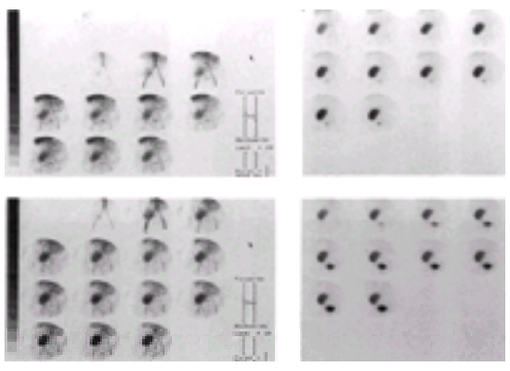

FIG. 2-7. Resolving acute tubular necrosis. **Upper left:** One day after transplant, the first minute of blood flow is normal. **Upper right:** One day after transplant, the subsequent 30 minutes of imaging demonstrate reduced extraction, clearance, and excretion of nuclide, consistent with acute tubular necrosis. **Lower left and right:** Three days later, flow images are still normal, and extraction, clearance, and excretion of nuclide are improved, consistent with resolving acute tubular necrosis.

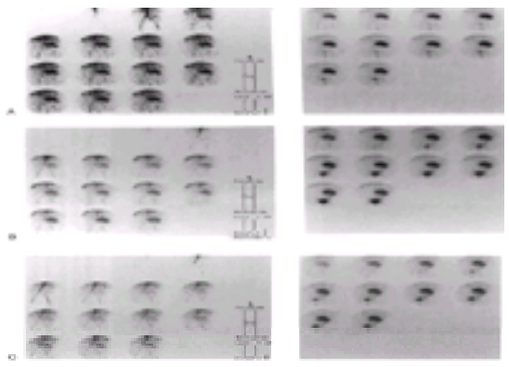

FIG. 2-8. A,B: Transplant rejection. **Upper left and right:** One day following transplant. The 1-minute blood flow images are relatively normal and the 30-minute images demonstrate moderately reduced function. At this stage, the diagnosis could be acute tubular necrosis or rejection. **Lower left and right:** Sixteen days after transplant, the kidney is not as well seen on flow images, but the functional images demonstrate improved extraction and excretion of nuclide. **C:** Transplant rejection. Twenty-one days following transplant of the same kidney, there is poor visualization of the kidney on blood flow images and only mild degradation of function. This is a characteristic pattern for rejection.

c. **Acute glomerulonephritis.** Scintigraphy has no significant role in the diagnosis or management of this entity.
d. **Acute interstitial nephritis.** A characteristic pattern of intensely increased uptake of ^{67}Ga persists more than 72 hours after injection (Fig. 2-9).

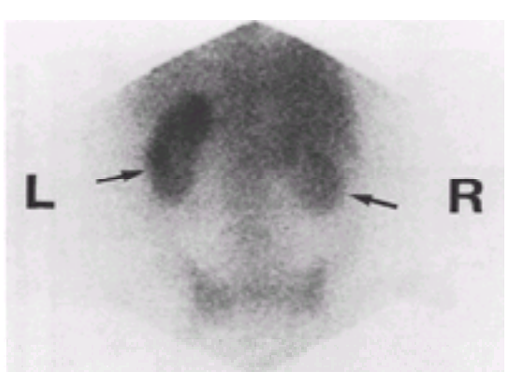

FIG. 2-9. Interstitial nephritis. Intensely increased uptake is seen in the left kidney and moderately increased uptake is seen in the right kidney.

e. **Pyelonephritis.** ^{99m}Tc-DMSA is advocated for the diagnosis, assessment, and management of acute pyelonephritis. Photopenic defects indicative of pyelonephritis can be unifocal or multifocal. Defects representing acute infection will resolve on follow-up studies, whereas persistent defects are consistent with permanent scarring (Fig. 2-10). Gallium citrate Ga 67 can be used to diagnose pyelonephritis, but the agent can be visualized for up to 72 hours in the normal kidney, so diagnosis can be delayed. Although white blood cells labeled with ^{111}In are specific for infection, the procedure is relatively more time-consuming and costly than a ^{99m}Tc-DMSA study.

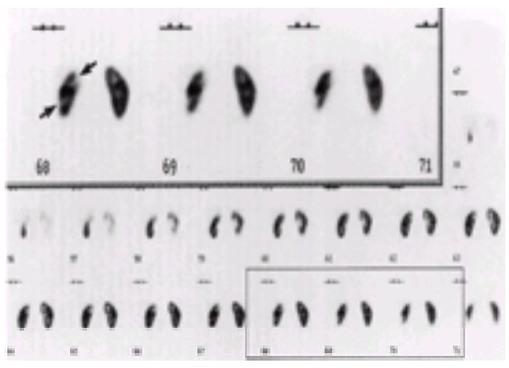

FIG. 2-10. Pyelonephritis: ^{99m}Tc-DMSA study. Coronal views from a tomographic study with magnification of select views demonstrate cortical defects (*arrows*) in the right kidney, consistent with known acute pyelonephritis.

3. Postrenal abnormalities
   a. **Hydronephrosis and obstruction.** Differentiation of obstructive from nonobstructive hydronephrosis may be achieved by furosemide renal scanning. Administration of intravenous furosemide (10 to 40 mg) in the hydronephrotic, nonobstructed kidney initiates a diuresis that clears activity from the kidney and pyelocalyceal system. A normal response to furosemide is characterized by 50% emptying of the kidney and pelvis by 20 minutes after injection (Fig. 2-11). In instances of collecting system obstruction, the tracer activity in the renal pelvis fails to clear or even accumulates further. An indeterminate result (some emptying, but <50% in 20 minutes) will occur in approximately 15% of all cases and is caused by the following:

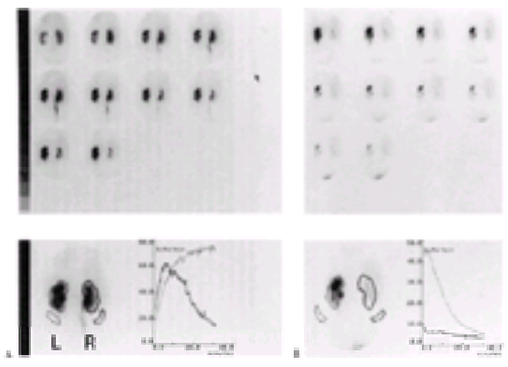

FIG. 2-11. Furosemide renal scan. Patient with known hydronephrosis by ultrasound presented for evaluation of possible obstruction. **A:** Thirty-minute ^{99m}Tc-MAG3 functional images and renogram demonstrate steadily increasing counts in the left kidney (*lighter gray curve*). **B:** Images obtained immediately following injection of intravenous furosemide. Counts in the left kidney rapidly decrease, confirming a nonobstructed excretory system.

      1. Blunting of diuresis by markedly depressed renal function
      2. Masking of tracer clearance by grossly distended renal pelvis and ureter
      3. Confusion caused by the presence of vesicoureteral reflux, which can be prevented by catheterization of the bladder
      4. Marked bladder distention that may result in poor emptying of the upper tracts; it is wise to have the patient void before the study is begun. Occasionally, retention of tracer may occur only after furosemide administration, which indicates functional obstruction at high rates of urine flow.

   b. **Urinary leakage** is diagnosed with greater sensitivity by nuclear imaging than by contrast radiography. Depending on the site of the leak, extravasation can be loculated or dispersed throughout the peritoneal cavity (Fig. 2-12). In posttransplant patients, extravasation is generally seen as an area of increased activity in the region of the vesicoureteral anastomosis. When extravasation is suspected but not visualized initially, it is helpful to obtain delayed images before and after emptying of the bladder. A urinoma may present as a photon-deficient area if it represents urine that has accumulated before the injection of the radionuclide tracer.

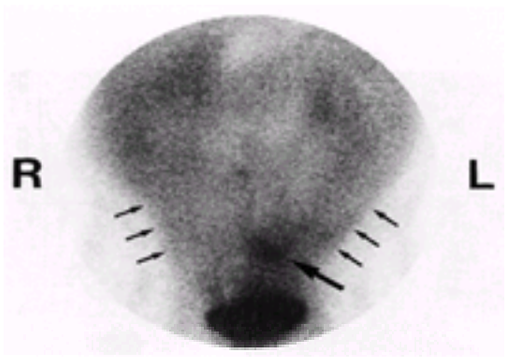

FIG. 2-12. Urinary leakage: postoperative peritoneal urinary ascites following ureteral tear. Throughout the abdomen, ^{99m}Tc-MAG3 is seen diffusely (*small arrows*), with pooling at the site of the obstructed damaged ureter (*larger arrow*).

   c. **Ureteral reflux studies.** Radionuclide cystography (RNC) permits continuous monitoring of the dynamics of bladder filling and emptying. It is more sensitive than radiographic cystography, especially for low-grade reflux. A small dose of tracer, most commonly ^{99m}Tc-pertechnetate, is introduced into the bladder through a transurethral catheter. Sequential posterior imaging of the bladder, ureters, and kidneys is performed at 5-second intervals during bladder filling and at 2-second intervals during voiding. Vesicoureteral reflux is easily detected and graded (Fig. 2-13), and bladder volume can readily be calculated. It is recommended that a conventional contrast voiding cystogram (VCUG) be performed as the first study on each patient to obtain anatomic information. RNC is then used for subsequent studies and for the screening of siblings. This is because the radiation dose from an RNC study is one-thousandth of the dose from a VCUG study.

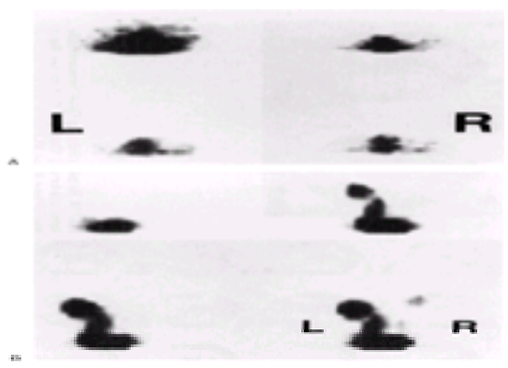

FIG. 2-13. A: Normal radionuclide cystography. Posterior projection. The lower right image was taken after voiding. (Courtesy of Dr. Elizabeth Oates, New England Medical Center, Boston, MA.) Vesicoureteral reflux. Posterior views demonstrate grade III reflux on the left and grade II reflux on the right. (Courtesy of Dr. Elizabeth Oates, New England Medical Center, Boston, MA.)

d. **Testicular imaging.** Testicular scanning is used primarily to differentiate acute testicular torsion from other causes of acute scrotal pain, such as acute epididymitis. This distinction is important because acute testicular torsion mandates immediate surgical intervention. The testicle can rarely be saved if surgery is delayed more than 6 hours after onset of ischemia.
   1. **Technique.** Following the intravenous bolus injection of ^{99m}Tc-pertechnetate, serial images of the testicles are obtained at 1-second intervals for the first minute as an assessment of testicular blood flow. Static images of the scrotum are obtained immediately following the blood flow images.
   2. **Clinical application.** Normally, flow to the testes is equal bilaterally (Fig. 2-14). In acute testicular torsion, the delayed perfusion images show decreased activity over the affected testis (Fig. 2-15). Delayed torsion will demonstrate an intense halo of activity around the infarcted testis (Fig. 2-16). In epididymitis (and/or orchitis), increased perfusion through the spermatic cord vessels is noted, as it is in other inflammatory processes involving the testicle, and increased activity is noted on the involved side (Fig. 2-17). Radionuclide scanning of the scrotum in trauma, hydrocele, spermatocele, varicocele, testicular tumors, and abscesses produces results of varying specificity and does not have a prominent clinical role at this time.

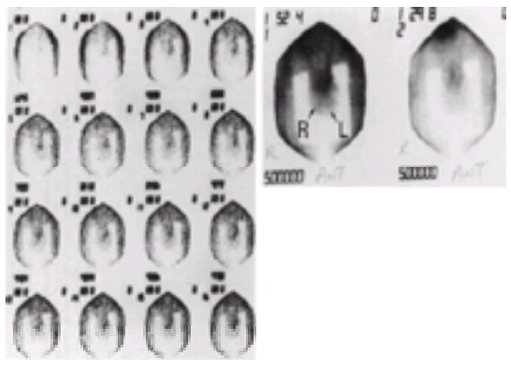

FIG. 2-14. Normal testicular scan. Uptake is symmetric in the scrotal sacs (*arrows*). (Courtesy of Dr. Victor Lee, Boston Medical Center, Boston, MA.)

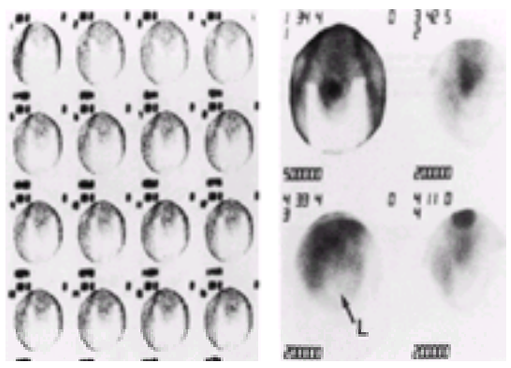

FIG. 2-15. Acute testicular torsion. Uptake is decreased in the left scrotal sac (*arrow*). (Courtesy of Dr. Victor Lee, Boston Medical Center, Boston, MA.)

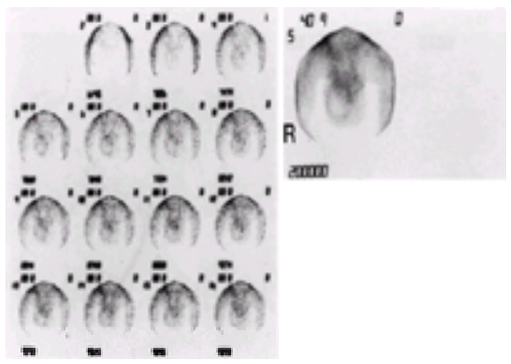

FIG. 2-16. Delayed torsion. A photopenic (cold) right testicle (*thin arrow*) with a hyperemic ring (*thick arrow*) visualized on flow and immediate static imaging. (Courtesy of Dr. Victor Lee, Boston Medical Center, Boston, MA.)

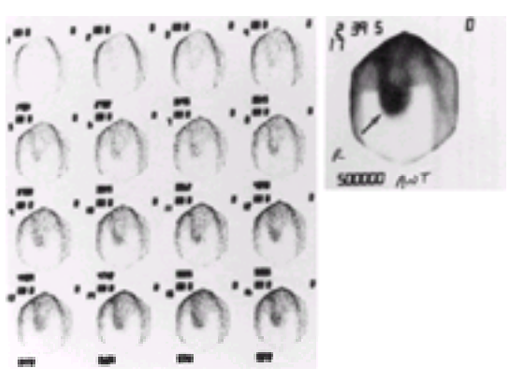

FIG. 2-17. Epididymitis. Increased flows and immediate uptake in right scrotal sac. (Courtesy of Dr. Victor Lee, Boston Medical Center, Boston, MA.)

Suggested Reading

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Eggli DF, Tulchinsky M. Scintigraphic evaluation of pediatric urinary tract infection. *Semin Nucl Med* 1993;23:199–218.

Kim CK, Zuckier LS, Alavi A. The role of nuclear medicine in the evaluation of the male genital tract. *Semin Roentgenol* 1993;28:31–42.

Sfakianakis GN, Bourgoignie JJ, Jaffe D, Kyriakides G, Perez-Stable E, Duncan RC. Single-dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987;28:1383–1392.

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Chapter 3 Endoscopic Instruments and Surgery

Robert A. Edelstein

Although we have seen an explosion of new technology in the past 10 years, many older urologic instruments continue to be used. The first instrument incorporating a lens system for viewing the bladder, a sheath and a source of light, was built by Max Nitze in 1877. In subsequent years, the quality of the view has been improved by the development of the Hopkins rod-lens and fiberoptic light transmission. Today's instruments provide an excellent image displayed on television screens. The central role of endoscopy requires the practitioner to gain a thorough understanding of urologic instrumentation. The following section reviews some of the catheters, instruments, and techniques commonly used by the urologist in the lower urinary tract. For a discussion of the instruments and techniques specific to the upper urinary tract, see Chapter 10.

I. Urologic Catheters and Instruments

A. **Catheters.** Catheters are hollow tubes used to relieve urinary retention, irrigate the bladder, instill medication or radiographic contrast, obtain urine for examination, and measure residual urine volume. Many types are also useful as nephrostomy tubes. Catheters are most commonly calibrated according to the French (F) scale, in which each unit equals 0.33 mm in diameter. A catheter designated 30F, for example, has a diameter of roughly 10 mm.

1. The **Robinson catheter** (Fig. 3-1) is a straight rubber tube used for short-term catheterization, as in measurement of residual urine and instillation of medication, chemotherapeutic agents, or contrast material into the urinary bladder. It is also useful for intermittent self-catheterization in the treatment of chronic urinary retention. The tip of the Robinson catheter is rounded, with one or two drainage ports along the side. If a Robinson catheter is left indwelling, it must be secured to the glans penis by suture or tape.

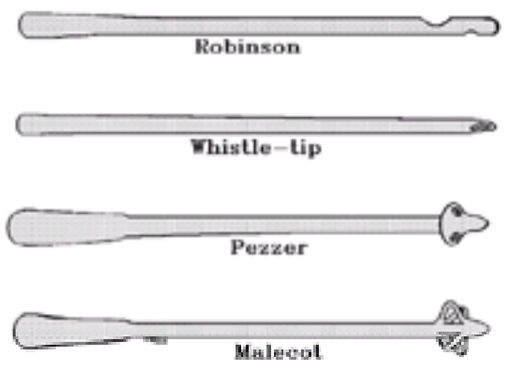

FIG. 3-1. Commonly used straight and self-retaining catheters.

2. The **coude catheter** (Fig. 3-2) is curved at the tip (hence the name, the French word for “elbow”). A straight catheter cannot always pass through a hypertrophied or strictured bladder neck. The curved shape of the coude catheter is designed to guide it over the bladder neck. In addition, this specialized catheter is slightly stiffer than the Robinson catheter. Coude catheters are manufactured with and without retention balloons.

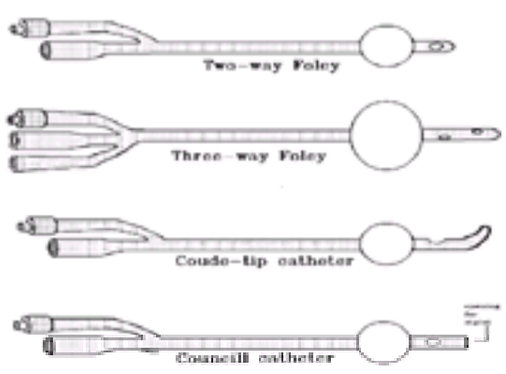

FIG. 3-2. Various types of self-retaining balloon catheters.

3. The **Foley catheter** (Fig. 3-2) is a straight catheter with a retention balloon near the tip. Several varieties are available, with short- or long-nose tips, two or three lumen sizes, and 5-mL or 30-mL balloons. Two-lumen catheters have one channel for drainage and one for inflating the balloon. Three-lumen catheters have an additional channel for irrigating the bladder and are used most commonly when ongoing hematuria is expected, such as after transurethral resection of the prostate (TURP). Foley catheters are available in sizes from 12F to 30F, with the smallest three-lumen catheter being 18F. The balloons can be overinflated if necessary to at least twice their stated capacity without breakage. Silicon or silicon-coated catheters are said to produce less tissue reaction and less encrustation than rubber catheters. They also have a larger lumen diameter than catheters made of rubber and thus are preferred by some for long-term indwelling catheterization.
4. The **Pezzer catheter** (Fig. 3-1) is self-retaining with a mushroom-shaped tip. It is most commonly used for suprapubic cystotomy drainage. The catheter should be secured to the skin by suture or tape.
5. The **Malecot catheter** (Fig. 3-1) is similar to the Pezzer except that the drainage ports at the tip are wider. This may be particularly useful when bloody fluids, such as from a nephrostomy, are drained.
6. The **whistle-tip catheter** (Fig. 3-1) is a straight catheter with a beveled opening at the tip and another opening in the side. It provides better irrigation and drainage than the Robinson catheter.
7. **Councill catheters** (Fig. 3-2) are similar to Foley catheters, except that they have an opening at the end to allow use with a screw-tip stylet that can be attached to a filiform. This type of catheter is most commonly used in bypassing a urethral stricture or false passage. Councill catheters are especially useful when passage of any other type of catheter is difficult. They are not used to dilate the urethra. The catheter is passed into position over a previously placed guide wire, or it can be used with a Councill stylet, which has a male screw tip that fits through the perforation to engage a filiform. After a stricture is dilated with filiforms and followers, the Councill catheter is attached to the filiform and guided into the bladder. The stylet and filiform (or guide wire) are then removed through the lumen of the Councill catheter.

8. **Catheter stylets** are malleable metal guides that, when placed into a Foley or other type of catheter, can be used to provide stiffness and shape. There are two type of stylets—one with a blunt tip, used with a Foley catheter, and one with a screw tip, used with a Councill catheter. This procedure is useful to accomplish passage through a urethral stricture or tight bladder neck. Catheter stylets also may be used following TURP to avoid undermining the bladder neck. When a catheter stylet is used, the bladder should always be full to avoid injuring the posterior bladder wall.

B. **Dilators** are used to stretch the urethra to aid passage of large-caliber instruments or in the treatment of urethral strictures. A large variety of dilators are available, and the most common are described below.

1. **Van Buren sounds** are solid metal sounds curved in the shape of the male urethra (Fig. 3-3). Ranging in size from 16F to 40F, they are most commonly used for dilating urethral strictures and for stretching the normal urethra to accommodate larger instruments.

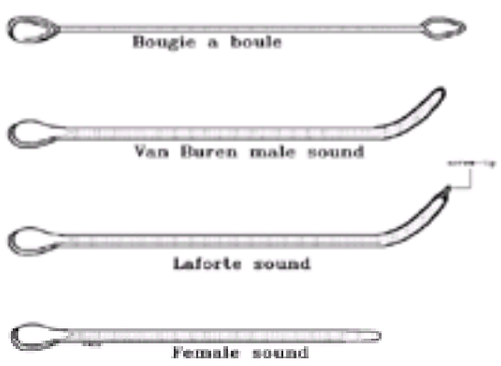

FIG. 3-3. Top to bottom: Rigid metal urethral instruments used for calibration (*bougie à boule*), male urethral dilatation (Van Buren sound), attachment to a filiform (Laforte sound), and female urethral dilatation (female sound).

2. **Filiforms** and **followers** are specialized instruments for dilating urethral strictures. Filiforms are very thin, very pliable solid catheters ranging in size from 1F to 6F (Fig. 3-4). They are made of solid plastic or have a woven fiber core with smooth-coated surfaces. Filiform tips may be straight, pigtailed, or of the coude type. They have a female screw tip on the proximal end to allow attachment of the follower. The follower (Fig. 3-4) is made of material similar to that of the filiform but of a larger caliber (12F to 30F), and it may be solid or hollow. After introduction of the filiform into the bladder, the follower is screwed onto the end of the filiform. Both are advanced through the urethra into the bladder and withdrawn to permit changing of the follower to a larger size. The filiform always remains in the urethra as a guide for the followers.

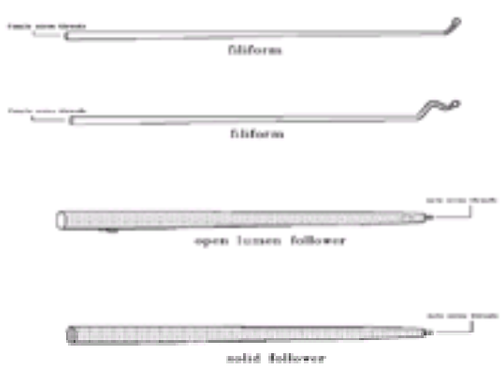

FIG. 3-4. Filiform catheters and followers.

3. **Coaxial dilators** are based on the principle of using a guide wire instead of a filiform for passage through a urethral stricture. A flexible wire is passed into the bladder, and progressively larger dilators are advanced into the bladder over the wire. A variation is the balloon dilator, which is passed over a guide wire and inflated at the area of the stricture.
4. ***Bougies à boules*** (Fig. 3-3) are acorn-tipped calibrators used to determine urethral and meatal size. They are available in sizes ranging from 8F to 40F.
5. **Female sounds** are similar to Van Buren sounds but are shorter in length and less curved or straight. Sizes range from 14F to 40F (Fig. 3-3).

C. Diagnostic and operating instruments

1. **Rigid cystourethroscopes** (Fig. 3-5) are hollow metal instruments designed for endoscopic observation and surgery. Their sheaths range in size from 8F to 26F. These instruments have obturators that are inserted into the sheath to aid passage into the bladder. This can be done either blindly or (preferred) under direct vision. Interchangeable fiberoptic lenses allow a view ranging from 0 to 120 degrees. The 0-degree (forward) lens is best for intraurethral work, and the 30-degree (forward-oblique) lens allows visualization of either the urethra or the bladder (panendoscopy). The 70-degree (lateral) lens is used frequently for inspecting the interior of the bladder, whereas the 120-degree (retrograde) lens provides retrograde viewing of the bladder neck. The telescope is connected by means of a fiberoptic light bundle to a bright source of light. Visualization is aided by irrigating with fluid (usually sterile saline solution or water) through special ports on the side of the cystourethroscope sheath. For example, operating instruments, such as biopsy forceps or cautery (Bugbee) electrodes, and ureteral catheters can be passed through the sheath and manipulated within the bladder by the Albarran bridge. The Albarran bridge utilizes a lever or wheel near the eyepiece to manipulate a small bar at the end of the device. This bar is used to deflect and control a variety of instruments, including flexible biopsy forceps, ureteral catheters, and cautery (Bugbee) electrodes, to name a few (Fig. 3-6).

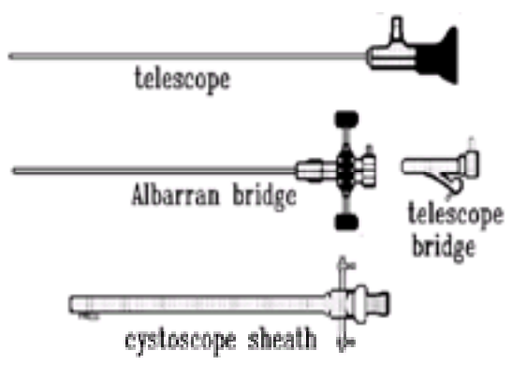

FIG. 3-5. Top to bottom: Telescope for cystoscope, Albarran deflecting bridge and standard bridge, cystoscope sheath.

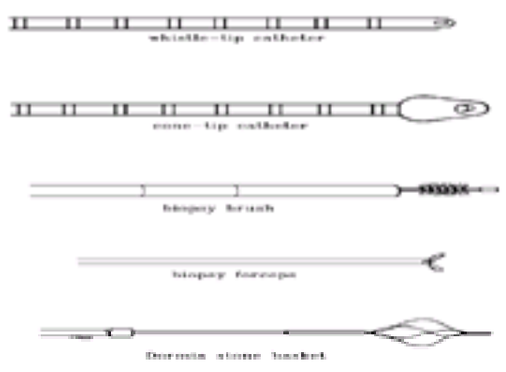

FIG. 3-6. Top to bottom: Types of catheters and instruments that can be directed by means of the Albarran deflecting bridge.

2. **Flexible instruments** (Fig. 3-7) have recently been developed for cystoscopy, ureteroscopy, and nephroscopy. Their main advantage is that they are small in caliber and can be used easily under local anesthesia in an outpatient or office setting. Flexible instruments do not provide as clear a view as rigid instruments do, however. Moreover, operative and diagnostic procedures are limited with the use of flexible instruments by the capacity of the irrigating and working channels, which is less than in rigid instruments. The flexible cystoscope is used most commonly in the office setting for routine diagnostic viewing of the bladder.

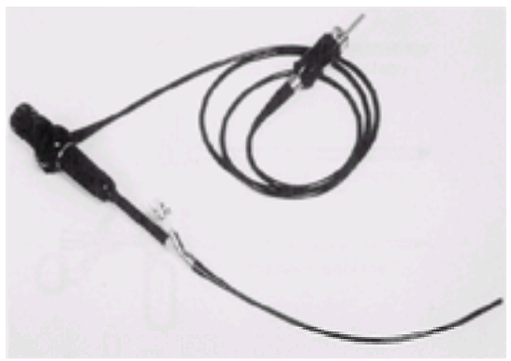

FIG. 3-7. Flexible cystoscope. The small handle near the eyepiece controls tip deflection. A working channel that traverses the length of the cystoscope allows passage of instruments.

3. **Ureteroscopy and nephroscopy** performed via the lower urinary tract have now become commonplace with the advent of smaller-caliber rigid, semirigid, and flexible instruments (Fig. 3-8). Through these instruments, diagnostic imaging, biopsies, and treatment of stones and tumors of the upper urinary tract are possible. In the case of larger intrarenal stones, a percutaneous tract may be established under ultrasound (US) or computed axial tomographic (CT) control. A rigid nephroscope may be passed through a percutaneous sheath directly into the kidney. Endoscopic surgery of the upper urinary tract is further discussed in Chapter 10.

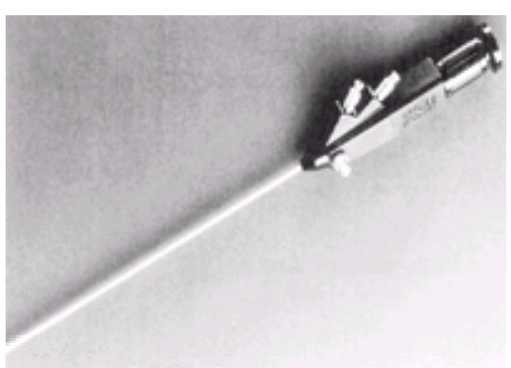

FIG. 3-8. Semirigid ureteroscope, used to access the ureter through the bladder. (Courtesy of Applied Medical, Urology Division, Laguna Hills, CA.)

4. **Resectoscopes** (Fig. 3-9) are instruments designed for resecting tissue in the lower urinary tract under direct vision. A large variety of special tips can be fitted to the mechanism of the resectoscope, depending on the particular operative need. These tips are used to transmit electric current to the tissue to achieve either resection or coagulation, depending on the type of current output from the electrosurgical generator. Continuous-flow models have been developed to eliminate the necessity of intermittent emptying. Constant suction or gravity is used to achieve continuous inflow and outflow, permitting more efficient resection and greater safety. When used properly, continuous-flow resectoscopes prevent excessive distention of the bladder and allow more efficient resection.

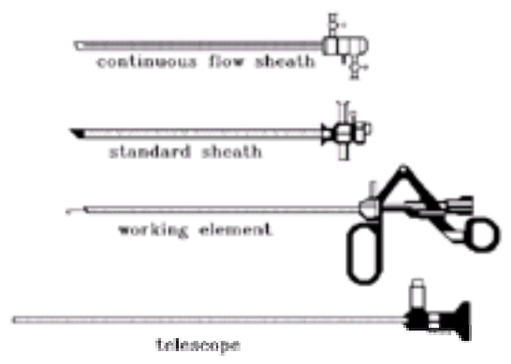

FIG. 3-9. Components of continuous-flow resectoscope.

5. **Urethrotomes** (Fig. 3-10) are instruments designed to incise urethral strictures under direct vision. The modern optical urethrotome permits direct visualization and incision of the stricture. A “cold knife” is actuated by an Iglesias-type working element.

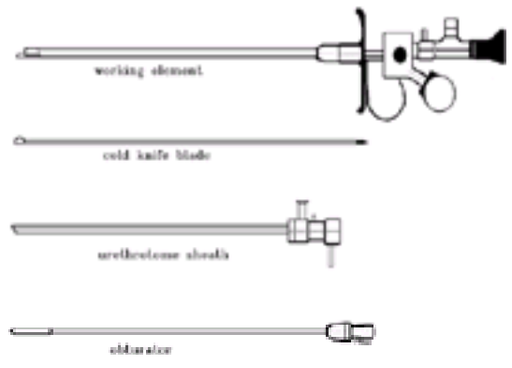

FIG. 3-10. “Cold knife” urethrotome and sheaths.

6. **Lithotrites** are older instruments rarely used today. They are hand-activated instruments used to crush or fragment urinary stones in the bladder. The Bigelow lithotrite was used blindly to feel the bladder stone, grasp it, and crush it. The Hendrickson lithotrite has the great advantage of permitting direct visualization of the stone while it is being crushed. The lithotrite has largely been replaced by the newer technologies of electrohydraulic, pneumohydraulic, laser, and ultrasonic stone disruption. These newer types may also be used for percutaneous or ureteroscopic fragmentation of upper urinary tract stones.
7. **Laser energy** may be delivered through rigid or flexible endoscopes. A variety of laser types may be used. The properties of each type vary, depending on the wavelength and power generated. Lasers may be used to fragment urinary tract stones (see Chapter 10) and to treat prostatic enlargement (see Chapter

6).

8. **Video monitoring** of endoscopic procedures has now become commonplace (Fig. 3-11). Small, high-resolution color cameras attach to the eyepiece of the endoscopes and allow real-time projection on large television monitors in the operating room. This is invaluable for both teaching and allowing an assistant to share the operator's view. Video monitoring of endoscopic procedures offers several distinct advantages: (1) a standing, comfortable position; (2) magnified, binocular vision; and (3) greater eye protection from blood and irrigating fluid.

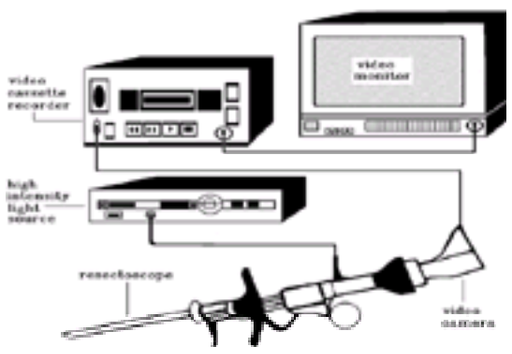

FIG. 3-11. Typical setup for video monitoring of endoscopic surgery.

D. Biopsy and aspiration needles
   1. The **Tru-cut type of needle** is a cutting trochar that removes a core of tissue for pathologic analysis. It is generally used with a spring-loaded gun (Fig. 3-12) that is able to obtain tissue cores rapidly and efficiently. Either the perineal or the transrectal route may be used to approach the prostate. Guidance may be by transrectal finger palpation, or a transrectal US probe may be used.

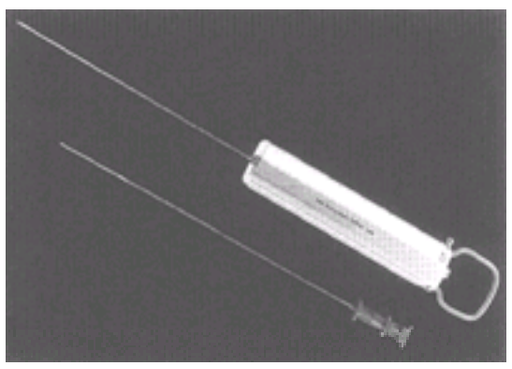

FIG. 3-12. Disposable Tru-cut type of biopsy needle with reusable spring-loaded actuator.

   2. The **Vim-Silverman needle** is now less often used, having been replaced by the Tru-cut type of needle and spring gun. It contains two opposed cutting blades, which are advanced into the prostate from within an introducer sheath. This needle is usually advanced through the perineum, and local anesthesia is required.
   3. **Suction aspiration needles** of various designs are available. They obtain cytologic material by suction produced by a syringe attached to the needle or by removal of the obturator.

E. **Percutaneous cystostomy trochars.** If the bladder cannot be entered through the urethra, a percutaneous cystostomy tube can be placed into the distended bladder. The technique of percutaneous cystostomy is described later. The following types are available:
   1. The **Hurwitz type of trochar** consists of a large-bore metal sheath around a sharp, solid obturator. This permits placement of a standard Foley type of catheter into the bladder.
   2. The **Stamey trochar** places a Malecot catheter into the bladder (Fig. 3-13).

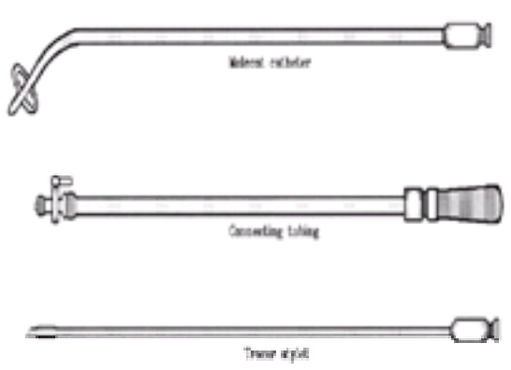

FIG. 3-13. Components of Stamey percutaneous cystotomy kit.

   3. The **Argyle catheter** uses a Foley-type balloon catheter, which also has an irrigating port.
   4. The **Cystocath** is an 8F or 12F simple tube retained in the bladder by means of a flange glued and sutured to the suprapubic skin.

II. Clinical Applications

A. **Catheterization technique.** Catheterization kits generally contain sterile gloves, sterile paper towels, sterilizing solution, lubricating jelly, a syringe filled with 10 mL of water, and a container for bacteriologic specimens packed in a large plastic basin. Some kits also provide a catheter (Robinson or Foley type) as well as an irrigating syringe. A drainage bag, generally not provided, must be obtained before the procedure is begun if long-term catheterization is expected.
   1. **Male patients.** With the patient supine, legs partially abducted, the catheterization kit is opened and the gloves put on. The sterile towels are used to drape the penis. The sterilizing solution, lubricating jelly, and catheter should be prepared before the patient is touched with the gloves. The penis is grasped gently behind the glans with one hand, and slight upward traction is applied to straighten the urethra. The glans and penile shaft are cleansed around the meatus with the opposite hand. If desired, urethral anesthesia may be obtained by instilling 10 mL of 1% to 2% lidocaine jelly through the meatus. Lack of patient allergy to lidocaine should be confirmed first, and 5 minutes should be allowed for the anesthetic effect. The catheter, well lubricated, is inserted into the urethral meatus and gently advanced until almost the entire catheter is inside the urethra. If the patient is uncircumcised, care should be taken to replace the foreskin over the glans to prevent paraphimosis. Force should never be used in urethral catheterization. If the catheter does not enter the bladder easily, the most likely cause is spasm of the external sphincter, followed by urethral stricture or bladder neck obstruction. Prostatic enlargement rarely prevents the passage of a catheter. If urine is not obtained or there is doubt regarding the position of the catheter, the catheter balloon must not be inflated because this may cause severe urethral trauma or rupture.
      a. **External sphincter spasm** may be overcome by reassuring the patient, using large amounts of lubricant, telling the patient to take a deep breath, and applying minimal steady pressure against the sphincter with the catheter until sphincter fatigue occurs. If a patient is particularly anxious, between 5 and 7 mL of 1% to 2% viscous lidocaine can be introduced into the urethra. Intravenous or oral sedation with diazepam is very rarely required.
      b. If difficult catheterization is encountered in a patient known or suspected to have urethral stricture, retrograde urethrography should be carried out to assess the urethra (see Chapter 1). In clearly impassable strictures, percutaneous suprapubic cystotomy is indicated for temporary relief of urinary retention.

c. **Bladder neck obstruction** is often the cause of difficulty in passing a urethral catheter. The coude catheter or catheter stylet is especially useful to guide the catheter over an enlarged median lobe, for example, and the risk for traumatizing the urethra with a straight catheter is avoided.

2. **Female patients.** Catheterization of female patients is usually quite simple. With the patient supine, legs abducted, and knees flexed, the catheterization kit is prepared as described previously. After the sterile gloves are put on, the left hand is used to spread the labia majora to expose the urethral meatus. The meatus and introitus are cleansed with sterilizing solution, and the lubricated catheter is introduced into the urethra. Once urine is obtained from the bladder, the Foley balloon is inflated. If the urethral meatus is not obvious on initial examination, then the anterior vaginal wall should be inspected for the presence of an abnormally positioned (hypospadias) meatus.
3. **Children.** Catheterization in female children is similar to that in female adults except that the catheters used are in the 8F to 12F range. In male children, some prefer to use an 8F feeding tube rather than a Foley catheter because the Foley catheter balloon is somewhat larger than the catheter itself, making it difficult to pass. Also, the lumen of the feeding tube is larger than that of the Foley, making drainage more efficient.

B. Endoscopic diagnosis

1. **Cystourethroscopy**, also called panendoscopy, is the endoscopic examination of the urethra and bladder.
   a. **Indications and contraindications.** Indications for cystourethroscopy include (1) hematuria; (2) a need to obtain tissue for histologic examination; (3) a need to obtain anatomic information regarding the bladder, prostate, or urethra; or (4) a need to obtain access to the upper urinary tract. The major contraindication is genitourinary infection, especially acute cystitis and prostatitis, as instrumentation in this setting may precipitate urosepsis.
   b. **Precautions.** Patients with valvular cardiac disease or artificial heart valves should be protected from bacteremia with antibiotic prophylaxis. The American Heart Association recommends the following regimen: 1 hour before instrumentation, 2 g of ampicillin and 1.5 mg of gentamicin per kilogram of body weight are given, both agents either intramuscularly (IM) or intravenously (IV). Eight hours after instrumentation, the dose is repeated. If penicillin allergy is present, vancomycin is started at 1 hour before instrumentation; 1 g is given IV over 60 minutes, and 1.5 mg of gentamicin per kilogram is given IV or IM. Eight to twelve hours after instrumentation, administration of both antibiotics is repeated. Adequate renal function should be confirmed by determination of creatinine clearance before antibiotics are administered.
   c. **Sterilization of instruments.** Sterilization of endoscopic equipment cannot be achieved by heat or steam because these methods damage the optical systems. Alternative methods commonly used include soaking in 2% glutaraldehyde (“cold” sterilization) or exposing the equipment to ethylene oxide (“gas” sterilization). Twenty minutes of exposure to glutaraldehyde solution kills all bacterial organisms, spores, fungi, and viruses. The glutaraldehyde solution is rinsed from the instruments with sterile saline solution or water before the patient undergoes instrumentation. Ethylene oxide sterilization is equally effective but requires 24 hours of aeration to remove the agent before the instrument is used. Recently, automated sterilizing systems employing exposure to warm peracetic acid (e.g., Steris) have become popular as well.
   d. **Technique.** Most lower tract endoscopy in adults can be carried out using 1% to 2% intraurethral lidocaine (Xylocaine) for local anesthesia in an office or outpatient surgical setting. Pediatric cystoscopy requires general anesthesia. The smallest instrument consistent with the objectives of the procedure should be selected.
      1. **Rigid instruments.** In both male and female patients, the cystourethroscope may be passed blindly into the bladder with the solid obturator or, preferably, under direct vision with the visual obturator and a 0-degree lens. Urine obtained when the bladder is entered should be sent for bacteriologic culture. If the patient has a history of genitourinary malignancy, urine should be sent for cytologic examination. In male patients, the 30-degree lens provides good visualization of the pendulous, bulbous, and prostatic portions of the urethra. With the instrument located at the verumontanum, the extent of prostatic enlargement and the patency of the bladder neck can be assessed. In female patients, the 30-degree lens permits visualization of the urethral mucosa. After the instrument is passed through the bladder neck, the trigone and ureteral orifices can be visualized. Examination of the bladder interior is facilitated by exchanging the 30-degree lens for the 70-degree lens. Systematically examining the entire surface of the bladder mucosa, the endoscopist notes any tumors, stones, trabeculation, or diverticula. Inflammatory changes and bladder capacity should also be noted. In fact, the results of endoscopic procedures should never be described as “normal,” as this provides no information to subsequent examiners. All aspects of the procedure should be noted in detail in the operative report. At the conclusion of the examination, the bladder should be emptied and the cystoscope removed.
      2. **Flexible cystoscopy.** The flexible cystoscope is passed in the same way as a Foley catheter while the lumen is observed through the instrument. The instrument is torqued to obtain a view of the entire bladder mucosa, trigone, and ureteral orifices. The view of the prostatic urethra is not as clear as with rigid instruments, but a general impression of the prostatic size can be obtained.
2. A **mucosal biopsy** is indicated for any mucosal lesion within the bladder or urethra in which tumor is suspected. This procedure can be accomplished endoscopically by using either rigid or flexible biopsy forceps. The rigid biopsy forceps cleanly remove tissue samples of up to 5 mm in diameter; however, some areas of the bladder are difficult to reach with the rigid forceps, such as the dome and anterior wall. The flexible biopsy forceps are available in sizes ranging from 5F to 9F. Although the size of the tissue fragment obtained usually is 2 mm or less with the flexible forceps, all areas of the bladder are accessible. Fulguration can be achieved by using flexible Bugbee electrodes. The electrodes are manipulated with the Albarran bridge to control minor bleeding from biopsy sites or destroy small bladder tumors.
3. **Ureteral catheterization** is a basic technique used for retrograde pyelography, intubation of the ureter for short-term or long-term drainage of the upper urinary tract, and brush biopsy. Ureteral catheters range in size from 4F to 10F and have various tips, such as the whistle tip, cone tip, and spiral tip (Fig. 3-6). Ureteral catheters designed for long-term drainage, called ureteral stents, incorporate some method of fixation within the ureter (e.g., the “double-J” stent). The whistle tip is used primarily for short-term drainage but can be used for contrast studies as well. The cone or bulb tip is ideally suited for retrograde pyelography. The spiral tip is designed to intubate an angulated orifice. The ureteral orifice is located by reference to the interureteric ridge with the 70-degree (lateral) lens. The ureteral catheter is fixed with the Albarran bridge so that the tip of the catheter is visible at the 6-o'clock position of the viewing field. The tip of the catheter is then advanced into the orifice. For retrograde pyelography, a 6F or 8F cone-tip catheter is used to occlude the ureteral orifice during injection of contrast.
4. **Complications** of endoscopic procedures include bleeding, perforation, and infection.
   a. **Minimal bleeding** or **hematuria** is quite common following instrumentation in male patients and usually clears spontaneously within the first 24 hours. The patient should be advised to maintain a high fluid intake to promote diuresis and prevent formation of obstructing clots. Repeated endoscopy is indicated to control bleeding that does not clear within 24 hours.
   b. **Perforation** of the urethra or bladder can occur when excessive force is used. The diagnosis is made by retrograde urethrography. If minimal extravasation is present, antibiotic coverage and urinary drainage for 1 or 2 days is usually sufficient treatment. If major extravasation into the perineum or scrotum has occurred, drainage of the fluid collection may be necessary. Perforation of the bladder is rare but can occur. A cystogram should be obtained to determine whether the perforation is intraperitoneal or extraperitoneal. Extraperitoneal perforations generally can be managed by bladder drainage (urethral or suprapubic). Intraperitoneal perforations require surgical exploration to rule out injury to the bowel or other organs, closure of the perforation, and suprapubic diversion.
   c. **Infection** is a well-known complication of urethral instrumentation. Bacteriuria occurs in approximately 2% of patients after cystoscopy. Bacteremia and sepsis (“urethral chill”) occur rarely following routine cystoscopy and urethral dilation, but they should be anticipated if purulent urine or an abscess is encountered. Patients at risk for endocarditis should receive prophylaxis as previously described.
   d. **Acute urinary retention** may develop following instrumentation of men with prostatic enlargement. Following short-term catheter drainage, many patients resume the voiding pattern they had before instrumentation.

C. Endoscopic procedures

1. **Urethral strictures** may be congenital or acquired. With the advent of modern antibiotic therapy, postgonococcal strictures are becoming less common; traumatic strictures are seen more frequently. Most strictures can be managed at the time of diagnosis by endoscopic means. For short strictures, it is best to place a filiform through the lumen of the stricture under direct vision and gently dilate the stricture with followers. Alternatively, a guide wire can be passed through the stricture under direct vision, and a coaxial balloon dilator passed over the wire. Blind passage of Van Buren sounds in the face of urethral stricture, even in the best of hands, can cause urethral perforation. For long strictures, use of an optical urethrotome is recommended (Fig. 3-10). A guide wire, ureteral catheter, or filiform is placed through the stricture under direct vision, and the stricture is incised, usually at the 12-o'clock position. For long strictures, the entire instrument must be moved to complete the incision. Longer, complex strictures may require formal operative urethroplasty.
2. **Bladder calculi** may be endemic, as in Egypt, or acquired, secondary to obstruction or foreign bodies. Most bladder calculi can be managed endoscopically obviating the need for open cystolithotomy. Small calculi of less than 5 mm can be washed out through the cystoscope sheath or removed with foreign-body cystoscopic forceps.
   a. **Mechanical lithotripsy.** Larger calculi may be difficult to fragment by means of US or electrohydraulic lithotripsy. Occasionally, it may be necessary to crush such stones under direct vision with the Hendrickson lithotrite. This instrument is passed into the bladder in a blind fashion, similar to the method of cystourethroscopy. A fiberoptic telescope is placed through the instrument, allowing visualization of the area between the jaws. Once the stone is grasped under direct vision, the jaws are closed to crush the stone. Stones larger than 3 cm are generally too large to fit within the jaws of the lithotrite. This instrument must be used with extreme care to avoid bladder perforation.
   b. **US lithotripsy.** By means of a rigid US transducer passed through an endoscope, vibrations are generated that can fragment bladder calculi. The transducer incorporates suction to remove fragments and provide cooling. The transducer must be in contact with the stone to transmit the US energy. With larger stones, US lithotripsy can be time-consuming. This method is also quite useful for renal calculi when the instrument is passed through a nephroscope.

c. In **electrohydraulic lithotripsy**, a spark discharge within a liquid produces shock waves that fragment the stone. Under endoscopic control, the tip of the flexible transducer probe is placed very near but not touching the stone. Bursts of repetitive sparks from a generator lasting 1 to 2 seconds are used to fragment the stone, and irrigation is used to wash the fragments out of the bladder.
d. In **pneumohydraulic lithotripsy**, a probe delivers 12 to 15 ballistic shocks per second directly to the stone. It appears to be quite effective and costs much less than laser lithotripsy.

3. **Bladder and urethral tumors** of less than 1 cm in size can be managed entirely by endoscopic means. Specimens are obtained with flexible or rigid biopsy forceps as discussed previously. Occasionally, the biopsy removes the entire tumor. The base and any remaining tumor can then be fulgurated with a Bugbee or roller ball electrode.

D. Transurethral surgery

1. **General principles.** Major endoscopic surgery can be accomplished safely with adequate light, adequate irrigating capacity, and proper use of the electrosurgical unit. The instruments should be checked before intraurethral use for proper vision, function, and alignment. Electrosurgical units provide two types of current: cutting and hemostatic. High-frequency, undamped current cuts or vaporizes tissue, whereas lower-frequency, damped current tends to heat tissue and produce coagulation. The resultant effect is used to achieve endoscopic hemostasis. A third type of current, produced by blending cutting and hemostatic currents in varying proportions, is useful in resecting vascular tissues with minimal bleeding. The electric current is returned to the electrosurgical unit via a broad, highly conductive grounding plate. Careless application of the grounding plate can result in electric burns to the patient or to personnel in contact with the patient.
2. Benign prostatic hyperplasia (BPH) is the most common cause of urinary retention in elderly male patients. In more than 90% of instances, resection of the obstructing portion of the gland with the resectoscope is possible. Determining whether an enlarged gland is resectable endoscopically or requires open surgery is based largely on the ability and experience of the surgeon. In general, however, the smaller the gland, the more difficult is an open procedure and the easier is an endoscopic procedure. A detailed description of technique is beyond the scope of this chapter. Several general principles follow:
   a. The larger the sheath size selected, the larger the resecting ability of the instrument; however, the risk for urethral trauma and stricture is increased by use of too large a sheath. A 26F sheath is a good compromise.
   b. With liberal use of lubricating jelly, the urethra should be dilated carefully with Van Buren sounds until it is at least 2F larger than the selected sheath.
   c. If stricture or meatal stenosis prevents passage of an adequate sized sheath, the problem should be surgically corrected. Alternatively, TURP can be accomplished through a perineal urethrostomy.
   d. Careful observation endoscopy of the anterior urethra, prostate, and bladder with a standard cystoscope should be completed before the resection is begun if not previously performed. This procedure provides information on the location of important landmarks such as the ureteral orifices, bladder neck, verumontanum, and external (striated muscle) sphincter.
   e. Irrigating fluid must be nonconductive (to prevent dissipation of the electrosurgical current), isotonic (to prevent hemolysis when absorbed into the intravascular space), optically clear, and nontoxic. The most commonly used solution is 3% sorbitol. Excessive absorption of irrigating fluid during TURP (post-TURP syndrome) leads to hypertension, bradycardia, changes in mental status, and potentially seizures. Post-TURP syndrome is discussed in Chapter 5.
   f. Resection technique varies widely among experienced urologic surgeons. Some surgeons prefer to resect or vaporize the bladder neck and median lobe (if any) first. Others prefer the classic Nesbit technique of resecting first at the roof of the prostate and proceeding in the capsular plane. The decision can be based on preference and experience. Alternatively, smaller glands may be treated by making deep incisions through the bladder neck at the 5- and 7-o'clock positions (transurethral incision of the prostate), which allows the bladder neck to open during voiding.
   g. At the completion of the procedure, it is important to obtain excellent hemostasis and visually ascertain that all prostate chips have been removed from the bladder with the Ellik evacuator. Both blood clots and chips can obstruct the catheter postoperatively.
   h. If there is difficulty passing a Foley catheter at the completion of the procedure, use of a coude catheter or catheter stylet is advisable. The bladder should be full to prevent injury to the posterior bladder wall. Ordinarily, a 22F continuously irrigating Foley catheter with a 30-mL balloon is used after TURP.
3. **Bladder neck obstruction** may result from dysfunction of the smooth muscle or from scarring secondary to trauma or surgery. The condition may be surgically managed either by incision with the urethrotome or by electrocautery (knife electrode). Alternatively, bladder neck obstruction may be treated by resection and removal of obstructing tissue; however, some say this method leads to further scarring.
4. **Prostate cancer** that has advanced to cause urinary obstruction may be resected in a manner similar to that described for BPH if there are no plans to attempt cure. The endoscopic landmarks may be obliterated by the growth of the tumor, however, making resection of prostate cancer difficult.
5. **Bladder tumors** can be managed endoscopically in most instances. As mentioned previously, biopsy specimens can be taken from small bladder tumors (<1 cm), which are then fulgurated with a Bugbee electrode or laser. Larger tumors require resection under general or spinal anesthesia. Careful endoscopy under anesthesia should be performed to determine whether any tumors were missed during the initial cystoscopy. Care must be taken in applying cutting current because perforation of the bladder wall can occur during the resection in up to 5% of instances. Intraperitoneal perforation requires open surgical treatment.
6. **External sphincterotomy** is occasionally chosen for relief of vesico-sphincter dyssynergia in neurogenic bladder dysfunction, although other therapeutic choices, such as intermittent catheterization, have reduced the need for this procedure. In vesicosphincter dyssynergia, the striated sphincter contracts when the bladder contracts, interfering with normal voiding. The striated urethral sphincter is incised with either a standard resecting loop or a knife electrode at the 12-o'clock position.
7. **Complications of transurethral surgery.** The following complications occur with sufficient frequency or have sufficient impact on the patient's life to warrant discussion with the patient preoperatively:
   a. **Incontinence.** Some degree of incontinence is common following TURP, usually caused by inflammation and detrusor instability. This type of incontinence usually resolves completely within 6 weeks of surgery. True incontinence from sphincteric insufficiency, however, occurring in about 0.5% of cases, does not resolve spontaneously and is a disastrous complication of transurethral surgery.
   b. **Impotence.** Although the mechanism of this complication is not understood, it occurs in a tiny fraction of patients following TURP.
   c. **Retrograde ejaculation** is a common result of TURP and bladder neck resection, occurring in up to 90% of patients.
   d. **Bleeding.** Significant hematuria may occur immediately after TURP or may be delayed until 10 days to 2 weeks after TURP. Immediate bleeding is caused by poor hemostatic technique during surgery, whereas delayed bleeding is thought to be caused by sloughing of necrotic tissue and eschar in the prostatic fossa.
   e. **Epididymoorchitis**
   f. **Urethral stricture and bladder neck contracture**

E. Miscellaneous procedures

1. **Percutaneous cystostomy** is a useful method of draining the bladder when intraurethral access is not available. The various types of cystostomy trochars were described previously. The skin is anesthetized with 1% to 2% intradermal and subcutaneous lidocaine. With a No. 11 blade, a small incision is made in the skin and anterior rectus fascia. The location of the full bladder is then confirmed by aspirating urine through a long spinal needle, or by US. The trochar is then advanced between the rectus muscles in a slightly caudal direction and into the distended bladder. When urine is obtained, the stylet can be removed. If the cystostomy tube does not irrigate freely, a cystogram should be obtained to confirm its location within the bladder. Percutaneous cystostomy is contraindicated in the presence of surgical scars in the suprapubic area because small bowel may be interposed in the retropubic space. If the bladder is not distended sufficiently to permit blind trochar cystostomy, the long spinal needle may be used to fill the bladder with saline solution before trochar cystostomy is performed. After successful percutaneous cystostomy, the tube is connected to a urinary drainage bag and secured to the skin with a flange, tape, or suture.
2. **Needle biopsy of the prostate** is indicated in the evaluation of any prostatic nodule or indurated area, or in cases of an unexplained elevation of the serum Prostatic Specific Antigen (PSA) level. The types of biopsy needles have been described previously. Access to the prostate is via the perineal or transrectal route. The perineal approach requires the use of local anesthesia in the perineal skin. The tip of the biopsy needle is guided into the prostate by the examiner's finger in the rectum, or by transrectal US. Several cores of tissue from different parts of the gland should be taken for examination. Transrectal biopsy is similar except that anesthesia is usually not required. Because the risk for sepsis with the transrectal route is slightly greater than with the perineal approach, patients should ideally be prepared with an enema before the procedure and should receive broad-spectrum antibiotics for 24 hours afterward. The quinolone antibiotics may be useful in this setting.
3. **Fine-needle aspiration** offers an alternative to tissue biopsy in the diagnosis of prostate cancer; the two procedures provide roughly equivalent sensitivity and specificity. The technique of fine-needle aspiration is similar to that of transrectal needle biopsy described previously. The discomfort to the patient is considerably less, however, and antibiotic coverage is not required if the perineal route is utilized. After the prostate is entered with the tip of the aspiration needle, suction is provided by a syringe or obturator. The material is smeared on a glass slide, immediately placed in 95% alcohol for fixation, and sent for cytologic examination. Several areas of the prostate should be sampled.
4. **Perineal urethrostomy** is sometimes required for transurethral access to the prostate when the caliber of the urethra is inadequate, or occasionally if the patient has had a penile prosthesis placed in the past. With the patient under general or spinal anesthesia in the dorsal lithotomy position, a Van Buren sound is placed in the urethra with the tip in the bladder. The handle of the sound is moved toward the patient's abdomen to place the bulbous urethra on tension. With a surgical blade, the perineal skin is incised vertically for 2 to 3 cm over the bulbous urethra. The incision is deepened until the sound is

encountered. The urethral mucosa is fixed to the perineal skin with sutures, and the transurethral instruments are passed through the urethrostomy into the bladder.

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Chapter 4 Nontraumatic Genitourinary Emergencies

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A urologic emergency arises when a condition requires rapid diagnosis and immediate treatment. This chapter focuses on typical nontraumatic genitourinary emergencies seen in the emergency department, outpatient clinic, or inpatient ward. Emergencies arising secondary to trauma are discussed separately in Chapter 18. The evaluation of hematuria is discussed in Chapter 7, and the management of urinary stone disease is described in Chapter 10. Chapter 17 provides a discussion of genitourinary sepsis.

I. Acute Adrenal Insufficiency

Adrenocortical insufficiency may be divided into two broad categories. **Primary adrenocortical insufficiency (Addison's disease)** in 70% of cases is thought to be caused by an autoimmune process. Twenty percent of cases are associated with tuberculosis. Other causes are adrenal hemorrhage, metastases from lung and breast malignancies, human immunodeficiency viral (HIV) infection, meningococcal septicemia (Waterhouse-Friderichsen syndrome), and sarcoidosis. Certain drugs can cause adrenal insufficiency, including ketoconazole, aminoglutethimide, and mitotane. **Secondary adrenocortical insufficiency** is most often of **iatrogenic origin** following long-term administration of glucocorticoids. Less common is **deficiency of adrenocorticotropin (ACTH)**, as occurs in pituitary tumors, infiltration, or infarction. A third category of adrenal hypofunction is seen in those enzymatic deficiencies that lead to congenital adrenal hyperplasia.

Primary adrenal insufficiency is relatively rare. The increasing use of exogenous steroids has made secondary adrenal insufficiency more common. Acute adrenocortical insufficiency (addisonian crisis) may acutely follow septicemia, adrenal hemorrhage, or adrenal surgery, or it may present as a rapid and overwhelming exacerbation of chronic adrenal insufficiency precipitated by sepsis, trauma, or surgical stress.

A. Clinical findings
   1. **Symptoms.** A high index of suspicion for adrenal crisis should be maintained for any patient with chronic adrenal insufficiency who exhibits weakness, fatigue, weight loss, anorexia and nausea, and/or fever. If the patient is untreated, hypotension and somnolence soon follow. Chronic adrenal insufficiency manifests itself only when more than 90% of the glands is destroyed.
   2. **Signs.** Hypotension is the cardinal sign. Hyperpigmentation (Nelson's syndrome) resulting from increased ACTH is a striking feature in more than 90% of addisonian patients but is characteristically absent in secondary adrenal hypofunction. Many or all of these signs may be absent in the acute setting because there is insufficient time for their development.

B. **Diagnosis.** The triad of hyponatremia, hyperkalemia, and hypotension is the *sine qua non* of diagnosis. Cortisol deficiency leads to fasting hypoglycemia. Basal levels of cortisol are subnormal and fail to increase following ACTH administration. Aldosterone secretion is low, resulting in salt wasting and a secondary rise in plasma renin levels.

C. **Treatment** consists of correction of volume deficits and hypoglycemia by infusing 5% dextrose in saline solution as well as administering glucocorticoids. An intravenous (IV) bolus injection of 100 mg of hydrocortisone sodium succinate or 2 mg of dexamethasone should be administered immediately. Maintenance therapy is provided by 50 mg of IV hydrocortisone sodium succinate for 6 to 8 hours. Mineralocorticoids are not necessary at this stage. During the first 24 hours, volume and electrolyte abnormalities should be corrected by administration of 5% dextrose in normal saline solution guided by central venous pressure (CVP) measurement. A vasopressor such as dopamine may be necessary to support the blood pressure. Once the patient is stable hemodynamically, a search for the underlying cause should be made. In particular, an occult infection or abscess should be ruled out. The dose of glucocorticoid is reduced by half for the second day. Once the patient tolerates oral intake, oral steroid replacement can be instituted in consultation with the endocrinologist.

II. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a fundamental defect of cortisol production. The resultant excessive ACTH stimulation produces hyperplasia of the adrenals with excessive androgen production *in utero*. It is recognized shortly after birth because of genital abnormalities—pseudohermaphroditism in girls and macrogenitosomia praecox in boys. Four principal types of CAH are recognized: 21-hydroxylase deficiency, 17a-hydroxylase deficiency, 11b-hydroxylase deficiency, and 3b-hydroxydehydrogenase deficiency (Fig. 4-1). **Deficiency of 21-hydroxylase** accounts for 90% of cases of CAH. It is the most common cause of ambiguous genitalia in the newborn and the only cause that is life-threatening (as a result of salt wasting). In newborn girls, the external genitalia exhibit virilization with severe hypospadias. Male newborns may appear normal at birth but may have excessive growth of the phallus if untreated. If girls are untreated, hirsutism, excessive muscle mass, and amenorrhea are the rule. Accelerated growth eventually leads to premature epiphyseal closure and short stature in adulthood. Two-thirds of infants have a salt-losing tendency as a consequence of aldosterone deficiency, which requires emergent treatment.

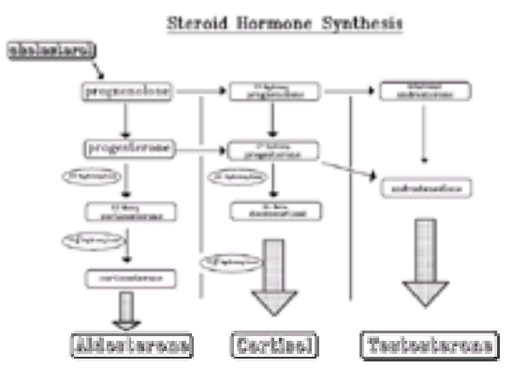

FIG. 4-1. Steroid hormone synthetic pathways.

A. **Diagnosis** is established by the clinical findings and by demonstration of an elevated level of 17-hydroxyprogesterone in plasma, or its metabolite pregnanetriol in urine.
B. **Treatment.** The salt-losing syndrome and the need for accurate sex assignment make this a neonatal emergency. Therapy consists of daily glucocorticoids to suppress pituitary ACTH secretion and minimize excess androgenicity. Prednisone is the drug of choice, except for infants, in whom hydrocortisone is usually used. If a salt-losing state is present, vigorous treatment consists of IV fluids, potassium-lowering agents, and mineralocorticoid replacement with 0.05 to 0.1 mg of fludrocortisone daily. The genital anomalies may require surgical correction later in life.

III. Renal Emergencies

A. **Renal arterial emboli** constitute 2% of arterial emboli. The main renal arteries are most frequently involved by systemic emboli from the left atrium in association with atrial fibrillation, artificial heart valves, the vegetations of endocarditis, or a mural thrombus from a myocardial infarct. Iatrogenic emboli are

being increasingly seen because of the widespread use of invasive vascular procedures. The intrarenal arteries are end arteries, so their occlusion leads to a wedge-shaped infarction of the renal parenchyma. These infarcts may be unilateral or bilateral, although they are more common on the left. Clinically, a spectrum ranges from no symptoms in a large number of patients to acute flank pain that may radiate to the groin, nausea, vomiting, and fever when infarction occurs. This picture closely mimics that of a ureteral calculus. Microscopic or gross hematuria is found in 50% of cases. This may be accompanied by proteinuria, leukocytosis, and epithelial cells in the urine. Renal infarction causes a characteristic sharp rise in the SGOT (serum glutamic-oxaloacetic transaminase) level, followed by a prolonged elevation of lactate dehydrogenase.

1. The **diagnosis** is suspected when an intravenous urogram (IVU) or computed axial tomogram (CT) with contrast fails to visualize all or part of the kidney. Although visualization may be poor or delayed with ureteral stone, *some* nephrogram is usually seen. The presence of a cardiac or vascular lesion lends credence to the diagnosis. A dynamic technetium scan demonstrating nonperfusion of the kidney and selective renal arteriography are required to confirm the diagnosis.
2. The **treatment** of choice is systemic anticoagulation (heparin). Intraarterial fibrinolytic agents (streptokinase) if instituted promptly within 4 to 6 hours can lead to a significant recovery of renal function. The underlying cardiac disease usually precludes surgical embolectomy in these high-risk patients. Late-onset hypertension, a sequela of renal ischemia and activation of the renin-angiotensin system, may require nephrectomy.

B. **Renal vein thrombosis**. Rare in adults, it is frequently unilateral and usually associated with membranous glomerulonephritis and nephrotic syndrome, invasion of the renal veins and vena cava by tumor, or retroperitoneal disease. In infants and children, it is more commonly bilateral and associated with severe dehydration resulting from diarrhea or vomiting. In its clinical presentation, renal vein thrombosis closely mimics acute pyelonephritis and ureteral calculus. The patient presents with severe flank pain, hematuria, and fever. Signs of sepsis and shock are variable. A large tender, smooth mass is usually felt in the flank, which represents the passively congested kidney.

1. **Diagnosis.** Gross or microscopic hematuria caused by focal renal infarction is invariably found. Thrombocytopenia is also a consistent finding in the acute setting, and its absence should make one suspect the renal vein thrombosis to be in the resolving stage. Proteinuria is more common in the adult type of thrombosis, where it may be massive. Rising blood urea nitrogen (BUN) and creatinine are found quite frequently, even in unilateral thrombosis. The IVU shows a large kidney with a poor or absent nephrogram. Ultrasonography (US) usually shows an enlarged hypoechoic kidney with a renal vein or vena caval thrombus. CT and magnetic resonance imaging (MRI) are sensitive, but selective renal venography remains the definitive test.
2. **Treatment.** This depends on the age of the patient. In infants and children with bilateral renal vein thrombosis, the prognosis is dismal; prompt rehydration, antibiotics for infection, and correction of electrolyte imbalance form the mainstay of treatment. In adults, early heparinization and selective IV fibrinolysis (streptokinase or urokinase) have yielded promising results. Surgical thrombectomy is reserved for caval thrombosis. Following renal vein thrombosis, renal function usually recovers completely. In a small subset of patients, nonfunction, renal hypertension, or chronic renal infection may necessitate delayed nephrectomy.

IV. Urinary Retention

Acute urinary retention is the primary nontraumatic emergency involving the bladder.

A. **Diagnosis.** The most common causes are prostatic enlargement or cancer, prostatitis or abscess, prostatic infarction, urethral stricture, blood clots, medications, and neuropathic and psychogenic conditions. The history should include the voiding pattern before retention, past urologic surgery, and medications with anticholinergic side effects, especially common cold remedies containing nasal decongestants and antihistaminic compounds. The physical examination should focus on the suprapubic area to determine whether a distended bladder can be palpated or percussed. In most cases, pressure on the bladder during the examination will produce discomfort or pain. With long-standing chronic retention, the patient feels no discomfort from pressure on the distended bladder. A rectal examination should be performed to determine the size of the prostate and possible presence of prostatic abscess.

B. **Treatment.** Placement of a Foley catheter, if possible, is the treatment of choice. In many cases, this can be made difficult by the presence of urethral stricture, prostate enlargement, or prostate cancer. The basic aspects of urethral catheterization are discussed in Chapter 3.

1. **Difficult catheterization.** If the catheter does not enter the bladder easily, the most likely cause is spasm of the external sphincter, followed by urethral stricture and then bladder neck contracture or hypertrophy. Prostatic enlargement rarely prevents the passage of a catheter, as the prostate lobes are easily pushed aside by the catheter, especially one with a 22F diameter. If the patient is known or suspected to have urethral stricture, retrograde urethrography should be carried out to assess the urethra (see Chapter 1). If this shows a clearly impassable stricture, percutaneous suprapubic cystotomy should be performed for temporary relief of urinary retention. If no stricture is evident, a coude catheter should be tried—a maneuver that is often successful in negotiating a prominent bladder neck. The coude catheter should be oriented with the tip pointing anteriorly during passage.
2. **Filiforms and followers.** Filiforms are narrow, solid catheters with various configurations at the tip (see Fig. 3-4). Because they can cause severe injury to the urethra, they should be used only by experienced persons or under supervision. They are most useful in bypassing urethral strictures and false passages. With adequate lubrication, the filiform is passed gently until it meets resistance in the urethra. The first filiform is left in place and another one is passed adjacent to it. If it fails to pass, a third or fourth one can be passed. By trying each filiform in turn, one hopes that one of them will enter the urethral lumen and pass into the bladder. If this happens, the other filiforms should be removed and a small 8F or 10F follower should be screwed on. The follower then follows the filiform into the bladder, where it curls upon itself. After passing the first follower, it is withdrawn to the meatus and unscrewed from the filiform, and the next size follower is screwed on and passed into the bladder. This process is repeated until the stricture or urethra is adequately dilated.
3. **Councill catheter.** After the stricture is dilated, place a well lubricated Councill screw-tip stylet in a Councill catheter (see Fig. 3-2) and shape it like a Van Buren sound. Screw the stylet onto the filiform and allow the filiform to guide the catheter into the bladder. Withdraw the stylet and filiform through the catheter lumen and inflate the catheter balloon.

V. Scrotum and Perineum

Acute onset of scrotal pain and swelling without a history of antecedent trauma is a common management problem in emergency departments. Conditions in the differential diagnosis include acute epididymoorchitis, torsion of testicular appendages, mumps orchitis, and incarcerated inguinal hernia, but only three must be treated emergently: acute testicular torsion, periurethral abscess, and scrotal (Fournier's) gangrene.

A. **Torsion of the testis.** Testicular torsion results in twisting of the spermatic cord and occlusion of the venous or arterial supply to the testis. Thus, testicular torsion is a true vascular emergency. If not treated emergently (within 4 to 6 hours after onset of pain), complete infarction of the testis results, followed by atrophy of the testis. Although testicular torsion can occur at any age, the age incidence is bimodal, with the condition most common during adolescence (ages 10 to 20 years) and less common in the neonatal period. Fifty percent of cases of torsion occur during sleep. Testicular torsion is broadly classified into two types.

1. **Extravaginal.** This form is seen in neonates. The entire testis and tunica twist in a vertical axis on the spermatic cord as a consequence of incomplete fixation of the gubernaculum to the scrotal wall, which allows free rotation within the scrotum.
2. **Intravaginal.** This more common form of torsion is found in adolescents and adults. A congenital high investment of the tunica on the cord, which produces the “bell-clapper” deformity, allows the testis to rotate on the cord (Fig. 4-2). Because this anomaly is bilateral, there is a significant risk for a contralateral metachronous torsion. Spasm of the cremaster muscle causes the right testis to rotate clockwise and the left counterclockwise as observed from the foot of the bed.

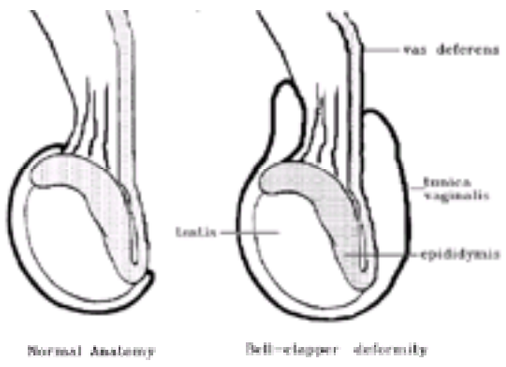

FIG. 4-2. Normal testicular anatomy (*on the left*) compared with the “bell-clapper” deformity, characterized by high insertion of the tunica vaginalis on the cord.

a. **Clinical features.** The classic presentation of sudden and severe testicular pain, nausea, vomiting, and a high testis with local tenderness is diagnostic. Not infrequently, one can elicit a past history of similar attacks, which presumably represent intermittent episodes of torsion. Physical examination reveals exquisite testicular tenderness. The testis lies transversely and more cephalad than normally. If one can palpate the epididymis in an anterior location at this stage, the diagnosis of torsion is strongly supported.
b. **Differential diagnosis.** The most frequent misdiagnosis is that of epididymoorchitis (Table 4-1). It is generally less acute and usually accompanied by a urinary infection or prostatitis. Although the maneuver is not always reliable, elevation of the testicle increases pain in torsion and decreases pain in epididymoorchitis (Prehn's sign). Although rare, torsion of the appendix testis—a remnant of the Mül-lerian duct—presents in a similar fashion. The tenderness, however, is well localized to the upper pole of the testis, and a characteristic blue dot sign on the skin of the scrotum may be appreciated.

	Torsion	Inflammation
Mode of onset	Abrupt	Few hours to days
Affected testis	Higher than opposite	No change in position
Epididymis	Usually nonpalpable	Palpable and tender
Urethral discharge	Absent	May be present
Cremasteric reflex	May be absent	Usually present
Response to elevation (Prehn's sign)	No change in pain	Pain relieved
Fever	Usually absent	May be present

Table 4-1. Differentiating spermatic cord torsion from acute epididymoorchitis

c. **Diagnosis.** It is almost axiomatic to consider an acutely painful swollen testis in an adolescent as torsion until it is proven otherwise at surgery. Color Doppler and color duplex Doppler sonography to assess arterial flow and radionuclide scanning with ^{99m}Tc-pertechnetate have been used with an accuracy of 90%. Both methods are based on the premise that arterial flow to the testis is decreased in torsion and increased in epididymitis. Unfortunately, no method is totally reliable, and testicular imaging is only an adjunct to a good history and physical examination.
d. **Treatment** depends on the interval from onset of pain to presentation in the emergency department. Within 4 hours of onset, manual detorsion of the testicular cord under local anesthesia should be attempted. (Remember that the testes twist toward the midline as seen from the feet.) If manual detorsion is successful, elective bilateral orchidopexy is indicated within the next few days. If detorsion is not successful, immediate surgical exploration is indicated. If the presentation is between 4 hours and 24 hours after onset of pain, immediate surgical exploration, detorsion, and bilateral orchidopexy should be performed. If more than 24 hours have passed since onset of pain, surgical exploration is indicated, but preservation of testicular function is doubtful. A nonviable testis should be removed and a testicular prosthesis placed. This is to prevent infectious complications and the potential of autoimmune injury to the contralateral testicle.

B. **Periurethral abscess.** Periurethral abscess usually results from spontaneous rupture of a urethral abscess caused by urethral stricture. The purulent collection may present in the perineum as a warm, tender, erythematous, sometimes fluctuant mass. If the abscess has drained spontaneously, purulent material can be expressed. Diagnosis consists of retrograde urethrography to demonstrate patency of the urethra and any fistulous connection between the urethra and abscess cavity. The purulent drainage should be examined for acid-fast bacilli and cultured. Treatment consists of surgical incision and drainage with diversion of the urine by Foley catheter or, preferably, by percutaneous cystostomy.
C. **Fournier's gangrene.** First described by Jean Alfred Fournier, a French venereologist, Fournier's gangrene is the sudden onset of fulminant gangrene of the external genitalia and perineum in an apparently healthy person. A form of necrotizing fasciitis, it usually begins in the scrotum or penis and may spread along fascial planes (beneath Scarpa's fascia) to the perineum and abdominal wall up to the axilla.
1. **Diagnosis**. Fournier's gangrene presents suddenly with marked swelling and erythema of the genitalia, fever, chills, and malaise. The mean duration of symptoms is 5 days. Physical examination is the cornerstone of diagnosis. Blistering of the scrotal or penile skin overlying a cellulitic area with yellow-brown fluid is pathognomonic of underlying necrotizing fasciitis. Crepitus may be elicited at this stage, and a feculent odor caused by anaerobes is usually present. If untreated, gangrenous sloughing soon ensues. The testes and spermatic cord are usually spared.

   If a urethral source is suspected from a history of stricture or urethral instrumentation, a retrograde urethrogram is indicated. If the rectal examination suggests a bowel source, proctoscopy should be performed. Cultures reveal polymicrobial flora with gram-negative rods (*Escherichia coli*, *Pseudomonas* species, and *Klebsiella* species), gram-positive cocci (b-hemolytic streptococci, *Staphylococcus aureus*, *Enterococcus*), and anaerobes (*Bacteroides fragilis*, *Clostridium perfringens*). Histology reveals marked vascular thrombosis and obliterative endarteritis, probably from bacterial spread. It is common for patients to have predisposing systemic conditions such as alcoholism (50%) or diabetes (33%). The source of infection is genitourinary (50%), colorectal (33%), or cutaneous (20%). The common denominator seems to be a depressed immune state, as both diabetes and alcoholism are known to impair the immune system.
2. **Treatment.** The basic tenets of management include the following:
   a. **Radical debridement** of all necrotic and gangrenous tissue must be performed emergently.
   b. Blisters and abscess cavities not included in the initial debridement are **incised and drained**.
   c. **IV broad-spectrum antibiotics** designed to cover both aerobic and anaerobic organisms are administered, followed by more specific therapy once the results of culture are obtained. We use a regimen of 4 g of piperacillin every 6 hours, 80 mg of gentamicin IV every 8 hours, and 60 mg of clindamycin IV every 8 hours. As an alternative to clindamycin, 500 mg of metronidazole can be given IV every 8 hours.
   d. **Supportive measures**
      1. **Hyperbaric oxygen therapy** in patients with extensive anaerobic infection has given promising results.
      2. **Cystostomy or colostomy** may be required for temporary diversion in patients with periurethral or perirectal suppuration.
      3. **Systemic corticosteroids** have been found to be useful in isolated cases unresponsive to standard measures.
      4. **Wound care** following debridement involves application of wet-to-dry saline dressings for local debridement.
      5. **Delayed split-thickness skin grafting** of denuded genitals is sometimes required. In most cases, remaining scrotal skin can be mobilized to cover the testicles.
   e. **Prognosis.** Despite extensive therapeutic measures, the overall mortality approaches 45%, which stresses the need for prompt diagnosis and early treatment of this condition. Common postoperative complications include prolonged sepsis, coagulopathy, and pulmonary insufficiency.

VI. Penis

A. **Phimosis** is the inability to retract the foreskin of the penis. Chronic low-grade infection eventually leads to loss of elasticity and scarring of the foreskin. The patient usually complains of erythema, itching, or pain on intercourse. Most commonly, there is a mild associated infection (balanoposthitis), which should be treated with a broad-spectrum antibiotic such as tetracycline (250 mg four times daily by mouth). The phimosis is then treated electively by dorsal slit or circumcision. Rarely, the patient presents with tight phimosis and severe balanitis. Under these circumstances, semiemergent dorsal slit is indicated to promote drainage. Once the infection is controlled, elective circumcision can be performed. Very rarely, tight phimosis may present as a cause of urinary obstruction.
B. **Paraphimosis** is a condition in which the foreskin becomes trapped in a retracted position behind the glans. Most commonly, this occurs in a patient with preexisting phimosis. With time, the entrapped foreskin becomes edematous, and the glans itself becomes engorged. Rarely, vascular insufficiency of the glans can occur. Treatment consists of firm compression of the glans to decrease edema and continuous traction on the foreskin, combined with counterpressure on the glans. Field block of the penis with 1% lidocaine (Xylocaine) is sometimes helpful. When this treatment is unsuccessful, incision of the constricting ring under local anesthesia should be performed. Once the inflammation and edema have subsided (3 to 4 days), elective circumcision is indicated.
C. **Priapism** is characterized by persistent erection (more than 4 hours) accompanied by pain and tenderness. Etiologically, it is classified as follows:
1. **Primary** or **idiopathic** (30% to 50% of cases)
2. **Secondary**
   a. **Thromboembolic disease:** sickle cell trait or disease, thalassemia, thrombocytopenia, polycythemia
   b. **Medications and drugs:** intracavernosal vasodilators, trazodone, thorazine, alcohol, marijuana, antihypertensives, heparin
   c. **Infiltrative:** leukemia, lymphoma, bladder or prostate carcinoma
   d. **Miscellaneous:** penile trauma (high-flow priapism), dialysis, total parenteral nutrition
   e. **Neurogenic:** central nervous system and spinal cord disorders, diabetic neuropathy

3. **Pathophysiology.** The failure of detumescence is usually caused by insufficient outflow or less commonly by an increased inflow of blood. This has led to the classification of priapism as type I (low flow, ischemic or venoocclusive) and type II (high flow, nonischemic or arterial). Prolonged erection results in edema of the cavernosal trabeculae with eventual stasis or thrombosis, which in turn occludes venous drainage via the emissary veins. The intracorporal hypoxia, hypercarbia, and acidosis cause endothelial damage with fibrosis, scarring, and eventual impotence in 50% of cases. For this reason, priapism must be considered a vascular emergency and managed with appropriate haste.
4. **Diagnosis.** In the ideal setting, any erection lasting more than 4 hours should be considered priapism, and the person should seek urologic help. However, pain does not ensue until 6 to 8 hours, and in reality most patients present with an erection of at least 24 hours' duration. Prompt treatment at this stage may still preserve potency, but with increasing duration of priapism the incidence of erectile dysfunction rises precipitously. On presentation, a careful history directed to eliciting known causes of priapism should be taken. The most common cause today is cavernosal self-injection with vasodilators. One should inquire about other medications taken. A history of “stuttering” priapism (recurrent episodes of self-limiting priapism) is typical of sickle cell disease. Because most cases of priapism are of the low-flow, ischemic variety, pain is a constant accompaniment. However, a history of penile or perineal trauma with a constant painless erection should suggest high-flow, arterial priapism. Physical examination confirms the presence of priapism; in contrast to what occurs in a normal erection, in priapism only the corpora cavernosa are involved; the glans penis and corpus spongiosum are soft and flaccid.
4. **Treatment.** The goal of treatment is rapid detumescence with relief of associated pain and preservation of potency. The duration of priapism is important in determining the eventual outcome. With increasing duration (>24 hours), the incidence of permanent impotence rises to approximately 50% despite prompt treatment. It is imperative to counsel the patient and family members regarding impotence regardless of success in treating the current episode of priapism.
   a. **Corporal aspiration and irrigation** form the mainstay of initial treatment if the patient presents within 24 hours. Blood is aspirated from the corpora with a 19-gauge butterfly needle and sent for blood gas analysis to determine the degree of ischemia. A typical corporal aspirate in type I ischemic priapism reveals dark blood with an oxygen tension below 30 mm Hg, carbon dioxide tension above 60 mm Hg, and pH below 7.25. In contrast, bright red corporal blood with a high oxygen content in a patient with a history of perineal trauma should prompt duplex Doppler sonography. This will usually visualize the site of an arterial-lacunar fistula as the cause of the arterial priapism and help guide therapy. The corpora are then irrigated with normal saline solution until the aspirate is bright red. If aspiration and irrigation alone fail, intracorporal injection of a-adrenergic agonists is indicated. The drug of choice is phenylephrine at a dose of 0.5 to 1 mg in each corpus because of minimal systemic side effects. Other agents may also be used (Table 4-2).

Agent	Dose
Norepinephrine	20–80 μg IC
Epinephrine	0.05–0.1 mg IC
Phenylephrine	0.5–1 mg IC
Ephedrine	50–100 mg IC

IC, intracavernosally.

Table 4-2. a-Adrenergic agents for priapism

   b. **Supportive measures** in the form of narcotic analgesics, warm or cold enemas, IV ketamine (may cause hallucinations), hypotensive agents, and anticoagulants may be tried as adjuncts to more specific measures. Ketamine, with its dissociative anesthesia, successfully achieves detumescence in up to 50% of early cases, obviating the need for more elaborate procedures. If an underlying cause is known, it should be corrected immediately.
   c. **Sickle cell disease** should be treated with hydration, alkalinization, and transfusion to increase the hemoglobin level to above 10 mg/dL, thereby reducing intracorporal acidosis and sludging. Patients with stuttering priapism may benefit from injections of leuprolide acetate (luteinizing hormone-releasing hormone agonist) once a month.
   d. **Leukemic infiltration** of the corpora may respond to irradiation of the penis and systemic chemotherapy.
   e. **Surgical treatment.** If the patient presents after 24 hours or if detumescence fails to occur after repeated injections of phenylephrine, surgical treatment should be instituted. Surgical shunting of the corpora cavernosa can be achieved either by creation of a fistula between the glans penis and the corpus cavernosum, or by a more elaborate shunt. The Winter procedure is a simple and safe method involving the creation of a fistula between the glans penis and the corpus spongiosum with a Travenol biopsy needle (Fig. 4-3). It produces a temporary fistula and can be performed under local anesthesia at the bedside. Results are mixed because of early closure of the fistula. The Al-Ghorab procedure involves the creation of a glans-cavernosum shunt by removal of small, 5-mm strips of tunica albuginea from each corpus. Rarely, more extensive shunts may be required, such as a dorsal vein-to-corpora, saphenous vein-to-corpora, or a side-to-side cavernosum-spongiosum shunt. Arterial high-flow priapism with a documented arterial-lacunar fistula would require selective embolization with autologous clot. Following detumescence, the patient is closely monitored for a recurrence of the priapism. Postoperative tight bandaging of the penis, which may lead to edema, necrosis, and even gangrene, should be avoided.

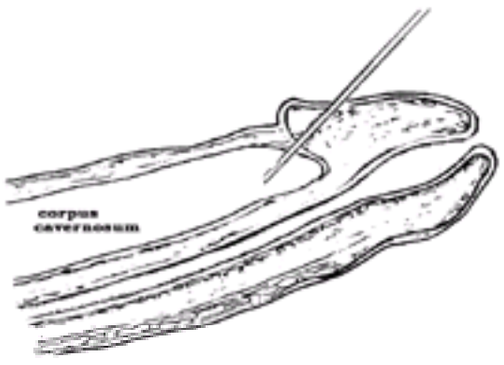

FIG. 4-3. Winter procedure for priapism.

5. **Prognosis.** Despite early and effective treatment, the incidence of long-term impotence remains close to 50%. Normally, the first partial erection should be observed within 3 months of the creation of a surgical fistula. If it does not occur, a search for either corporal fibrosis or a persistent fistula should be made. Cavernosography will reveal whether a surgical fistula is still patent and requires operative closure. Corporal fibrosis will eventually require a penile prosthesis.

VII. Autonomic Dysreflexia

Autonomic dysreflexia is characterized by dangerous systolic hypertension, sweating, and paradoxical bradycardia (Fig. 4-4). This syndrome is seen only in patients with spinal cord injury above T-6, a viable distal cord, and intact thoracolumbar sympathetic outflow. The most common genitourinary causes are a distended bladder, urinary infection, and stones. Autonomic dysreflexia may be precipitated during cystometry, cystoscopy, endoscopic surgery, or extracorporeal lithotripsy. It can be prevented by spinal anesthesia, but general anesthesia is not effective unless it is quite deep. Other causes are fecal impaction and decubitus ulcers. Some degree of autonomic dysreflexia occurs in 85% of quadriplegic patients. If the patient is untreated, cerebrovascular accidents, convulsions, and death may ensue.

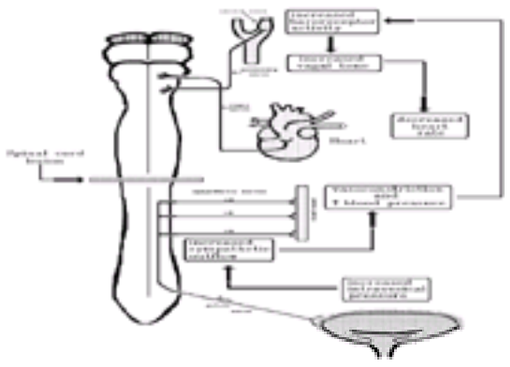

FIG. 4-4. Pathophysiology of autonomic dysreflexia.

A. **Diagnosis.** The patient complains of severe headache and profuse sweating. Arterial systolic blood pressure is increased by a mean of 40 mm Hg, and diastolic blood pressure is increased by a mean of 25 Hg over baseline. The heart rate is depressed to levels of 60 or even lower, with the mean decrease being 20 beats/min.
B. **Treatment.** The immediate goal of management must be rapid reduction of blood pressure and removal of the precipitating cause, generally bladder distention. If very rapid reduction in blood pressure is needed, we prefer a sodium nitroprusside drip at a rate of 25 to 50 µg/min, with a maximum dosage of 200 to 300 µg/min. Alternatively, one can give diazoxide as a bolus of 50 to 150 mg IV every 5 minutes or as an infusion. If less immediate control of hypertension is desired, we use nifedipine given orally or sublingually in a dose of 10 to 30 mg. Severe reflex bradycardia may be managed with IV atropine in a dose of 0.4 to 1.6 mg. Long-term prophylaxis of autonomic dysreflexia is accomplished with 1 to 4 mg of prazosin orally twice daily.

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Chapter 5 Fluid and Electrolyte Disorders

Mike B. Siroky

I. Physiology

A. **Total body water** constitutes about 50% of body weight in adult women and 60% in adult men. The total body water is divided into extracellular fluid (ECF) (about one-third) and intracellular fluid (ICF) (about two-thirds).
B. **Extracellular fluid** comprises interstitial fluid (about three-fourths) and plasma (about one-fourth). The major cation in the ECF is sodium; the major anions are chloride, bicarbonate, and plasma proteins.
C. **Intracellular fluid** constitutes most of the body water. The major cations are potassium and magnesium; the major anions are phosphates and proteins.
D. **Physiologic mechanisms** maintain proper plasma osmolality and serum sodium concentration by regulating body water. These mechanisms may be divided into extrarenal and intrarenal types. Extrarenal mechanisms are thirst, pituitary secretion of antidiuretic hormone (ADH), and adrenal secretion of mineralocorticoids. Intrarenal mechanisms are the water permeability of the collecting duct (affected by ADH), sodium and chloride resorption in the distal tubule (affected by mineralocorticoids), and the volume delivered to the distal tubule.
E. **Volume depletion** or **hypovolemia** is caused by loss of sodium and water in varying proportions (Table 5-1). Such volume contraction may be accompanied by normal serum sodium levels, hyponatremia (serum sodium <135 mEq/L), or hypernatremia (serum sodium >150 mEq/L) (Table 5-2). If sodium and water are lost in approximately isotonic proportions (e.g., ileostomy), the serum sodium concentration remains normal and the ICF volume is little affected. If the loss is hypotonic (e.g., nasogastric suction, diarrhea, severe glycosuria), hypernatremia will result. However, the clinical signs of hypovolemia will be attenuated by movement of water from the intracellular space to the ECF. Hypertonic loss does not occur naturally. However, if naturally occurring isotonic or hypotonic losses are replaced with water only, the effects of hypertonic loss are reproduced (i.e., hyponatremia with hypovolemia).

I. Gastrointestinal
A. Emesis or nasogastric drainage
B. Diarrhea
C. Bowel fistulae
1. Ileostomy
2. Colostomy
II. Renal
A. Salt-wasting nephropathy
1. Medullary cystic disease
2. Polycystic disease
3. Interstitial nephritis
4. Analgesic nephropathy
5. Partial urinary obstruction
B. Renal tubular acidosis, proximal type
C. Osmotic diuresis
1. Glucose (diabetes mellitus)
2. Loop diuretics
3. Osmotic diuretics (urea, mannitol)
4. Radiographic contrast media
D. Water diuresis
1. Central diabetes insipidus
2. Nephrogenic diabetes insipidus
E. Postobstructive diuresis
III. Adrenal insufficiency
IV. Sequestration
A. Large surgical wound
B. Ileus
C. Burns
D. Peritonitis

Table 5-1. Causes of volume depletion

Hyponatremia	Normal serum sodium	Hypernatremia
Nasogastric suction	Ileostomy	Nasogastric suction
Diarrhea	Biliary fistula	Sweating
Renal disease	Pancreatic fistula	Diarrhea

Table 5-2. Causes of hypovolemic states classified by serum sodium levels

F. **Volume excess** refers to expansion of the ECF from retention of varying proportions of sodium and water (Table 5-3). If this expansion of ECF is clinically evident, edema or ascites may be noted. The cause may be renal failure, cardiac failure, or liver disease.

I. Acute and chronic renal failure
II. Congestive heart failure
III. Liver cirrhosis
IV. Water intoxication
A. Psychogenic polydipsia
B. Transurethral resection syndrome
V. Inappropriate secretion of ADH (Schwartz-Bartter syndrome)
A. Carcinoma of lung, duodenum, pancreas
B. Pulmonary disease
1. Viral or bacterial pneumonia
2. Tuberculosis
3. Aspergillosis
C. CNS disorders
1. Encephalitis and meningitis
2. Stroke
3. Brain tumors
4. Brain abscess
5. Subdural hematoma
6. Guillain-Barré syndrome
7. Head trauma
D. Anesthesia
E. Generalized trauma

ADH, antidiuretic hormone; CNS, central nervous system.

Table 5-3. Causes of volume excess

II. Sodium and Volume Disorders

A. **Volume depletion** is most commonly caused by gastrointestinal losses, administration of diuretics, primary and secondary renal disease, adrenal disease, and sequestration of fluids—“third-space loss.” Depending on the severity of the volume depletion, the manifestations include poor skin turgor, postural hypotension, and dry mucous membranes (5% depletion); weakness, apathy, sunken eyes, and hypotension (10% depletion); or shock and coma (15% depletion). The serum sodium is often normal, but the blood urea nitrogen (BUN) is elevated out of proportion to the creatinine. The hematocrit and serum albumin concentration are also elevated. If renal and adrenal function are normal, the urinary sodium concentration is very low (serum sodium <15 mEq/L), the urine is highly concentrated (osmolality >600 mOsm/L and specific gravity >1.020), and its volume is decreased. Under these circumstances, the cause is most likely gastrointestinal—vomiting or diarrhea. Substantial ECF volume may be sequestered in the peritoneal cavity with peritonitis or pancreatitis and in the bowel

lumen with ileus. If the urinary sodium is greater than 20 mEq/L, one should suspect underlying salt-wasting renal disease, Addison's disease, diabetes insipidus, or previous administration of diuretics. Administration of diuretics is the most common cause and is accompanied by hypokalemia in most instances. Salt-wasting renal disease is usually accompanied by a serum creatinine level in excess of 3 mg/dL. Addison's disease is characterized by hyperkalemia.

1. **Postobstructive diuresis** refers to excessive and prolonged polyuria following relief of urinary obstruction. The phenomenon is caused by a combination of physiologic diuresis (urea osmotic diuresis), pathologic diuresis (impairment of renal salt and water reabsorption), and iatrogenic diuresis (glucose osmotic diuresis and water diuresis resulting from intravenous therapy). The impairment of renal salt and water reabsorption is caused by short-term unresponsiveness to antidiuretic hormone and mineralocorticoid. Another factor may be elevated levels of atrial natriuretic peptide, which produces natriuresis and diuresis.
    a. **Diagnosis** True postobstructive diuresis is rare and occurs only following relief of bilateral urinary obstruction or relief of obstruction of a solitary kidney. The typical patient at risk is one with moderate-to-severe azotemia caused by chronic outflow obstruction. In addition to azotemia, laboratory values may indicate hyperkalemia and metabolic acidosis. Urinalysis will reveal low specific gravity (1.002 to 1.10), low osmolality (<400 mOsm/L), and low urine sodium (<40 mmol/L). The mean duration of diuresis is 2.2 days, but in 72% of instances the duration is 2 days or less. The median urine volume excreted is approximately 8 L.
    b. **Management** is facilitated by identifying as early as possible patients who are at greatest risk for development of a high-volume prolonged diuresis leading to sodium, potassium, and volume depletion. It is useful to follow therapy by daily determination of supine and upright blood pressure, body weight, and serum and urine electrolyte levels.
        1. **Low-risk patients** have no peripheral edema, congestive heart failure, or mental confusion. Azotemia is mild (serum creatinine >2.0 mg/dL). They can be allowed free oral intake of fluids. Intravenous (IV) fluid replacement is necessary only if one or more of the following are present: orthostatic hypotension, tachycardia, mental confusion, hyponatremia, or urine output greater than 200 mL/h. IV fluids consist of 50% normal saline solution or 5% dextrose in 50% normal saline solution plus 20 mEq potassium chloride. The hourly rate should be half the amount of the previous hourly urine output.
        2. **Moderate-risk patients** are characterized by the presence of one or more of the following: mild peripheral edema, congestive heart failure, and azotemia (serum creatinine <4.0 mg/dL). Therapy is essentially the same as for low-risk patients except that IV fluid replacement should be started early in treatment.
        3. **High-risk patients** have one or more of the following: a serum creatinine level above 4.0 mg/dL, mental obtundation, congestive heart failure, and noticeable peripheral edema. IV fluid therapy as mentioned above should be instituted after obstruction is relieved. If the patient is hyponatremic, urine output is replaced milliliter for milliliter with normal saline solution. Appropriate amounts of potassium, calcium, and bicarbonate may be added. As the serum creatinine falls below 4.0 mg/dL and as the body weight falls, the rate of diuresis should fall as well.

B. **Volume excess** in urologic patients is caused most commonly by concomitant medical disorders such as congestive heart failure, acute and chronic renal failure, and liver cirrhosis. A syndrome of inappropriate ADH secretion has been described in various conditions. The inappropriate secretion of ADH causes impaired renal excretion of water and mild ECF expansion, usually without edema, leading to a secondary natriuresis from the kidney. The postoperative and posttraumatic patient may have mild increases in ADH secretion. Overzealous fluid therapy in these patients will result in mild fluid overload and hyponatremia.

The post-transurethral resection syndrome (Table 5-4), specific to urology patients, occurs in 2% to 10% of patients undergoing transurethral resection of the prostate (TURP) and is characterized by cardiovascular and neurologic manifestations. The incidence depends in a general way on gland size and resection time (Table 5-5). It is caused by absorption of excessive amounts of irrigating fluid from the prostatic fossa during transurethral prostatectomy. The solute in these isotonic irrigating fluids is most commonly sorbitol or glycine. Once these solutes are metabolized, the effect is equivalent to the administration of solute-free water—hence the term water intoxication. Because the ECF is expanded and hyponatremia results, the neurologic manifestations are attributable to edema of the brain cells; however, some investigators place more emphasis on the role of the hyponatremia itself. In addition, glycine (but not sorbitol) may be metabolized to ammonia, and hyperammonemia has been documented in about one-third of patients receiving glycine irrigation during TURP (Fig. 5-1). **Treatment** should be individualized according to the severity and type of symptoms as well as the presence of preexisting medical conditions.

Cardiovascular	Neurologic
Early	
Bradycardia	Restlessness
Hypertension	Confusion
Dyspnea	Visual disturbances
Cyanosis	Twitching
Angina	Seizures
Late	
Hypotension/shock	Obtundation/coma

TURP, transurethral resection of prostate.

Table 5-4. Symptoms and signs of post-TURP syndrome

Variable	Incidence
Gland size	
<45 g	0.8%
>45 g	1.5%
Resection time	
<90 min	0.7%
>90 min	2.0%

TURP, transurethral resection of prostate.

Table 5-5. Variables affecting the incidence of post-TURP syndrome

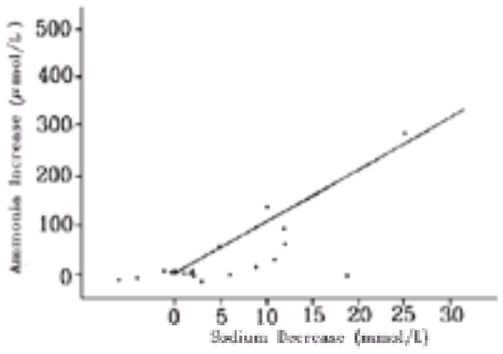

FIG. 5-1. Correlation between increase in blood ammonia level and decrease in serum sodium observed in patients undergoing TURP with 1.5% glycine irrigation. (Adapted from Shepard RL, Kraus SE, Babayan RK, Siroky MB. The role of ammonia toxicity in the post transurethral prostatectomy syndrome. *Br J Urol* 1987;60:349.)

1. **Predominantly neurologic symptoms.** In most patients with mild neurologic manifestations and serum sodium concentrations above 110 mEq/L, induction of diuresis with IV furosemide (20 to 40 mg) is usually sufficient to correct the imbalance. Furosemide may be ineffective because of low serum sodium levels, and in such cases, 1 to 2 g of mannitol per kilogram may be given IV. In patients who are comatose or manifest seizures, more rapid correction of the

hyponatremia by administration of 3% normal saline solution (1 L/12 h) is indicated, in addition to administration of anticonvulsants and general metabolic support. Administration of hypertonic saline solution is not necessary in patients without severe neurologic manifestations and in fact is contraindicated in patients with signs of cardiovascular overload. There is no specific remedy for hyperammonemia caused by glycine metabolism. The patient usually recovers within 12 to 24 hours with general supportive care.

2. **Predominantly cardiovascular symptoms.** These patients should be aggressively managed as if they had pulmonary edema. Early monitoring with a Swan-Ganz catheter is recommended. Endotracheal intubation should be considered if the patient becomes severely dyspneic or hypoxemic. If the capillary wedge pressure is elevated, diuretic therapy should be instituted to reduce volume excess. In severe cases, shock may ensue and should be treated with infusion of colloids and adrenergic drugs.

III. Metabolic Acid-Base Disorders

A. **Metabolic acidosis** is a systemic disorder resulting from accumulation of fixed acid with decreased plasma bicarbonate concentration. Acid may accumulate because of its ingestion, increased endogenous production, or impaired excretion. Metabolic acidosis is classified according to the presence of either “elevated anion gap” or “normal anion gap.” The anion gap is defined as the difference between the serum sodium concentration and the sum of the serum chloride and bicarbonate. The presence of an increased anion gap (>14 mEq/L) implies the addition of acid to the system, such as occurs in renal failure, ketoacidosis, lactic acidosis, and poisoning with salicylates, methanol, or ethylene glycol. A normal anion gap (12 mEq/L) implies the loss of bicarbonate with retention of chloride, which occurs in renal tubular acidosis, urinary diversion, pancreatic fistula, and diarrhea.

1. **Renal failure** results in metabolic acidosis with increased anion gap. This is because (1) with reduction in glomerular filtration, there is inability to excrete sulfates and phosphates, and (2) with reduced tubular mass, there is inability to form sufficient urinary ammonium and thus excrete acid.
2. **Renal tubular acidosis** is characterized by a renal tubular defect leading to inability to acidify the urine. This condition results in a hyperchloremic (normal anion gap) acidosis. In contrast to patients with renal failure, patients with renal tubular acidosis have little or no reduction in glomerular filtration. Daily alkali therapy usually corrects the metabolic derangement. Two types of renal tubular acidosis are recognized:
   a. **Distal (type I, classic)** renal tubular acidosis is characterized by inability of the distal tubule to excrete hydrogen ion. Hypokalemia is a frequently associated finding.
   b. **Proximal (type II, bicarbonate-wasting)** renal tubular acidosis is characterized by inability of the proximal tubule to absorb adequate amounts of filtered bicarbonate.
3. **Urinary diversion** is performed to divert urine from the bladder to the skin or to fashion a bladder substitute with various intestinal segments, including stomach, jejunum, ileum, transverse colon, and sigmoid colon (Table 5-6). A variety of unique metabolic derangements may be seen in patients who have bowel segments interposed in the urinary tract. Except for stomach (see below), most are associated with various degrees of metabolic acidosis.

Bowel segment	pH	Na	Cl	K	Incidence	Treatment
Stomach	-	0	-	-	5%	H_2 blocker omeprazole
Jejunum	-	-	-	-	25–40%	Saline infusion
Ileum	-	0	-	0,-	75%	Alkalinization; chlorpromazine; nicotinic acid
Colon	-	0	-	-	75%	Alkalinization; chlorpromazine; nicotinic acid

-, increased; –, decreased; 0, no change.

Table 5-6. Electrolyte changes following urinary diversion

   a. **Jejunum** is characterized by an enormous capacity for allowing solutes and water to move passively across the mucosa. Hypertonic urine in the jejunal lumen leads to loss of sodium, chloride, and water.
   b. **Ileum** has a much lower absorptive capacity than jejunum, and the absorptive process is much slower. It has been shown that the ileum actively absorbs ammonium and chloride from the urine. Potassium and urea are also absorbed passively by the ileum.
   c. **Colon** has absorptive processes similar to those in the ileum, except that there is less propensity to absorb potassium.
4. **Acid-base disturbances** following urinary diversion vary in character and degree depending on the particular segment of bowel, the contact time between the urine and bowel mucosa, and the presence of impaired renal function.
   a. **Jejunal conduit** is sometimes performed in patients who require a high urinary diversion and in patients who have received radiation to the ileum. In 25% to 40% of patients with jejunal conduits, a syndrome characterized by nausea, vomiting, anorexia, and muscle weakness develops in the early postoperative period. Laboratory tests reveal a hyponatremic, hypochloremic, hyperkalemic acidosis with azotemia. The pathogenesis involves significant losses of sodium and chloride from the jejunum into the urine in the lumen (Fig. 5-2). The salt loss triggers increased aldosterone production in an attempt to conserve sodium. Aldosterone acts on the distal renal tubule to promote resorption of sodium and hydrogen ions with excretion of potassium. This process, however, results in a concentrated, potassium-rich, sodium-poor urine. On entering the jejunal conduit, the potassium is absorbed and even more sodium is lost. Urea is also absorbed passively from the conduit, which when combined with the contracted ECF and diminished glomerular filtration rate results in azotemia. The syndrome is more likely to occur as the length of the jejunal conduit increases. The treatment is oral replacement with sodium chloride tablets as well as correction of acidosis with bicarbonate (300 to 600 mg of sodium bicarbonate orally three times daily). Acutely hypovolemic patients require IV therapy with normal saline solution and bicarbonate.

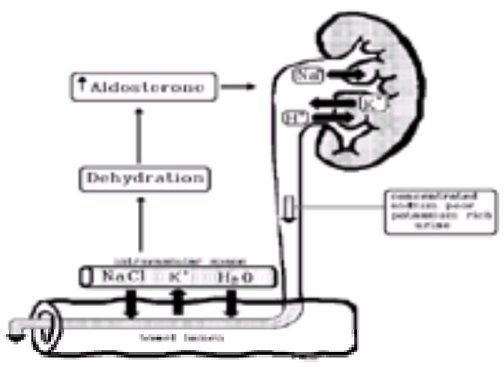

FIG. 5-2. The pathophysiology of the jejunal loop syndrome.

   b. **Ileal conduit** has a low incidence of clinically significant metabolic complications. Although mild metabolic acidosis is present in most patients with ileal conduit, clinical symptoms develop in only 5% to 10% of patients. Serum electrolyte determinations reveal increased chloride, decreased bicarbonate, and normal or low potassium levels. Hyperchloremic acidosis in a patient with ileal conduit implies the presence of some degree of intrinsic renal failure, obstruction of the conduit, or excessive conduit length. If there is conduit dysfunction, catheter drainage of the conduit may be sufficient. Most patients with laboratory evidence of acidosis should be treated even if asymptomatic to prevent mobilization of bone calcium. Most patients respond well to oral administration of 15 to 30 mL of potassium and sodium citrate (Polycitra) in water four times daily. Agents specifically meant to block chloride absorption may also be used: 25 to 50 mg of chlorpromazine twice daily or 400 mg of nicotinic acid twice daily.
   c. **Colon conduits** may be constructed from transverse colon or sigmoid colon. In terms of metabolic complications, colon conduits offer no advantages over ileal conduits and are more likely to lead to hypo-kalemia than ileal segments. Treatment is the same as for ileal segments except that oral potassium supplementation may be required.
   d. **Ureterosigmoidostomy** is a form of continent urinary diversion that was widely used to substitute for the bladder before the advent of the ileal conduit, but it is rarely used today. In this operation, the ureters are anastomosed in a nonrefluxing manner to the sigmoid colon, which acts as a reservoir for both urine and feces. Nearly 80% of patients with ureterosigmoidostomy exhibit some degree of hyperchloremic acidosis. Potassium loss may occur because of chronic diarrhea. Metabolic acidosis is seen most often, in its severest form in patients with some degree of renal insufficiency. Thus, renal

insufficiency is a relative contraindication to this form of urinary diversion. Treatment is similar to that described above for ileal conduits, with the aim being to maintain the serum bicarbonate level at nearly normal levels. In acutely ill patients, rectal tube drainage is rapidly effective in restoring acid-base balance; it should be combined with administration of IV fluids containing additional potassium (20 to 40 mEq of potassium chloride per liter) and bicarbonate (one to two ampules of sodium bicarbonate).

e. **Continent urinary diversions** are increasingly being used as a bladder substitute. Despite the long contact time between urine and bowel mucosa, there has been a rather low reported incidence of hyperchloremic acidosis in these patients. The treatment is the same as for patients with ileal segments described above.

B. **Metabolic alkalosis** may occur as a result of several different mechanisms:

1. **Loss of chloride in excess of sodium** accompanied by contraction of ECF occurs because of protracted vomiting, nasogastric suction, and the use of potent diuretics. This contraction alkalosis is the most common cause of metabolic alkalosis. Because the patient is depleted of chloride, the renal tubule increases its absorption of filtered bicarbonate, producing metabolic alkalosis. The urinary chloride concentration is usually very low (<10 mEq/L). Treatment is aimed at correcting the salt and water deficit with IV salt solutions and correcting the accompanying hypokalemia.
2. **Excess renal absorption of bicarbonate** without ECF contraction occurs when the renal tubule is stimulated to resorb sodium by aldosterone or cortical mineralocorticoids. Filtered bicarbonate is resorbed with the sodium, and chloride is lost in the urine (urinary chloride >20 mEq/L). This mechanism is seen in hyperaldosteronism, Cushing's syndrome, and Bartter's syndrome. Metabolic alkalosis may also result from ingestion of alkali and severe potassium depletion. The underlying disorder is treated, and potassium deficits are corrected. Spironolactone may block the effects of aldosterone and other mineralocorticoids on the renal tubule.
3. **Gastrocystoplasty.** Stomach actively secretes hydrogen and chloride ions into the lumen, resulting in acidic urine and release of bicarbonate into the bloodstream. This excess bicarbonate is excreted in the urine and partially neutralizes the acid secreted by the stomach segment. The acid secretion is, however, mainly stimulated by gastric distention after ingestion of a meal. Thus, the patient has episodes of metabolic alkalosis. Treatment consists of 300 mg of cimetidine four times daily or 20 mg of omeprazole daily, which is a potent inhibitor of gastric acid secretion.

IV. Potassium

A. **Potassium balance** is primarily determined by the kidneys, which serve as the major organ of potassium excretion. Total body potassium is partitioned such that 64% is in the ICF and 24% is in the ECF, including plasma; thus, changes in the serum potassium concentration only roughly indicate the status of total body potassium. The serum potassium level may change because of (1) alteration in total body potassium stores or (2) alteration in the transcellular partition of potassium. Total body potassium is decreased with excessive gastrointestinal or renal losses. The kidneys are unable to eliminate potassium completely from the urine even in the face of severe potassium depletion, as they can sodium. The total body potassium is increased with acute renal failure. The transcellular distribution of potassium in the body is affected by the following:

1. **Serum pH.** In systemic acidosis from any cause, hydrogen ions enter cells in exchange for potassium, causing hyperkalemia. Despite the fact that potassium depletion may exist in a patient with metabolic acidosis, the serum potassium level may be normal or even increased. Systemic alkalosis has the opposite effect.
2. **Insulin and glucose** cause movement of potassium into cells and may cause hypokalemia.

B. **Hypokalemia** is defined as a serum potassium level less than 3.5 mEq/L and may develop secondarily to inadequate oral intake (rarely), gastrointestinal losses (gastric, intestinal, colonic, or biliary), or urinary losses (renal tubular acidosis, osmotic diuresis, hyperaldosteronism, hyperadrenalism). Patients who undergo ureterosigmoidostomy are prone to the development of hypokalemia in association with the classic hyperchloremic acidosis because of colonic loss of potassium from passive diffusion and chronic diarrhea. Hypokalemia is also a potential problem in patients with postobstructive diuresis.

1. **Manifestations** may be neuromuscular (weakness, paresthesias, depression of deep tendon reflexes, paralysis), cardiac [electrocardiographic (ECG) abnormalities, increased sensitivity to digitalis], and nonspecific (nausea, irritability, nephropathy). ECG findings include flattened T waves, presence of U waves, and depressed ST segments.
2. **Treatment** consists of replacement of the potassium deficit by the oral route whenever feasible. This may be accomplished with 10% potassium chloride liquid supplement in doses of 40 to 60 mEq daily. IV therapy is reserved for patients unable to tolerate oral feedings or those with severe hypokalemia. In general, not more than 100 mEq should be given IV daily to avoid overcorrecting the problem and producing hyperkalemia. Concomitant alkalosis should be corrected with bicarbonate.

C. **Hyperkalemia**, defined as a serum potassium level in excess of 5.0 mEq/L, may result from acute renal failure, adrenal insufficiency, or major trauma, especially crush injuries. As mentioned previously, systemic acidosis causes transcellular redistribution of potassium and elevates the serum potassium level. Hemolysis of red cells in the blood sample is a common artifactual reason for hyperkalemia.

1. **Manifestations** are potentially more life-threatening than those of hypokalemia. Cardiac manifestations become common at potassium levels above 6.5 mEq/L. Clinically, these include bradycardia, hypotension, and arrhythmias. ECG findings are peaked T waves, depressed ST segments, prolonged PR intervals, and widened QRS complexes. Neuromuscular manifestations also can occur, resembling those described under hypokalemia. If hyperkalemia is suspected by clinical or ECG evidence, treatment should be initiated while laboratory confirmation is awaited.
2. **Treatment** of hyperkalemia involves measures that move potassium into cells, antagonize the toxic effects of potassium, or promote excretion of potassium from the body.
   a. **Glucose and insulin** given IV cause a rapid shift of potassium into the intracellular compartment. One ampule of 50% dextrose (25 g of dextrose) with 10 units of regular insulin should be infused IV over 5 minutes. Potassium levels should begin to fall within 30 to 60 minutes.
   b. **Sodium bicarbonate** causes systemic alkalosis, which promotes movement of potassium intracellularly. One ampule of 7.5% sodium bicarbonate (44.6 mEq of bicarbonate) may be given IV over 5 minutes. A second ampule can be given after 15 to 30 minutes if ECG changes persist or do not improve. Alternatively, 90 mEq of sodium bicarbonate may be added to 1 L of IV fluid containing 5% or 10% dextrose and given over a 3-hour period.
   c. **Calcium gluconate** antagonizes the toxic effects of hyperkalemia on the myocardium and neuromuscular tissues. Five to ten milliliters of 10% calcium gluconate should be given IV over 2 minutes with constant ECG monitoring. If ECG abnormalities do not improve within 5 minutes, a second dose may be given. Although calcium acts rapidly, its effect is short-lived, and other means of reducing extracellular potassium should also be used. Calcium may induce arrhythmias in patients receiving digitalis and should be given only with careful rhythm monitoring and when defibrillating equipment is available.
   d. **Ion-exchange resins**, such as Kayexalate, work by exchanging potassium for sodium. It is important to remember that approximately 1.5 mEq of sodium is added to the body for each 1.0 mEq of potassium removed; thus, patients are at risk for cardiovascular overload. The recommended oral dosage is 20 to 50 g of Kayexalate dissolved in 200 mL of 20% sorbitol solution given every 4 hours. If more rapid action is desired or if oral intake is not feasible, Kayexalate may be given as a rectal enema (50 gm Kayexalate powder dissolved in 200 mL of 20% dextrose solution).
   e. **Hemodialysis** is effective in the treatment of hyperkalemia but is usually reserved for situations in which it is necessary for other reasons, such as acute uremia (see Chapter 21).

V. Calcium

A. **Calcium balance** depends on the interaction of intestinal absorption, bone storage, and renal tubular excretion. This balance is maintained by the combined actions of vitamin D and parathyroid hormone (PTH). More than 98% of total body calcium is stored in bone, and approximately 45% of total serum calcium is bound to protein (primarily albumin). The remainder constitutes the ionized fraction, which is physiologically active and controls PTH secretion.

1. **PTH** acts to elevate the serum calcium level by mobilizing calcium from bone, increasing renal tubular resorption of filtered calcium, and increasing intestinal absorption of calcium. In addition, PTH promotes renal tubular excretion of phosphate.
2. **Vitamin D** promotes intestinal absorption of calcium and phosphorus and also mobilizes skeletal calcium into the serum; however, vitamin D is inactive until it is metabolized to its active form (1a,25-dihydroxycholecalciferol) in the kidney. The rate of this metabolic conversion is controlled by PTH. By this mechanism, the parathyroid gland controls the intestinal absorption and bone storage of calcium.

B. **Hypercalcemia** is a potentially life-threatening complication of neoplastic disease (or cancer chemotherapy). It has been estimated that 10% to 20% of patients with malignancy have hypercalcemia. Although most commonly associated with breast and lung tumors, lymphomas, and leukemias, almost any malignancy can produce hypercalcemia. In most solid tumors, hypercalcemia is the result of bone metastases, but osteolysis from tumor production of prostaglandins has been reported rarely. Finally, ectopic production of PTH, termed **pseudohyperparathyroidism**, in solid tumors accounts for approximately 2% of instances of hypercalcemia and is most commonly caused by squamous cell carcinomas of the lung (33%), renal carcinoma (33%), and gynecologic tumors. The differential diagnosis of hypercalcemia should include primary hyperparathyroidism, immobilization, vitamin D intoxication, use of thiazide diuretics, and sarcoidosis. Patients with hypercalcemia may present with changes in mental status (psychosis, obtundation, coma), gastrointestinal function (nausea, vomiting, constipation, abdominal pain), or urinary function (polyuria, nocturia). ECG changes include a shortened QT interval and occasionally arrhythmias. **Treatment** of acute hypercalcemia may involve various strategies. The presence of stupor or coma, renal failure, or cardiac arrhythmia in association with a serum calcium level of more than 15 mg/dL is termed hypercalcemic crisis and requires urgent treatment as follows:

1. **Saline diuresis** is induced by rapid IV infusion of normal saline solution or lactated Ringer's solution at a rate of 250 to 500 mL/h. Presentation of a large sodium load to the renal tubule enhances calcium excretion in the urine. Clearly, careful monitoring of the central venous pressure is required, especially in

patients with cardiac disease, and the central venous pressure should not be permitted to rise above 10 cm H_2O. Furosemide should be given simultaneously in doses of 20 to 40 mg every 2 hours IV to enhance calcium excretion further and maintain the water diuresis.

2. **Glucocorticoids** may be used when less rapid reduction of serum calcium is desirable (e.g., in chronic hypercalcemia associated with malignancy). Sixty milligrams of oral prednisone per day will reduce the serum calcium over several days. Glucocorticoids affect serum calcium by decreasing the rate of bone metabolism, decreasing intestinal absorption of calcium, and promoting its renal excretion.
3. In instances of severe hypercalcemia (serum level >15 mg/dL) that are refractory to standard treatment, mithramycin has been effective. Because of potential side effects, such as thrombocytopenia, renal failure, and hepatic failure, mithramycin should not be used as a first-line agent in the treatment of hypercalcemia. The drug is given by slow IV infusion (15 to 25 µ/kg) during 4 to 6 hours. A hypocalcemic effect is seen within 12 hours and lasts 3 to 7 days. Rapid reduction of serum calcium can be achieved by **hemodialysis**, which is the treatment of choice in patients with oliguric renal failure. Perhaps the most rapid reduction of serum calcium follows IV administration of 15 to 50 mg of **sodium EDTA** (ethylenediamine tetraactic acid) per kilogram over 4 hours, but this agent can cause nephrotoxicity.

C. **Hypocalcemia** may be secondary to vitamin D deficiency, bowel malabsorption, magnesium deficiency, hypoparathyroidism, pseudohypoparathyroidism, and acute pancreatitis. Apparent hypocalcemia can result from hypoalbuminemia because, as discussed previously, approximately 45% of the serum calcium is bound to albumin. In hypoalbuminemia, the ionized calcium level is unaffected, and the patient will not manifest signs of hypocalcemia. Because most hospital laboratories report total serum calcium rather than ionized calcium, one must estimate the ionized calcium level by assessing the serum albumin and serum calcium levels together. A useful rule of thumb is that each fall of 1 g/dL in serum albumin accounts for a decrease of 0.8 mg/dL in serum calcium.
   1. **Renal failure** commonly leads to hypocalcemia. As discussed, the kidneys convert vitamin D to its active form, and this function is impaired in renal failure. Another factor in renal failure is hyperphosphatemia, which promotes precipitation of calcium in bone and other tissues. Hypocalcemia from enhanced bone deposition of calcium may occur rarely in patients with osteoblastic bone metastases from carcinoma of the prostate, breast, or lung.
   2. **Paresthesias**, especially in the circumoral area, may be an early symptom of hypocalcemia. Tetany (increased neuromuscular irritability) is the classic sign of hypocalcemia. Latent tetany may be elicited by tapping over the facial nerve to produce twitching (Chvostek's sign) or by inflating a blood pressure cuff above systolic pressure for 3 minutes to produce carpal spasm (Trousseau's sign). Other manifestations include psychosis, development of cataracts, and prolongation of the QT interval on the ECG.
   3. **Treatment** of hypocalcemia depends on the acuteness of onset and the likelihood of laryngeal spasm or convulsions, or both. The onset of tetany caused by **acute hypocalcemia** requires emergent treatment with 20 mL (two ampules) of 10% calcium gluconate IV over 15 minutes. It is important to remember that alkalosis decreases the ionized calcium concentration and can potentiate the effects of hypocalcemia. Also, magnesium depletion interferes with PTH responsiveness and thus can cause hypocalcemia. If the serum magnesium is less than 0.8 mEq/L, severe magnesium depletion is present and should be corrected with 1 to 2 g of 10% magnesium sulfate IV over 15 minutes. Following acute therapy, calcium can be provided IV (600 mg of calcium gluconate per liter of 5% dextrose in water) or orally (2 to 4 g of elemental calcium per day).

VI. Magnesium

After potassium, magnesium is the second most important intracellular cation and is an activator of many metabolic enzymes. Magnesium is absorbed in the ileum and excreted by the kidney.

A. **Hypomagnesemia** may occur because of dietary deficiency, malabsorption, or renal losses. The most common clinical condition producing magnesium deficiency in the United States is chronic alcoholism with its associated malnutrition, malabsorption, and alcohol-induced magnesuria. Renal magnesium wasting in urologic patients may occur in renal tubular acidosis, the diuretic phase of acute tubular necrosis, drug-induced nephrotoxicity (aminoglycosides, *cis*-platinum), and therapy with loop diuretics. Clinically, the symptoms of hypomagnesemia resemble those of hypocalcemia and include seizures, personality changes, and cardiac tachyarrhythmias. As discussed previously, hypomagnesemia may be the cause of hypocalcemia. **Treatment** involves administration of 2 to 3 g of magnesium sulfate IV over 1 to 2 minutes followed by 1 g intramuscularly (IM) every 4 to 6 hours, depending on the patient's magnesium level and clinical status.
B. **Hypermagnesemia** occurs most commonly in patients with renal failure who receive magnesium-containing antacids or laxatives, such as milk of magnesia, Mylanta, and Maalox.
   1. **Hemiacidrin and stone disease.** Urologic patients are at particular risk from the use of hemiacidrin (Renacidin) to accomplish chemolysis of urinary (struvite) stones (see Chapter 10). Hemiacidrin is a mixture of magnesium hydroxycarbonate, magnesium acid citrate, and calcium carbonate. The magnesium in Hemiacidrin replaces the calcium in urinary stones, thus producing a more soluble salt. However, infusion of hemiacidrin into the infected upper tract at high pressure may lead to magnesium toxicity. This is also a problem in patients with ileal segment diversion because magnesium is absorbed through the ileal mucosa. Magnesium toxicity is manifested as hypotension, nausea, and vomiting, usually at serum levels of between 3 and 5 mEg/L. At serum levels of 7 mEq/L, drowsiness and depression of deep tendon reflexes ensue. At serum levels above 12 mEq/L, respiratory arrest and coma are likely. During stone chemolysis with hemiacidrin, daily determinations of magnesium and phosphate are indicated.
   2. **Treatment of hypermagnesemia** in patients undergoing hemiacidrin infusion consists of immediate cessation of infusion. The patient should receive 10% calcium gluconate (10-mL ampule) IV over 5 minutes, and diuresis should be induced by IV administration of saline solution with 20 to 40 mg of furosemide. If symptoms of hypermagnesemia persist, hemodialysis is indicated.

Suggested Reading

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Chapter 6 Lower Urinary Tract Symptoms

Mike B. Siroky

I. Pathogenesis of Lower Urinary Tract Symptoms

For most lower urinary tract symptoms, the final common pathway is the bladder. Bladder dysfunction may be primary or secondary to outflow obstruction. Obstructive lesions rarely manifest themselves in their own right; rather, they cause symptoms almost exclusively by inducing bladder dysfunction, either bladder overactivity or underactivity. Management requires an understanding of the relevant pathophysiology and an orderly approach to diagnosis and therapy. With the advent of many new noninvasive therapies, therapeutic choices have increased significantly in the last decade.

II. Definitions

The most common **lower urinary tract symptoms (LUTS)** are urinary frequency, urgency, and hesitancy, weak stream, and nocturia. This symptom complex was previously referred to as prostatism, but the increasingly preferred terminology is LUTS. The reason for this change is that the term prostatism implies that these symptoms are caused by enlargement of the prostate, which is often not the case. For example, bladder instability in the absence of outflow obstruction can produce the same symptoms as prostatic obstruction and accounts for 30% of instances of "prostatism." **Voiding symptoms**, previously called obstructive symptoms, are hesitancy, intermittency, weak stream, dribbling, double voiding, and use of abdominal straining to void. A weak stream is characterized by diminished force, diminished caliber, and prolonged voiding time. **Storage symptoms**, previously called irritative symptoms, are frequency, urgency, urge incontinence, nocturia, dysuria, and sometimes enuresis. Urinary frequency refers to decreased volume of voidings and a decreased interval between voidings (<2 hours). Frequent voiding in large volume is **polyuria**. Urinary frequency is commonly associated with urgency, which is the sudden desire to urinate. **Nocturia** refers to urinary urgency that awakens the patient from sleep, and it should be distinguished from other reasons for voiding at night, such as insomnia, peripheral edema, and use of diuretics at bedtime. **Acute retention** refers to the sudden onset of complete inability to void in a patient who may or may not have had urinary symptoms previously. **Chronic retention** refers to the presence of postvoiding residual urine in the bladder of a patient who is able to void, albeit poorly.

III. Differential Diagnosis

LUTS may result from a wide variety of conditions (Table 6-1), some of which are obstructive, some nonobstructive. These may be classified anatomically as follows:

Outflow obstruction
Benign prostatic hyperplasia
Vesical neck obstruction
Urethral stricture
Meatal stenosis
Cystocele
Impaired detrusor function
Neuromuscular dysfunction
Detrusor instability
Impaired detrusor contractility
Psychogenic voiding dysfunction
Infection
Cystitis
Bacterial prostatitis
Prostatic abscess
Urethral diverticulum
Neoplastic
Prostate cancer
Bladder cancer, including carcinoma in situ

Table 6-1. Some common causes of lower urinary tract symptoms in adults

A. **Anterior urethra. Meatal stenosis** presents most commonly in newborns or during infancy and may be congenital or secondary to ammonia dermatitis. In male adults, the condition may be secondary to inflammation of the prepuce (posthitis) or of the glans penis (balanitis). **Urethral stenosis** in female adults is uncommon and may be related to obstetric or sexual trauma. **Urethral strictures** in male adults most commonly result from trauma sustained during instrumentation, catheterization, or endoscopic surgery. Inflammatory strictures, whether caused by gonorrhea or nonspecific urethritis, occur most commonly in the bulbous urethra. Acute inflammation from gonococcal or nongonococcal urethritis may lead to urgent urination.
B. **Posterior urethra.** In male infants and newborns, **posterior urethral valves** are the most common obstructing lesion. These are congenital mucosal folds in the region of the membranous urethra that obstruct the flow of urine. In adults, **sphincter spasm** may result in obstruction when the striated urethral sphincter fails to relax during micturition because of either neurologic disease (spinal cord injury, multiple sclerosis) or psychogenic voiding dysfunction. When caused by neurologic dysfunction, it is termed **vesicosphincter dyssynergia**. **Benign prostatic hyperplasia (BPH)**, by far the most common cause of urinary obstruction in male adults, is discussed below. **Prostate adenocarcinoma**, although a common neoplasm, rarely causes obstruction until the disease is quite advanced. **Acute prostatitis** or **prostatic abscess** may rarely cause obstruction or even urinary retention as well as frequency, urgency, and dysuria.
C. **Bladder. Bladder neck obstruction** may occur when the bladder neck fails to open as a result of either neurologic disease (very rare), idiopathic dysfunction (not uncommon), or contracture (common). Bladder neck contracture is most often a result of trauma or surgery. Functional bladder neck obstruction is characterized by failure of the vesical neck to open completely during voiding without evident structural cause. This type of obstruction often masquerades as benign prostatic enlargement but typically occurs in a younger age group (30 to 45 years). **Cystocele** in female patients may cause obstruction by creating an acute angulation at the vesical neck.
D. **Bladder neuromuscular dysfunction** may present as urinary retention or voiding or storage symptoms. **Detrusor overactivity** may be associated with neurologic disease (**detrusor hyperreflexia**) or with nonneurologic causes (**detrusor instability**). Detrusor overactivity is characterized by the sudden onset of severe urinary urgency. In some cases, voiding occurs almost immediately after the onset of urgency, leading to urge incontinence. **Impaired detrusor contractility** is usually idiopathic and is common in elderly patients of either sex. It may occur after prolonged overdistention of the bladder wall. Patients with impaired contractility may have significant postvoiding residual urine, which does not necessarily indicate the presence of outflow obstruction. **Peripheral neuropathy** may involve the autonomic fibers supplying the detrusor muscle; common causes include diabetes mellitus, alcoholism, uremia, and surgical trauma. **Pharmacologic agents**, including nonprescription drugs, may have anticholinergic properties and precipitate urinary retention or impaired voiding. Among these are phenothiazines and antianxiety agents. a-Adrenergic agonists such as pseudo-ephedrine, ephedrine, and phenylpropanolamine are contained in many over-the-counter "cold" remedies and can cause acute retention. **Psychogenic voiding dysfunction** is characterized by lifelong detrusor instability or pelvic floor spasm leading to urge incontinence, impaired voiding, or discomfort in the suprapubic area or perineum.

IV. Benign Prostatic Enlargement

The term benign prostatic hyperplasia refers to well-defined histologic changes characterized by slowly progressive nodular hyperplasia of the periurethral (transitional) zone of the prostate (Fig. 6-1). At autopsy, more than 75% of men over the age of 80 have histologic evidence of benign prostatic hyperplasia. However, benign prostatic hyperplasia, which is a histologic diagnosis, should not be confused with benign prostatic enlargement, a clinical diagnosis. Because we rarely know the precise histologic findings in the prostate, benign prostatic enlargement is a preferable term for clinical use. There is no exact correlation between the presence of

LUTS, bladder outflow obstruction, and benign prostatic enlargement.

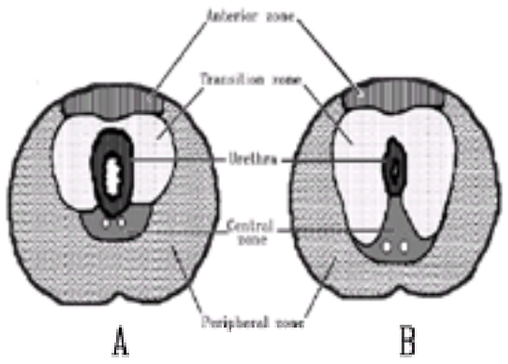

FIG. 6-1. Transverse section of **(A)** normal prostate and **(B)** prostate with benign hypertrophy.

A. **Bladder response to outflow obstruction.** The response of the detrusor muscle to the increased work load associated with outflow obstruction varies over time.
   1. **Early obstruction.** At this stage, the detrusor undergoes hyperplasia, and bladder contractility may be normal or slightly impaired. The bladder is able to empty completely or nearly completely; however, **bladder instability** is likely to develop in 60% to 80% of patients. Unstable bladder contractions are involuntary contractions that are difficult to inhibit. Such contractions produce the sensation of urgency even at low volumes and account for symptoms such as urinary frequency and urgency and nocturia.
   2. **Late obstruction.** The bladder is unable to empty completely, and postvoiding residual urine is present. Because of the obstruction, detrusor muscle contractility is significantly impaired. At this stage, residual urine results as much from poorly sustained bladder contractions as from inadequate detrusor pressure. The patient notes urinary hesitancy and intermittency and a weak stream and may complain of a sensation of incomplete voiding. With severe obstruction, the patient may use abdominal straining to void, and many male patients will sit to void to increase abdominal voiding pressure.
   3. **Decompensation.** The ability of the detrusor muscle to contract is severely impaired to the point that little effective pressure is generated. The bladder may empty by frequent, ineffective voiding or by dribbling (overflow or paradoxical incontinence).
B. **Secondary effects of obstruction.** Over time, outflow obstruction leads to characteristic changes in the bladder and upper urinary tract. These changes may be observed cystoscopically and radiologically.
   1. **Bladder trabeculation.** Prominence of the detrusor fibers observed through a cystoscope is termed trabeculation. It is a manifestation of increased collagen deposition in the bladder wall. This finding is often associated with outflow obstruction but may also be seen in unobstructed bladders (e.g., enuresis, neurogenic bladder dysfunction, idiopathic bladder instability). The interureteric ridge (Bell's muscle) becomes prominent, and the bladder neck is also hypertrophied. Hypertrophy of the vesical neck causes an acute angulation between the trigone and prostatic urethra, which is described cystoscopically as a *bas-fond* deformity.
   2. **Cellule formation.** Extreme degrees of trabeculation allow the vesical mucosa to be pushed between the muscle fibers of the bladder wall to form small pockets called cellules.
   3. **Diverticulum formation.** Herniation of the vesical mucosa through the detrusor muscle constitutes a bladder diverticulum. Acquired bladder diverticula contain no muscular components and are therefore prone to poor emptying even if the bladder is emptied by catheterization. Because of stasis of urine within the diverticulum, they are likely to harbor infection, stones, and urothelial cancer. A diverticulum near the ureteric orifice (Hutch diverticulum) may cause vesicoureteral reflux.
   4. **Bladder calculi.** In developed countries, bladder calculi form most commonly as a result of outflow obstruction, residual urine, stasis, and infection. The presence of a bladder calculus is strong evidence of long-standing bladder outflow obstruction. The most common mineral constituent of these stones is calcium oxalate. Stones also may occur within bladder diverticula.
   5. **Hydroureteronephrosis.** With hypertrophy and fibrosis of the detrusor wall, increased work is required to transport the urinary bolus from the ureter into the bladder. In the early stages, the condition appears radiologically as mild dilatation of the distal segment and elongation and some tortuosity of the ureter. Later, there is more marked dilatation of the entire ureter, marked elongation and tortuosity, and attenuation of the ureteral wall.

V. Diagnostic Approach

The patient with LUTS needs a well-planned assessment to determine (1) the nature and severity of symptoms, (2) whether there is objective evidence of obstruction, and (3) the effect of the obstruction on the upper urinary tract.

A. **Symptoms.** Because LUTS are rarely life-threatening, the nature and severity of symptoms are important criteria in determining therapy. Symptoms should be quantified with standardized symptom scores such as that developed by the American Urological Association (AUA) (see Appendix I). The questionnaire consists of seven questions to quantify symptoms and sections to determine how bothersome symptoms are and assess quality of life. The symptom score appears to separate symptomatic patients from control patients fairly well (Table 6-2). Although treatment should be individualized, as a general rule patients with a score of 7 or less are considered to have mild symptoms that probably do not require immediate treatment unless hydronephrosis or uremia is present. Patients with moderate symptoms (AUA score of 8 to 20) probably are in need of some therapy. Patients with severe symptoms (AUA score above 20) frequently require treatment to avoid development of complications.

AUA score	BPE patients (%)	Control subjects (%)
Mild (0–7 points)	20	83
Moderate (8–19 points)	57	15
Severe (20–35)	23	2

BPE, benign prostatic enlargement.

Table 6-2. Distribution of scores on the American Urological Association (AUA) symptom index

B. **History.** A detailed urologic history should be taken assessing prior surgery, infections, strictures, stones, tumors, or bleeding in the urinary tract. The general medical history should especially focus on vascular disease (cardiac, cerebral, and peripheral), pulmonary disease (asthma, chronic obstructive pulmonary disease), and habits (alcohol consumption, smoking). A detailed list of all medications (prescription and nonprescription) should be developed.
C. **Physical examination**
   1. In female patients, a **pelvic examination** is required to assess the presence of cystocele, urethral stenosis, or urethral diverticulum.
   2. **Flank and abdomen.** In thin patients, the bladder can be palpated or percussed when distended to more than 200 mL. In severe chronic retention, the dome of the bladder may reach almost to the umbilicus. Pressing on the distended bladder may cause discomfort or urgency, or both. The flank area should be palpated and percussed for evidence of mass or tenderness.
   3. **Male genitalia.** The male genitalia are best examined with the patient standing and facing the seated examiner. If this is not feasible, the patient may be supine. The glans and foreskin should be examined for signs of phimosis, infection, and meatal stenosis. The testes should be examined for size, consistency, and mass or tenderness. The spermatic cord may reveal varicocele or inguinal hernia.
   4. **Examination of the prostate** is best performed with patients bent over the examining table, supported on their elbows. An alternative and less desirable position is the lateral decubitus position with one leg drawn up toward the abdomen. The examiner's gloved, generously lubricated index finger is inserted slowly into the rectum. The purpose of the examination is to assess prostatic size, symmetry, and consistency; to assess anal tone; and to determine the

presence of rectal masses. A lax anal sphincter that the patient cannot contract may be indicative of peripheral neuropathy. In some patients, the seminal vesicles are easily palpable as thickened cords extending cephalad from the base of the prostate. An inexperienced examiner can confuse the seminal vesicles with prostate cancer. In young adult male patients, the prostate is usually described as about the size of a chestnut. The earliest change in benign prostatic enlargement is loss of the median depression, or furrow. With increasing size, the prostate extends laterally and cephalad until the examining finger cannot reach the base of the gland. It is important to remember that only the posterior lobe of the prostate is palpable through the rectal wall; however, this lobe gives rise to most prostate carcinomas. Early, treatable prostate cancer is most commonly found on prostate examination as an area of induration or fullness within the substance of the prostate and not as a nodule extending above the surface of the gland. For this reason, the examiner must assess the consistency of the prostate by firm palpation, which is somewhat uncomfortable for most patients and may produce urinary urgency. The normal prostate has a weight of approximately 20 g, and its consistency is approximated by the tensed adductor pollicis muscle at the base of the thumb. If any areas are more firm than this, the examiner should suspect prostate nodules and take biopsy samples. The differential diagnosis of a prostate nodule includes prostate cancer, asymmetric BPH, prostatic calculi, and granulomatous prostatitis. Approximately 50% of prostate nodules discovered on rectal examination are proved to be carcinoma on biopsy.

5. The **focused neurologic examination** should include perineal sensation and assessment of bulbocavernosus reflex. The bulbocavernosus reflex may be tested during the rectal examination by gently squeezing the glans penis to assess the presence of anal sphincter contraction. As mentioned above, a lax or unresponsive anal sphincter may indicate peripheral neuropathy.

C. **Laboratory tests** should include urinalysis, urine culture, complete blood count, and determination of serum creatinine, blood urea nitrogen (BUN), blood sugar, and serum electrolytes for most patients. For male patients more than 50 years of age, a test for prostate-specific antigen (PSA) is highly recommended.

D. **Assessment of upper tracts.** Routine assessment of the upper tracts is not recommended for the patient with LUTS unless hematuria, recurrent urinary tract infection, azotemia, prior urinary tract surgery, or a history of urinary stones is present. Ultrasonography (US) of the kidneys and bladder is the preferred means of initial radiologic assessment unless hematuria is detected (see Chapter 1). US is preferred because it offers rapid, accurate assessment of hydroureteronephrosis, prostatic size, and bladder residual. It is safer and less expensive than intravenous urography (IVU), especially in uremic or dehydrated patients, because it does not involve contrast injection or radiation. However, the presence of hematuria (gross or microscopic) is a strong indication for IVU because IVU offers more complete visualization of the urothelial surfaces than does US.

E. **Assessment of the lower tract** may include a variety of radiologic and other procedures. These tests are optional and should be selected based on the patient's history and other findings.

1. **Retrograde urethrogram (RUG).** This examination is performed by retrograde instillation of radiographic contrast into the male urethra. RUG is most useful in visualizing lesions of the anterior urethra, such as strictures, diverticula, and urethral perforations. Lesions of the posterior urethra (proximal to the genitourinary diaphragm) are poorly visualized by this technique because the striated urethral sphincter generally prevents contrast from completely filling the posterior urethra or bladder.
2. **Voiding cystourethrogram (VCUG).** The VCUG is performed by filling the bladder with radiographic contrast through a urethral catheter or suprapubic tube. The entire process of filling and voiding is monitored by fluoroscopy. Static films are obtained with the bladder full, during micturition, and after voiding. This is an excellent method of diagnosing vesical neck obstruction, vesicosphincter dyssynergia, and vesicoureteral reflux. It is also useful in assessing the presence of cystocele in female patients.
3. **Cystourethroscopy.** Endoscopy permits direct visualization of the entire lower urinary tract (see Chapter 3), making possible the diagnosis of most obstructive lesions, such as prostatic enlargement, vesical neck contracture, and urethral stricture. Changes in the bladder are indicated by the presence of trabeculation, cellules, and diverticula, which provide indirect evidence of obstruction.
4. **Uroflowmetry.** An electronic flowmeter can provide a recording of urinary flow rate versus time (Fig. 6-2). The peak flow rate is a sensitive indicator of outflow obstruction. The bladder volume at the start of micturition has an important effect on the peak flow rate and may be accounted for by the use of flow rate nomograms (Fig. 6-3). Uroflowmetry should always be performed in conjunction with estimation of **postvoiding residual urine volume**. This may be done by catheterization or by US examination (preferred). The normal peak flow should be more than 12 mL/s in normal male adults voiding more than 150 mL.

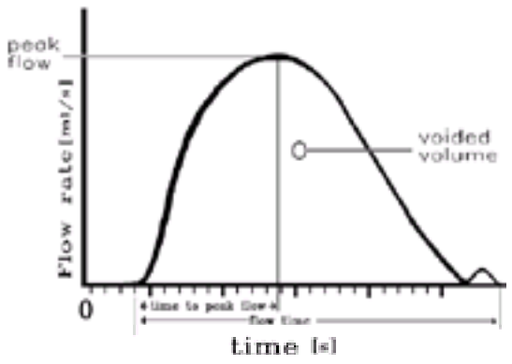

FIG. 6-2. Important parameters of uroflowmetry.

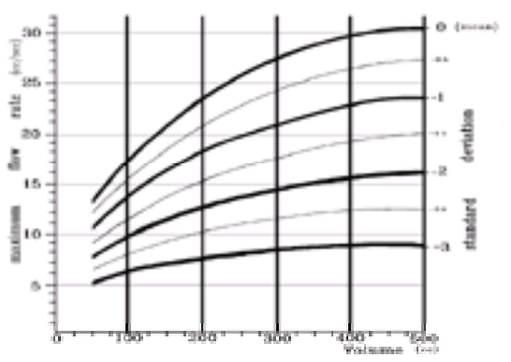

FIG. 6-3. Flow rate nomogram relating maximum or peak flow to intravesical volume.

5. **Cystometry.** The cystometrogram (Fig. 6-4) is a continuous recording of bladder pressure during gradual filling and during contraction. The examination is indicated in any patient with LUTS when detrusor instability, neurologic disease, or myogenic bladder failure is suspected. The finding of detrusor instability, even in asymptomatic volunteers, is common and should be interpreted in light of the patient's clinical picture. **Ambulatory cystometry** may be used in cases in which one needs a long-term view of bladder activity (24 to 72 hours). See Chapter 20 for a discussion of cystometrogram technique and interpretation.

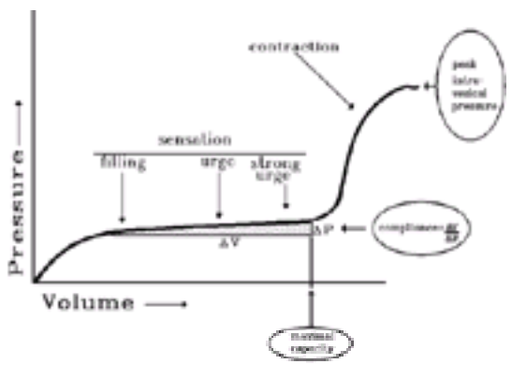

FIG. 6-4. Important parameters derived from normal cystometrogram curve, including sensation, capacity, compliance, and peak intravesical pressure.

6. **Pressure-flow studies** allow simultaneous measurement of voiding pressure and flow rate and are usually combined with fluoroscopy. These studies are indicated in complicated cases such as incontinence after prostatectomy and LUTS refractory to standard treatment.

VI. Treatment

A. **Distal urethra**
   1. **Meatal stenosis** is best managed by surgical meatotomy rather than dilation whenever possible.
   2. **Urethral strictures** occur most often in male patients after urethral infection or trauma and may be treated by various modalities.
      a. **Dilation** may be accomplished by means of van Buren sounds or filiforms and followers. Dilation of a stricture is generally not curative, as there is a high recurrence rate.
      b. **Visual urethrotomy.** With an optical urethrotome, the stricture can be visualized and incised with a movable knife blade. This is a safe and effective procedure, with a 1-year patency rate of 60%. Visual urethrotomy may be repeated multiple times as required. The neodymium-YAG (yttrium-aluminum-garnet) laser has been used to incise strictures in the urethra, but this technique is still under investigation.
      c. **Urethroplasty.** The visual urethrotomy has eliminated the need for urethroplasty in many cases. A urethroplasty is indicated in the face of rapid stricture recurrence following visual urethrotomy or difficult dilatation.

B. **Benign prostatic enlargement.** The treatment of benign enlargement is highly individualized and depends on the severity of symptoms and presence of complications (Fig. 6-5). Refractory urinary retention, upper tract deterioration, recurrent infection, hematuria, and bladder stones are strong indications for intervention according to most urologists. For patients without these findings, the level of symptoms is the main determinant of therapy and the timing of intervention.

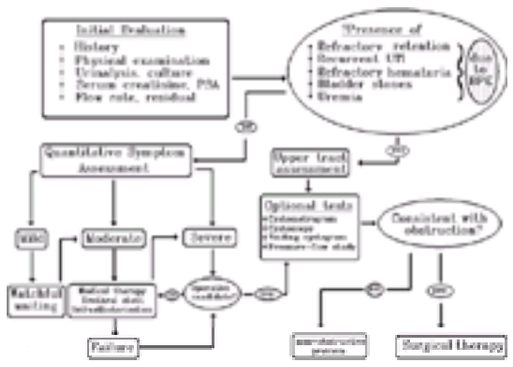

FIG. 6-5. Flow chart for the assessment and treatment of patients with lower tract symptoms caused by benign prostatic enlargement.

   1. **Watchful waiting** involves careful follow-up of symptoms and signs without active intervention and is recommended for the majority of patients with mild symptoms (AUA score of 0 to 7). Approximately 30% of patients will experience improvement with watchful waiting. On the other hand, the risk for symptom progression is low (1% to 5%).
   2. **Pharmacologic therapy**
      a. **a-Adrenergic blocking agents.** The prostate contains smooth muscle that is controlled by a_1-adrenoceptors (Table 6-3). a_2-Adrenoceptors are located on nerve endings rather than smooth muscle. a-Adrenergic blocking agents have side effects, such as dizziness, lightheadedness, and asthenia, that are related to their antihypertensive actions. Other side effects include nasal congestion, tachycardia, palpitations, nervousness, and retrograde ejaculation. Nonselective a-adrenergic blocking agents, such as phenoxybenzamine, tend to be associated with a greater incidence of side effects. With the advent of more selective agents, phenoxybenzamine is not generally used for benign prostatic enlargement today. From 50% to 75% of patients experience rapid improvement in symptoms with a-adrenergic blocker therapy.

Generic name	Brand name	Dose forms	Dose	
			Initial	Maximum
phenoxybenzamine	Dibenzyline	10-mg capsules	10 mg bid	40 mg tid
doxazosin	Cardura	1, 2, 4, 8-mg tablets	1 mg qd	8 mg qd
terazosin	Hytrin	1, 2, 5, 10-mg capsules	1 mg hs	20 mg hs
prazosin	Minipress	1, 2, 5-mg capsules	1 mg tid	20 mg qd
tamsulosin	Flomax	0.4-mg capsules	0.4 mg qd	0.8 mg qd

Table 6-3. a-Adrenergic blocking agents used in benign prostatic enlargement

      b. **Finasteride**, a 5a-reductase inhibitor, blocks the conversion of testosterone to dihydrotestosterone. Clinical experience has shown that finasteride reduces prostatic size by about 20%, improves urinary flow rate by about 2 mL/s, and reduces AUA symptom scores by 3.6. The dose is 5 mg by mouth daily. Side effects are minimal and include headache, minimal loss of libido, and occasional impotence. One important side effect is that finasteride lowers serum PSA by about 50% after 6 months of therapy.
      c. **Phytotherapy.** Pharmaceuticals derived from plant extracts are widely used outside the United States and increasingly within the United States. Although these compounds do not require a prescription, it is important for the urologist to be familiar with self-administered medications. The mechanism of action of many of these compounds is unknown or poorly understood. However, there is some evidence that they may inhibit 5a-reductase, aromatase, or growth factors.
         1. **Saw palmetto**, an extract from the berry of the American dwarf palm tree, is thought to act as a 5a-reductase inhibitor. However, there is doubt about this, as saw palmetto does not lower PSA levels. Nevertheless, saw palmetto does seem to alleviate symptoms, increase peak urine flow, and reduce prostate volume in a manner similar to that of finasteride.
         2. ***Pygeum africanum***, an extract of the bark of an African evergreen tree, is thought to inhibit prostaglandins E_2 and F_{2a} as well as fibroblast growth factors. Whether the compound acts on the prostate or has a protective effect on the bladder is unclear. Clinical studies have shown the compound to be more effective than placebo in reducing frequency, urgency, hesitancy, and incomplete emptying.
         3. **South African star grass** contains phytosterols, the most important of which is b-sitosterol. Clinical effects are similar to those of saw palmetto.
   3. **Prostatic stents.** Two essentially similar types of permanent intraurethral stents are available that differ in material and delivery system. Stents are not indicated in the treatment of median lobe enlargement. Stents are useful for high-risk patients because they can be placed under topical urethral lidocaine with IV sedation, local prostatic block, or light general anesthesia. If the patient is unable to void immediately after placement of a urethral stent, a temporary suprapubic catheter should be placed because a urethral catheter may displace the stent.
      a. The **titanium stent** (Titan, Boston Scientific) may be delivered over a high-pressure 7F (French) balloon catheter and left in place in the prostatic urethra. This rigid stent opens to 39F and is available in sizes ranging from 1.9 to 5.0 cm. Removal of the stent requires that it be pushed into the bladder, crushed, and removed through an endoscope sheath.
      b. The **cobalt-chromium stent** (Uro-Lume, American Medical Systems) is a somewhat flexible stent that expands to a size of 42F. This stent device, placed with transurethral insertion device (Fig. 6-6), is available in three lengths: 2.0 cm, 2.5 cm, and 3.0 cm. The proper size must be selected to prevent the stent from protruding past the verumontanum.

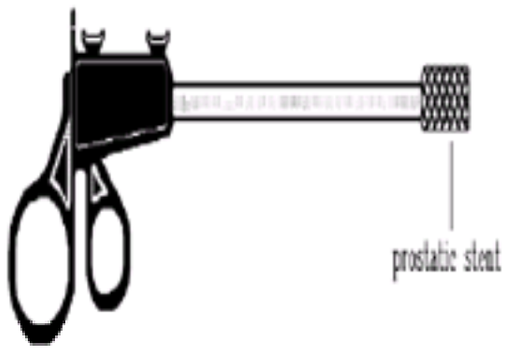

FIG. 6-6. Endoscopic instrument for placing intraprostatic stent.

4. **Balloon dilation of the prostate.** The use of high-pressure balloons to dilate the prostate generated some enthusiasm when the technique was initially introduced in 1990; however, long-term results have been disappointing. Improvement in subjective symptoms predominates over objective voiding parameters. However, this is a minimally invasive procedure that can be performed under light anesthesia, even in high-risk patients. It has been to some extent supplanted since the development of urethral stents.
5. **Transurethral microwave therapy (TUMT).** Microwave energy (Fig. 6-7), applied to the prostate by specialized 22F transurethral probes, may be used to heat the prostate to 42° to 45°C. Clinical experience indicates that more than 60% of patients experience an improvement of symptoms and 75% have improvement in flow rate (about 3 mL/s). TUMT may be performed in an outpatient setting with only mild sedation and takes about 1 hour. It is important to note that the prostatic probe can treat only a length of 3.5 cm. Transrectal ultrasound (TRUS) assessment of the prostate should show a prostatic length of at least 3.5 cm to accommodate the prostatic probe. Thus, patients with smaller prostates are not candidates for TUMT. If the prostate is significantly longer than 3.5 cm, only 3.5 cm will be heated. Up to one-third of patients may have urinary retention after treatment that requires catheterization. Other complications include hematuria, urethral bleeding, and/or hematospermia; these are usually mild and self-limited. Patients may require repeated treatment after 1 to 4 years.

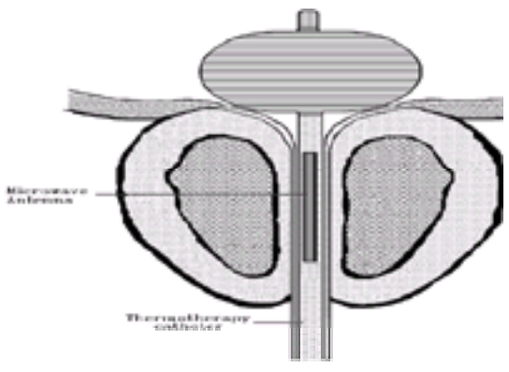

FIG. 6-7. Intraurethral catheter for thermotherapy of prostatic enlargement.

6. **Transurethral needle ablation (TUNA)** involves the transurethral application of radiofrequency energy at 490 kHz to the prostate lobes (Fig. 6-8A). This produces small areas of thermal injury that eventually produce changes in subjective symptoms, although the mechanism is unclear. There is no significant shrinkage of the prostate. About one-third of patients experience short-term urinary retention after TUNA. Symptomatic improvement is much more prominent than objective improvement, and long-term durability of the response is unclear. However, the procedure is well tolerated and can be performed under conscious sedation.

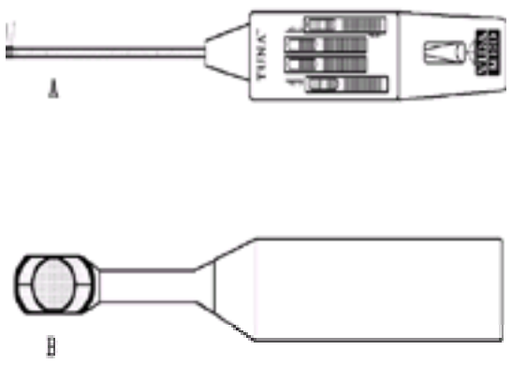

FIG. 6-8. A: Transurethral instrument for needle ablation of prostate (TUNA). **B:** Transrectal probe for high-intensity focused ultrasound (HIFU) treatment.

7. **High-intensity focused ultrasound (HIFU).** US energy can be focused with a parabolic reflector and is capable of producing significant thermal tissue injury. Current equipment consists of a rectal probe (Fig. 6-8B) that can image the prostate as well as emit HIFU. Because the patient must remain still during the treatment, general anesthesia is often required. Clinical efficacy is moderate, with flow increasing to an average of 13 mL/s at 1 year, but symptomatic improvement is significant. Most patients require some period of postoperative catheterization.
8. **Laser prostatectomy** offers several advantages over transurethral electrocautery resection of the prostate, including (1) lower morbidity and mortality rates and (2) cost savings through the ability to perform the procedure on an outpatient basis. The lower morbidity and mortality are a consequence of the sealing of blood vessels by the laser, which significantly reduces absorption of irrigating fluid as well as blood loss. To be effective, laser energy must be applied with sufficient energy to destroy prostatic tissue, but not so much as to produce charring of tissue. The three surgical approaches to laser prostatectomy are as follows:
   a. **Free-beam laser** energy may be delivered through a variety of side-firing laser-delivery fibers. These fibers may be passed through a 22F cystoscope. The neodymium-YAG laser produces light at 1,064 nm, which produces excellent coagulation and hemostasis. Neodymium-YAG laser prostatectomy is usually performed under regional, spinal, or general anesthesia. Local anesthesia with periprostatic infiltration of bupivacaine and lidocaine may also be used. Like most less invasive techniques, free-beam laser prostatectomy produces objective improvement in flow rate and postvoid residual, but not to the same extent as transurethral resection of the prostate (TURP). Laser prostatectomy produces significant prostatic edema that may actually increase bladder outlet obstruction immediately postoperatively. On the other hand, incontinence, retrograde ejaculation, and urethral stricture are extremely rare. The reoperation rate with 3 years of follow-up is about 5%, which is similar to that following TURP.
   b. **Contact laser** systems utilize neodymium-YAG or diode laser sources to heat a flexible contact fiber that is used to cut and coagulate tissue. There is no interaction between the laser and tissue. The contact laser can be used to perform bladder neck incision or prostatic ablation. Objective and symptomatic improvement is similar to that obtained with free-beam lasers. However, the reoperation rate at 1 year is about 15%.
   c. **Interstitial laser** systems utilize diode-source end-firing delivery fibers that are inserted directly into the prostatic adenoma to produce small spherical areas of tissue destruction. Applying laser heating for 3 to 5 minutes can produce areas of necrosis of 1.5 to 2 cm. Like free-beam lasers, interstitial lasers produce significant prostatic edema and may result in postoperative retention. Urethral catheterization for the first 5 days postoperatively is usually required. Objective and symptomatic results are similar to those obtained with other laser techniques.
9. **Transurethral incision of the prostate (TUIP)** is performed by making deep incisions through the bladder neck and prostate almost to the verumontanum. Orandi's original description included incisions at 5 and 7 o'clock, but other locations appear to work as well. Success seems to depend on adequate depth of the incisions, not their location. In addition, prostate size should not exceed 25 g and a significant median lobe should be absent. The main advantage of TUIP in comparison with TURP is shortened operating time, diminished blood loss, and diminished fluid absorption. In addition, TUIP has a much lower

incidence of retrograde ejaculation than does TURP. For the smaller gland, TUIP is at least as efficacious a treatment as TURP with lesser morbidity.

10. **Transurethral vaporization of the prostate (TUVP)** is a modified TURP in which a high-energy cutting current instantly heats and vaporizes prostatic tissue. Its main advantage is that fluid absorption is markedly less than with TURP. It is difficult to perform on very large glands. However, in treating large glands, one can use TURP initially to remove most of the obstructing tissue and then vaporize the remaining tissue with TUVP techniques.
11. **Transurethral prostatectomy (TURP).** This remains one of the most effective treatments for long-term control of adenomatous hyperplasia of the prostate. The prostate is resected by electrocautery from within the prostatic urethra. Irrigation with 3% sorbitol is used to maintain a clear visual field during the procedure. An average of 900 mL of irrigating fluid is absorbed into the extravascular and intravascular space through the prostatic capsule during TURP. Because the irrigating fluid is isotonic but electrolyte-free, the fluid absorption is manifested biochemically as hyponatremia, hypochloremia, and, in the case of glycine, hyperammonemia (see Chapter 5). Clinically, the patient complains of dyspnea and chest discomfort. There is accompanying hypertension, tachycardia, and mental confusion or obtundation. Although referred to as the post-TURP syndrome, these symptoms may in fact begin during the procedure or in the recovery room. See Chapter 5 for a discussion of treatment. The mortality rate following TURP is 0.5%. Immediate complications include sepsis and shock, hemorrhage (may require return to the operating room if severe), and perforation of the bladder or urethra with extravasation of urine. Pulmonary embolus may occur in the early postoperative period. Delayed complications include urethral stricture (10%), vesical neck contracture (10%), epididymitis or orchitis (2%), total permanent incontinence (1%), and erectile impotence (5%). Retrograde ejaculation occurs in approximately 50% of patients and should be discussed fully with the patient during the process of obtaining informed consent.
12. **Open prostatectomy.** Legitimate indications for open prostatectomy still exist, including prostatic enlargement beyond the capability of the surgeon to resect safely (generally more than 60 g), presence of **bladder calculi** not amenable to transurethral lithotripsy, and presence of **bladder diverticula** requiring excision. As in TURP, only the hyperplastic adenoma and not the entire prostate is removed. The choice of operative approach depends on the surgeon's preference, although there are also other considerations that apply:
    a. **Suprapubic prostatectomy** is performed through a suprapubic transvesical approach and is well suited to dealing with concomitant bladder pathology, such as diverticula and bladder stones. Postoperatively, a suprapubic tube is necessary until the bladder incision heals (5 to 7 days).
    b. **Retropubic prostatectomy** differs from suprapubic prostatectomy in that the prostate capsule rather than the bladder wall is incised to expose the prostate adenoma. Thus, there is usually no need for suprapubic bladder drainage postoperatively. The operation is poorly suited for glands that are not particularly large.
    c. **Simple perineal prostatectomy** is similar to the retropubic operation except the prostatic capsule is approached posteriorly through a perineal incision. Although little used today, it remains a valuable operative approach for patients who are obese or have pulmonary problems. Perineal prostatectomy is extremely well tolerated and avoids the postoperative complications associated with an abdominal incision.
13. **Preoperative preparation** in patients undergoing any type of prostatectomy, open or transurethral, involves several important considerations.
    a. Patients who are **uremic** (serum creatinine >1.5 mg/dL) have considerably increased morbidity and mortality rates from prostatectomy. For these patients, surgery should be delayed until urinary drainage permits improvement of their uremic state.
    b. **Specific antibiotic treatment** is indicated in patients who have bacteriuria or pyuria before prostatectomy. Whenever possible, one should obtain culture evidence of urinary sterilization before proceeding with prostatectomy.
    c. Blood loss in open prostatectomy tends to be higher than in TURP, and up to 5% of patients require blood transfusion. Patients undergoing open prostatectomy should have two units of autologous or bank blood available.
    d. An enema should be ordered the evening before surgery to ensure an empty rectum during the procedure and for the first few days postoperatively.
    e. Sleeping medication or an antianxiety agent may be needed the evening before surgery.
14. **Miscellaneous techniques.** When patients cannot undergo surgery or refuse surgical treatment, nonoperative temporizing measures should be considered.
    a. **Intermittent self-catheterization** is an excellent option in patients who are motivated, have good manual dexterity, and must await surgical treatment of benign prostatic enlargement.
    b. **Indwelling catheterization** is indicated in the short-term treatment (2 to 3 days) of acute urinary retention but is best avoided as a long-term solution. An indwelling catheter is associated with a high rate of bacteriuria and carries an increased risk for epididymitis, periurethral abscess, and generalized sepsis.
    c. **Suprapubic catheter drainage** as a temporizing measure may be accomplished by means of a Stamey cystotomy catheter.

C. **Detrusor overactivity**

1. **Pharmacologic therapy** remains the most commonly used therapy for detrusor overactivity (Table 6-4). Response rates vary from 25% to 80%, depending on how one defines a successful response. Decreasing urinary frequency and urgency is relatively easy, but complete cure of incontinence is much more difficult. Intolerance of side effects is a common limiting factor in the pharmacologic treatment of detrusor overactivity.

Generic name	Brand name	Dose forms	Dose	
			Initial	Maximum
oxybutynin chloride	Ditropan	5-mg tablets	1 tab tid	4 tabs daily
	Ditropan XL	5 mg/5 mL syrup	1 tspn tid (adult)	20 mg daily (adult)
	Ditropan syrup	5 mg/mL syrup	1 tspn bid (pediatric)	1 tspn tid (pediatric)
tolterodine tartrate	Detrol	1, 2-mg tablets	2 mg bid	2 mg bid
hyoscyamine sulfate	Levsin	0.125-mg tablets	1 tab q4h	12 tabs/24 h
	Levsin elixir	0.125 mg/5 mL elixir	1–2 tspn q4h (adult)	12 tspn/24 h (adult)
	Levsin elixir	0.125 mg/5 mL elixir	0.1–0.125 mL/kg (pediatric)	6 tspn/24 h (pediatric)
	Levsin injection	0.125 mg/1 mL injectable	0.5–1 mL SC, IM, or IV	
flavoxate hydrochloride	Urispas	100-mg tablet	1 tab tid	2 tabs qid
dicyclomine hydrochloride	Bentyl	10-mg capsules 20-mg tablets	20 mg qid	80 mg qid
	Bentyl syrup	10 mg/5 mL	2 tspn qid	4 tspn qid
	Bentyl injection	10 mg/mL	1–2 mL IM	
imipramine hydrochloride	generic	10, 25, 50-mg tablet	25 mg qid	50 mg qid

Table 6-4. Agents used in detrusor overactivity

    a. **Antimuscarinic/anticholinergic agents** include oxybutynin, tolterodine, hyoscyamine, and dicyclomine. Side effects such as dry mouth, blurring of vision, constipation, and drowsiness occur in more than 50% of patients receiving antimuscarinic agents. Indeed, patient dropout and noncompliance are major reasons for therapeutic failure. These agents are contraindicated in patients with angle-closure glaucoma. Tolterodine, a recently introduced antimuscarinic agent, has an efficacy similar to that of other agents but is much less frequently associated with dry mouth. Another advantage of tolterodine is twice-daily dosing as opposed to three or four times daily for most other agents. These differences may result in better patient compliance.
    b. **Antispasmodic agents.** Flavoxate is usually termed a spasmolytic agent, although its precise mode of action is unknown. Its adverse effect profile is similar to that of the antimuscarinic agents, including increased ocular tension.
    c. **Imipramine** is a tricyclic antidepressant found to have anticholinergic and sympathomimetic actions peripherally and serotoninergic effects centrally. It has long been used in the treatment of childhood enuresis but has considerable efficacy in adult detrusor overactivity. The drug may be used as first-line therapy or in combination with antimuscarinic agents. Imipramine is contraindicated in patients who are receiving monoamine oxidase inhibitors or who have severe hypertension.
2. **Biofeedback therapy** may be used alone or in conjunction with pharmacologic therapy. One simple biofeedback technique is the use of a voiding diary to record time and amount voided. The patient is rewarded with encouragement for increasing the time between voidings (Frewen regimen or “bladder drill”). More complex methods involve using urodynamic monitoring to provide auditory or visual feedback to the patient when bladder contractions occur. This enables the patient to learn techniques to suppress contractile activity. Success rates with biofeedback techniques vary from 30% to 80%, but there is a significant dropout rate of 40%.
3. **Electrical stimulation** of sacral nerves may be accomplished by intravaginal or intrarectal stimulating electrodes as well as implantable stimulators. The mechanism of electrical stimulation in modulating detrusor overactivity is unclear. It may promote urine storage by causing perineal muscle contraction, inhibiting detrusor activity, or blocking sensory input to the spinal cord. Recently, an implantable neuromodulator has been introduced that delivers low-level electrical stimulation to the S-3 nerve root. Initial trials with this device have been promising.

D. **Detrusor underactivity**

1. **Pharmacologic therapy** of detrusor underactivity is generally unsuccessful. Bethanechol chloride in oral doses of 50 to 100 mg four times daily is capable of increasing bladder wall tension, but the ability of this agent to produce effective bladder contractions has never been shown. However, it may be useful in selected cases as an adjunct to Valsalva or straining, especially in patients with intact bladder sensation. Side effects include flushing, sweating, headache, diarrhea, gastrointestinal cramps, and bronchospasm.
2. **Intermittent catheterization** is the best option for most patients with impaired voiding caused by detrusor underactivity. The patient must have some degree of manual dexterity and be motivated to carry out this form of treatment. See Chapter 3 for a discussion of catheterization technique.
    a. **Clean intermittent catheterization** does not require the use of sterile gloves or catheters. In male patients, the head of the penis is cleansed with povidone iodine, hexachlorophene, or soap, and a lubricated 14F straight catheter is inserted gently until urine flow is obtained (Fig. 6-9). In female patients, a short 12F or 14F catheter is used (Fig. 6-10). Any water-soluble lubricant can be used. The catheters may be cleaned with soap and water and

reused many times. For most patients, clean intermittent catheterization is the most convenient and cost-effective method of emptying the bladder.

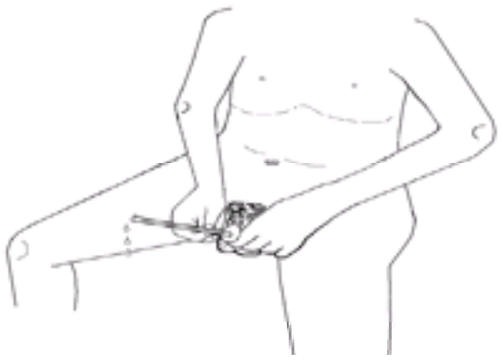

FIG. 6-9. Technique of clean intermittent catheterization in male patients.

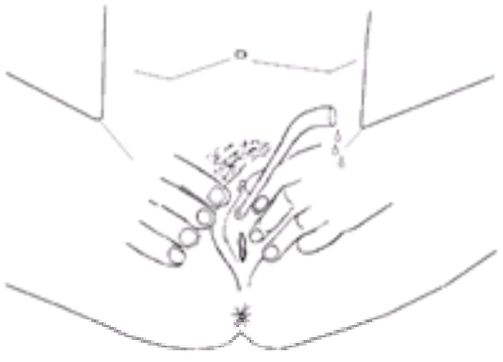

FIG. 6-10. Technique for clean intermittent catheterization in female patients.

b. **Sterile intermittent catheterization** differs from the clean technique in that sterile gloves are used during preparation of the skin and handling of the catheter, and a new catheter is used each time. This technique is indicated only in patients who are immune-compromised or who have had serious urosepsis while using the clean technique.

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Chapter 7 Hematuria and Other Urine Abnormalities

Caner Dinlenc and Mike B. Siroky

I. Interpretation of Urinalysis

A. **Urine specimen collection.** It is best to collect urine in the clinic or hospital rather than at home. Urine that is not freshly voided or has been collected in a drainage bag is unreliable for urinalysis.
   1. **Male adults.** Urine should be collected by the clean-catch midstream method. In uncircumcised male patients, the foreskin must be retracted and the meatus cleansed with an antiseptic solution such as povidone iodine, benzalkonium chloride, or hexachlorophene. The first 30 mL is passed without collection. The sterile specimen container is then placed into the urinary stream and approximately 50 to 100 mL is collected. The specimen container is capped immediately, and the urinalysis is performed as soon as possible after collection. The portion not used for urinalysis may be used for culture if indicated.
   2. **Female adults.** The technique is similar to that for male patients except that more effort and attention to detail are required. After the labia are separated with one hand, an antiseptic solution is applied to cleanse the urethral meatus. A wiping motion toward the perineum is used. After the first 25 mL is passed, the next 50 to 100 mL is collected in a sterile specimen container. If a satisfactory specimen cannot be obtained, catheterization should be used.
   3. **Children.** In very young patients, urine is usually obtained by cleansing the meatus with an antiseptic solution and placing a sterile plastic bag over the penis or vulva. Suprapubic needle aspiration of the bladder may be required to obtain a reliable urine specimen, and this is easily accomplished in young children because the bladder is located in a more intraabdominal position than in adults.

B. **Physical characteristics**
   1. **Color.** The normal yellow color of urine is caused by various amounts of urochrome, a product of hemoglobin degradation. The most important color abnormality is red or reddish brown urine, suggesting the presence of erythrocytes, hemoglobin, myoglobin, or pigments derived from medications or other substances (Table 7-1).

Table 7-1. Common causes of discolored urine

   2. **Turbidity or nontransparency** of the urine may be a consequence of phosphaturia, pyuria, chyluria, or bacteriuria.
   3. **Specific gravity and osmolality** are closely related measures of urine concentration. Specific gravity varies from 1.003 to 1.040, whereas osmolality varies from 50 to 1,200 mOsm/L. Excretion of heavy molecules such as radiologic contrast media or proteins may raise the specific gravity but not the osmolality of urine.

C. A variety of **chemical characteristics** of the urine may be tested by means of reagent dipsticks. Those of relevance to urology include pH, urine nitrite, leukocyte esterase, glucose, protein, and blood.
   1. The **pH** is a measure of renal concentrating ability and of reactions occurring in the urine. **Alkaline urine** (pH >6.5) is seen in renal tubular acidosis as well as in specimens obtained within 2 hours after a large meal or left standing at room temperature for several hours. Patients with infections caused by urea-splitting organisms (*Proteus* species, some *Escherichia coli*) tend to have particularly alkaline urine. **Acid urine** (pH <6.0) is seen in patients with uric acid calculi.
   2. **Bacteriuria** is detected by measuring urine nitrite levels. Many common intestinal bacteria contain nitrate reductase, an enzyme that converts urine nitrate to nitrite when exposed to urine for a minimum of 4 hours. Thus, best results are obtained on first-voided morning urine specimens. The test may produce a false-negative if the patient is voiding frequently, if the bacteria do not contain nitrate reductase, or if the urine contains low levels of nitrate. The presence of ascorbic acid in the urine may also produce a false-negative nitrite reaction.
   3. **Leukocytes** may be detected by measuring leukocyte esterase, an enzyme released when white cells lyse. A positive test result is equivalent to six or more leukocytes per high-power field. False-negative tests can occur in the presence of heavy proteinuria, glycosuria, or phenazopyridine, ascorbic acid, or nitrofurantoin in the urine.
   4. **Glucose** is spilled in the urine when the serum glucose level is 180 mg/dL or higher. Glycosuria may occur during pregnancy even with normal serum glucose levels. False-positive results may occur in the presence of aspirin, ascorbic acid, and cephalosporins.
   5. **Protein** excretion is estimated by measuring urinary albumin levels. The dipstick reaction is positive at albumin concentrations of 30 mg/dL or higher. The degree of proteinuria may be overestimated if the urine is extremely concentrated and underestimated if it is extremely dilute.
   6. **Blood.** The dipstick reagent reacts to hemoglobin (in red cells and free) as well as myoglobin. Thus, the reagent strip reaction is not specific for red cells. In general, more than three to five red cells per high-power field will produce a positive reagent-strip reaction. A false-positive test result may be caused by contamination with povidone iodine. Ascorbic acid in the urine may interfere with the reagent-strip reaction and give a false-negative result for hemoglobin. Microscopic examination of the urine can easily differentiate true erythrocyturia from other causes of positive reagent-strip reactions (Table 7-2).

Cause	Dipstick result	Microscopic result
Erythrocyturia	Positive	Positive
Myoglobinuria	Positive	Negative
Hemoglobinuria	Positive	Negative
Pigmenturia	Negative	Negative

Table 7-2. Differentiating the causes of red-colored urine

D. **Microscopic examination** is performed after centrifuging 10 mL of urine at 2,000 revolutions per minute for 5 minutes, discarding the supernatant, resuspending the sediment, and placing a drop of sediment on a glass slide for microscopy (Fig. 7-1).

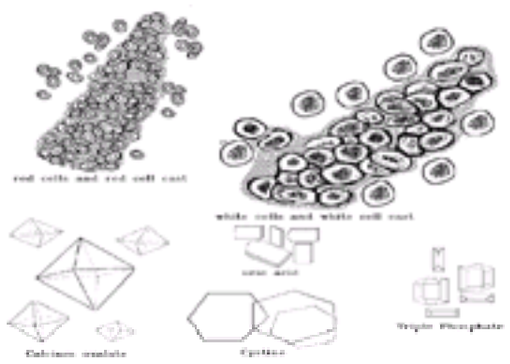

FIG. 7-1. Most common findings on microscopic examination of the urine.

1. **Red blood cells** are easily seen under the high-power (×400) lens of the microscope. The degree of microscopic hematuria is usually quantified as the number of red blood cells per high-power field. The finding of five or more red blood cells per high-power field should be considered abnormal. Red blood cell casts (Fig. 7-1) are cylindrical clumps of red cells in the shape of the renal tubules or collecting ducts and are indicative of a renal source (Fig. 7-1). Dysmorphic red cells are also highly suggestive of a glomerular source of hematuria.
2. **White blood cells** in the urine are indicative of inflammation anywhere along the genitourinary tract or even contiguous with genitourinary organs. More than five white blood cells per high-power field should be considered abnormal. White cell casts (Fig. 7-1) indicate a renal source. Leukocytes are often present in the urine without bacteriuria. The persistent presence of “sterile” pyuria should suggest the possibility of genitourinary tuberculosis.
3. **Crystals** are commonly seen on urine microscopy and are not pathologic as an isolated finding (Fig. 7-1). **Calcium oxalate** crystals look like small pyramids or squares and are seen in patients with calcium oxalate calculi or chronic inflammatory bowel disease. **Uric acid** crystals appear in acidic urine as small rectangular or rhomboid-shaped flat plates. So-called **triple-phosphate** or **struvite** crystals are composed of calcium-magnesium-ammonium phosphate and look like domed rectangles or coffin lids. These crystals precipitate only in urine that has a pH above 8. Such high pH levels generally occur only with infection caused by urea-splitting organisms. **Cystine** crystals occur in cystinuria when the urine pH falls below 7. The crystals appear as small plates with five or six sides, similar to a stop sign.

II. Hematuria

The causes of hematuria range from benign (exercise-related) to malignant (bladder carcinoma) (Table 7-3). Because the degree of hematuria bears no relation to the seriousness of the underlying cause, hematuria should always be considered a symptom of serious disease until proved otherwise. Hematuria is usually categorized as **gross** (visible to the unaided eye) or **microscopic** (more than five red cells per high-power microscopic field). Hematuria may be further characterized as initial, terminal, or total. Initial hematuria is said to indicate a source distal to the external sphincter, terminal hematuria has a source in the proximal urethra or bladder neck, and total hematuria has a source in the bladder or upper tract. Needless to say, the source of hematuria cannot be determined accurately from the history alone. **False hematuria** is discoloration of the urine from pigments such as food coloring and myoglobin. **Factitious hematuria** is the presence of red blood cells in the urine from a source outside the urinary tract (e.g., malingering). Patients attempting to obtain narcotic drugs often present with a history of renal colic substantiated by factitious hematuria. They may add blood to their urine after voiding and before presenting it for urinalysis.

Table 7-3. Some important causes of hematuria

Some causes of hematuria are summarized in Table 7-3. Because of the large number of diseases that may cause hematuria, it is helpful to categorize them as glomerular, renal, urologic, and hematologic. Approximately 20% of patients will have idiopathic hematuria even after exhaustive evaluation. Among patients with an identifiable cause, about one-third of instances are of renal origin and two-thirds are caused by middle or lower urinary tract lesions. The bladder is the source in 40% of patients with gross hematuria. Approximately 20% of patients with hematuria will be found to have a neoplasm, most commonly bladder carcinoma, 25% will have infections as the cause, and 20% will have calculi. The age, sex, and race of the patient are important indicators of the likely cause. In children, one should consider acute glomerulonephritis, urinary infection, and Wilms' kidney tumor. In men older than 60, bladder carcinoma and benign prostatic hyperplasia (BPH) are the most common causes of hematuria. In young female patients, cystitis is the most common cause. Hematuria is the most common presenting complaint of patients with sickle cell trait. This hematologic disorder accounts for approximately one-third of instances of hematuria in blacks.

A. **Diagnosis of hematuria.** When a patient presents with hematuria or a screening urinalysis shows a positive result for blood, the initial step is to establish the presence of red blood cells in the voided urine. This may not always be straightforward, as red coloration of the urine may be caused by erythrocyturia, hemoglobinuria, myoglobinuria, or pigmenturia (Table 7-1). Test results with the commonly available dipstick reagent strips will be positive in the presence of red cells, hemoglobin, or myoglobin, and thus they are not specific for erythrocyturia (Table 7-2). Only the microscopic examination can document the presence of red cells in the urine.
   1. **Three-glass test.** Modern radiologic and endoscopic techniques have reduced the need to perform the three-glass test, but it is still sometimes useful. Divide the urine specimen into initial, midstream, and terminal portions during collection. If red cells predominate in the initial portion, the source is most likely to be the anterior urethra, whereas predominance of red cells in the terminal portion would indicate a source in the posterior urethra. Approximately equal numbers of red cells in all three specimens would indicate a source in the bladder or upper urinary tract.
   2. **Urine culture and sensitivity** should be ordered to rule out infection.
   3. **Screening imaging studies.** We prefer ultrasound (US) imaging of the kidneys and bladder as the screening imaging study in most patients presenting with gross or microscopic hematuria (see Chapter 1). If US reveals hydronephrosis or the presence of stones, or if the upper urinary tract is not well visualized, retrograde pyelography should be carried out at the time of cystoscopy. The combination of US and retrograde pyelography eliminates the need for intravenous urography (IVU) in most but not all cases. IVU or computed axial tomography (CT) with contrast should be ordered if screening studies fail to reveal the cause of hematuria.
   4. **Cystourethroscopy** is indicated in all instances of hematuria. It is helpful in some instances to perform cystoscopy while the patient is bleeding to determine the site of bleeding. Biopsy specimens should be taken from any suspected lesions or areas. Retrograde pyelography, brush biopsy, or ureteroscopy may be performed in conjunction with cystoscopy.
   5. **Ureteroscopy** should be considered in instances of hematuria that can be localized to the upper urinary tract. A small biopsy forceps or a brush can be used to obtain tissue from any suspected areas.

6. **Urinary cytology** can be helpful in diagnosing urothelial malignancy. Cytologic results may be difficult to read in the presence of large amounts of blood in the urine. Urine cytology specimens from the upper tracts may be obtained by ureteral catheterization and barbotage with saline solution. The sensitivity of urine cytology is lower in low-grade tumors.
7. **Cancer-related proteins** specific for genitourinary malignancies have been developed in recent years. NMP-22 (Matritech) detects the nuclear matrix proteins shed during cell turnover in papillary transitional cell carcinoma, including carcinoma *in situ*. In patients with sterile urine, this test has a sensitivity approaching 86%. The bladder tumor antigen (BTA) test offers similar results and can be easily performed in the clinic or office in about 5 minutes. These tests can be used as substitutes for more expensive urinary cytology.

B. **Hematuria of obscure origin.** In approximately 20% of patients, no cause of hematuria can be identified even after extensive urologic evaluation. The question then becomes how to follow these patients. Never tell patients that there is “nothing wrong” or that their examination findings are “normal,” because an abnormality may turn up on future examination. It should be explained that the long-term significance of their persistent hematuria is unknown and that close follow-up is required. If an episode of gross hematuria develops, cystoscopy should be performed urgently in an attempt to visualize the source of bleeding. If the bleeding can be localized to one side, angiography or ureteroscopy should be considered. A careful drug history should be taken, with particular attention to occasional use of aspirin and nonsteroidal analgesics, which can induce coagulopathy. As long as microscopic hematuria persists, the patient must be followed by urinalysis and urinary cytology every 6 months. Renal US should be performed at 1- to 2-year intervals. If cytology becomes abnormal, cystoscopy is indicated.

C. **Specific causes of hematuria**
1. **Nephropathy and nephritis.** In children, glomerulonephritis accounts for about one-half of instances of hematuria. Most of the glomerulopathies cause hematuria and usually proteinuria as well. Proteinuria of significant degree (more than 2+) is very suggestive of glomerular disease, as is the presence of casts of red cells.
   a. **Acute poststreptococcal glomerulonephritis** occurs when circulating antibody-antigen complexes are trapped in the glomeruli. This type of glomerulonephritis occurs most commonly in children ages 3 to 10 years following streptococcal pharyngitis or impetigo. Approximately 2 weeks after the initial infection, the patient usually presents with fever, headache, and mild hypertension. Urinalysis reveals erythrocyturia, mild proteinuria, and casts. Frequently, serum antistreptolysin-O titers (ASL-O) are elevated and total serum complement levels are decreased. More than 95% of instances resolve spontaneously; serious renal insufficiency may develop in 58%.
   b. **Benign essential hematuria (Berger's disease)** is a form of acute focal glomerulonephritis seen predominantly in male patients between the ages of 12 and 55 (mean age at presentation, 25 years). This disorder, which is associated with the deposition of immunoglobulin A (IgA) and occasionally IgG in the glomerular mesangium, is also called **IgA nephropathy.** Typically, the patient presents within 1 to 3 days after an acute upper respiratory infection or other viral illness with a presenting complaint of gross hematuria (45%), incidentally discovered microscopic hematuria (30%), or proteinuria (20%). Almost all patients have proteinuria in excess of 0.5 g/d. Patients with Berger's disease tend to suffer recurrent episodes of gross hematuria with repeated viral infections and show persistent microscopic hematuria (often with casts of red cells) between relapses. Unlike the urine specimens of family members of patients with benign familial hematuria, the urine specimens of family members in this case are normal. Although most patients suffer no loss of renal function, in approximately 25% a slowly progressive renal failure associated with hypertension develops over a period of years. No specific treatment is available for this disorder.
   c. **Benign familial hematuria.** Between 25% and 50% of children investigated for idiopathic hematuria are found to have family members with microscopic hematuria. The disorder may affect patients of any age (mean age, 32 years), has a 2:1 female predominance, and is inherited as an autosomal dominant trait. The only means of making this diagnosis is by obtaining a urinalysis from the siblings and parents of patients found to have idiopathic hematuria. Proteinuria may be found in approximately 50% of patients; however, this condition, unlike Berger's disease, is usually associated with a minimal degree of proteinuria. The condition appears to have no long-term implications of renal disease.
   d. **Alport's syndrome,** also called progressive familial nephropathy, is characterized by familial renal failure and deafness. The disease predominantly affects younger male patients (mean age, 13 years). Hematuria occurs in about one-third of patients, and significant proteinuria is very common.
   e. **Goodpasture's syndrome** is characterized by hemoptysis, malaise, headache, and hematuria. The urine shows gross or microscopic hematuria, and renal function is abnormal. The disorder is thought to be caused by the deposition of antibodies against glomerular basement membrane in glomeruli and in the lung. Treatment involves high-dose corticosteroids and immunosuppressive agents.
2. **Exercise.** Hematuria accompanied by proteinuria and casts of red cells in the urinary sediment may occur after strenuous exercise, such as swimming, running, and team sports. All patients should be questioned regarding exercise when the history is taken. Even if exercise is temporally related to the onset of hematuria, exercise hematuria remains a diagnosis of exclusion after a complete workup has been performed.
3. **Sickle cell anemia.** This congenital disorder is caused by replacement of hemoglobin A with hemoglobin S, a less soluble molecule that is prone to polymerization (sickling) when exposed to low oxygen tension, low pH, or both. Patients with the homozygous form (hemoglobin SS; **sickle cell disease**), encountered rarely by urologic physicians, have severe anemia; intermittent vascular crises involving the chest, abdomen, and skeleton; and repeated infections (pneumococcal pneumonia, gram-negative osteomyelitis). There is no specific treatment, and these patients usually do not survive past the age of 30. The heterozygous form (hemoglobin SA, S-thalassemia, and SC; **sickle cell trait**) is present in approximately 8% of American blacks and can occur in white persons as well. Except for causing a mild renal tubular concentrating defect, sickle cell trait is generally asymptomatic; however, these patients are prone to episodes of hematuria of renal origin. The bleeding is probably related to the hypoxic, hypertonic, and acidotic conditions that prevail in the renal medulla. With onset of the sickling phenomenon, arteriolar obstruction leads to papillary necrosis and hematuria. For reasons not understood, bleeding occurs four times more often from the left kidney than the right and is slightly more common in female patients. In approximately 50% of instances, the patient will give a past history of episodes of self-limited gross hematuria.
   a. **Diagnosis** is easily accomplished by the sickle cell preparation. If the result of this test is negative and sickle cell trait is still suspected, hemoglobin electrophoresis should be ordered; however, the presence of sickle cell trait in a black patient does not establish this as the sole cause of bleeding. In one series, approximately 30% of patients with sickle trait hematuria were found to have infection or malignancy as a cause of bleeding. Thus, one must guard against ascribing all hematuria in black patients to the presence of sickle cell trait and carry out a complete urologic investigation, including appropriate radiologic studies and cystoscopy. At the same time, one must consider the possibility of sickle cell trait in white patients with hematuria of obscure origin.
   b. **Treatment** of sickle cell-associated hematuria involves nonspecific measures in many instances because the hematuria often resolves spontaneously. Such measures include bed rest, IV fluids, and oral or parenteral alkali therapy. Oxygen by nasal cannula probably has little effect on the oxygen tension in the renal medulla but is widely used nevertheless. For patients who do not respond to these measures, specific modalities aimed at reducing the tonicity, acidity, and low oxygen tension in the renal medulla have been described.
      1. **Infusion of distilled water** (500 mL over 15 minutes IV) is a safe procedure that reportedly can quickly terminate an episode of hematuria caused by sickling. For reasons that are not clear, the risk for producing intravascular hemolysis in patients with hemoglobin S is minimal.
      2. **Urinary alkalinization** has a sound physiologic basis in this disorder. Two grams of sodium bicarbonate orally four times daily or one ampule per 1,000 mL of IV fluid should adequately alkalinize the urine.
      3. **Diuretics** act to decrease the hypertonicity of the renal medulla. Both loop diuretics (ethacrynic acid, furosemide) and osmotic diuretics (mannitol, urea) are effective.
      4. **e-Aminocaproic acid (EACA)** is a potent inhibitor of urokinase, an enzyme that causes fibrinolysis in the urinary tract. EACA prevents dissolution of clots in the urinary tract and thus promotes hemostasis. For this reason, it has been used widely in many forms of urologic hemorrhage, including that caused by sickle hemoglobinopathies. The presence of disseminated intravascular coagulation must be ruled out before EACA is used. EACA is equally effective orally or IV for bleeding caused by sickle cell trait. An initial dose of 5 g IV is followed by a continuous infusion of 1 g/h. Hematuria usually ceases within 2 to 3 days of initiation of therapy. Maintenance therapy of 4 g orally four times daily should be continued for at least 6 weeks. The major side effect of EACA therapy has been ureteral obstruction from clots.
      5. **Local irrigation** with hemostatic agents such as oxychlorosene or silver nitrate may be effective in difficult cases. Irrigation through a ureteral catheter with 100 mL of 0.1% oxychlorosene or 1% silver nitrate has been reported to stop bleeding quickly.
4. **Hemorrhagic cystitis** associated with cyclophosphamide, ifosfamide, and radiation therapy may sometimes cause life-threatening bladder hemorrhage. **Radiation cystitis** occurs in approximately 10% of patients who have received pelvic radiation, but only a small number experience severe bladder hemorrhage. **Cyclophosphamide (Cytoxan)** and **ifosfamide** are alkylating agents whose toxic metabolite (acrolein) is excreted in the urine. Gross hematuria occurs in about 12% of patients receiving these agents and is dose-dependent. In most instances, the bleeding is self-limited (48 hours in duration), and the patients require transfusion of only 2 units. **Mesna** (2-mercaptoethanesulfonic acid) may provide prophylaxis against hemorrhagic cystitis caused by ifosfamide. The dose is 20% of the ifosfamide dose IV and is given 4 to 8 hours after each chemotherapy infusion. The **treatment** of hemorrhagic cystitis is as follows:
   a. **Cystoscopy** under anesthesia (spinal or general) should be performed if bleeding persists. All clots must be evacuated and whatever bleeding can be identified cauterized.
   b. **One percent alum** in sterile water is often effective. Alum is an aluminum salt that causes precipitation of proteins without systemic effects. Anesthesia is not required to administer intravesical alum, and it may be used at the bedside. The solution is administered continuously through a large-caliber three-way Foley catheter at a rate of 1 L/8 h.
   c. **EACA** may be effective in controlling bladder hemorrhage. The presence of disseminated intravascular coagulation must be ruled out before EACA is

used. The drug is given orally (loading dose of 5 g followed by 1 g/h for 8 hours), IV (loading dose of 5 g in 250 mL of diluent over the first hour followed by 1 g/h over 8 hours), or intravesically (5 g in 1 L of saline solution for bladder irrigation infused over 3 to 4 hours).

d. **Silver nitrate** induces thrombosis in bleeding vessels in the bladder mucosa but is milder than formalin. Under general or spinal anesthesia, 200 mL of 1% silver nitrate solution is placed in the bladder through a urethral catheter and drained after 15 minutes. The bladder is continuously irrigated with normal saline solution over the next 48 hours.

e. **Formalin** is a solution of gaseous formaldehyde in water. Because the maximum solubility of formaldehyde in water is 38%, such a solution is called 100% formalin. A 1% formalin (0.38% formaldehyde) solution is recommended for bladder irrigation; higher concentrations are likely to cause severe bladder necrosis and fibrosis. The following protocol is recommended:
   1. Under anesthesia (general or spinal), **all clots are evacuated** and a **cystogram is obtained** to assess the integrity of the bladder and rule out vesicoureteral reflux. Intravesical formalin is contraindicated in the presence of reflux but may be used if occlusive ureteral catheters are placed.
   2. With the Foley catheter drawn tightly against the bladder neck, 1% formalin is poured into the barrel of a Toomy (catheter-tip) syringe held 15 cm above the pubis and allowed to run into the bladder by gravity drainage. After 3 minutes, the bladder is drained completely by gravity. The formalin irrigation may be repeated until a total of 1,000 mL of formalin solution has been used.
   3. After formalin irrigation is completed, the bladder is washed with 1,000 mL of distilled water.

f. **Urinary diversion.** If the measures described are not successful, the patient should be returned to the cystoscopy room under anesthesia (preferably epidural or spinal) for placement of bilateral ureteral catheters or stents to divert the urine. For reasons that are not clear, urinary diversion has been observed to reduce or eliminate urinary bleeding. Cutaneous ureterostomy should be considered if permanent diversion is required.

5. **Hematuria associated with anticoagulation.** Hematuria occurs in 5% to 10% of patients receiving anticoagulation with heparin or sodium warfarin despite the fact that the coagulation levels are well within therapeutic range in most of these patients. About 25% of such patients have urologic cancer diagnosed on investigation of their hematuria. An additional 50% have benign urologic lesions causing hematuria, such as BPH, urethral stricture, and ureteral calculus. Thus, the onset of hematuria in a patient receiving anticoagulation has the same (if not greater) significance as in another patient and mandates a complete urologic evaluation.

6. **Coagulopathies presenting as hematuria.** Patients with hematuria of obscure origin should be screened for the presence of a coagulopathy. The prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), platelet count, and bleeding time should be determined. If coagulopathy is suspected, hematologic consultation is indicated. Although any coagulopathy may present as hematuria, the most common problems are the following:
   a. **Thrombocytopenia.** In general, bleeding problems are not encountered in patients with platelet counts above 50,000/µL. Decreased production of platelets in bone marrow may be drug-induced (antineoplastic agents, thiazide diuretics, estrogens, alcohol) or may be caused by replacement by malignancy (prostate cancer). Increased peripheral destruction of platelets occurs in idiopathic thrombocytopenic purpura and in disseminated intravascular thrombosis. In instances of splenomegaly, platelets may be sequestered in the spleen, causing peripheral thrombocytopenia (hypersplenism).
   b. **Hemophilia** is caused by congenital deficiency of factor VIII or factor IX. Deficiency of factor VIII is five times more common than deficiency of factor IX. Although hemarthrosis is the most common problem, approximately 30% of patients with hemophilia have hematuria, which can be a severe problem causing ureteral obstruction by clots. Both conditions are treated by infusion of fresh frozen plasma or cryoprecipitate. Factor VIII and factor IX concentrates are reserved for patients with severe hemophilia.
   c. **von Willebrand's disease** is a congenital deficiency of factor VIII characterized by prolongation of PTT and bleeding time with a normal platelet count. Spontaneous bleeding is rarer than in hemophilia. Treatment is administration of cryoprecipitate or fresh frozen plasma.
   d. **Disseminated intravascular coagulation** may result from sepsis, metastatic carcinoma (prostate, breast, gastrointestinal), liver disease, surgery, obstetric complications, massive trauma, or burns. Laboratory diagnosis is based on consumption of coagulation factors and platelets with elevated titers of fibrin degradation products. Treatment is based on correcting the underlying disorder and use of heparin in some instances.
   e. **Primary fibrinolysis** implies the destruction of fibrin in the absence of underlying coagulation and is extremely rare. It is said to occur in carcinoma of the prostate and during extracorporeal circulation. Treatment involves a combination of EACA and heparin because there is frequently an accompanying thrombotic process. Fresh frozen plasma is used to replace coagulation factors that have been consumed.

Suggested Reading

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Chapter 8 Evaluation of Renal Mass Lesions

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Renal masses are a common clinical problem, often detected in asymptomatic patients. The frequency of masses found incidentally by radiographic studies is increasing as studies with ultrasonography (US), computed axial tomography (CT), and magnetic resonance imaging (MRI) are becoming more routine. Primary masses originate from the renal parenchyma, connective tissue, and urothelium. These lesions can be classified as solid or cystic, malignant or benign, acquired or congenital, unilateral or bilateral, single or multiple, and primary or metastatic (Table 8-1). This chapter describes a systematic approach to the differential diagnosis of renal masses (Fig. 8-1).

Solid renal masses
Benign lesions
Angiomyolipoma
Oncocytoma
Xanthogranulomatous pyelonephritis
Mesoblastic nephroma
Benign mesenchymal tumors
Malignant lesions
Renal adenocarcinoma
Nephroblastoma (Wilms' tumor)
Sarcoma
Metastatic lesion
Cystic renal masses
Benign lesions
Simple cyst
Polycystic kidney
Multicystic kidney
Multilocular cystic nephroma
Calyceal diverticulum
Malignant lesions
Cystadenocarcinoma
Cystic necrosis of renal carcinoma
Renal carcinoma arising in simple cyst

Table 8-1. Renal mass lesions

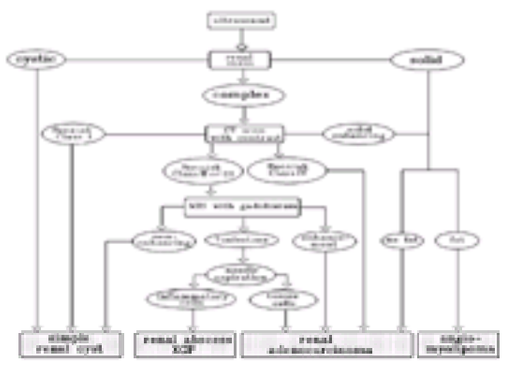

FIG. 8-1. Diagnostic decision tree for evaluation of a renal mass. For masses found to be solid on ultrasound, computed axial tomography is indicated for evaluation of metastatic disease but not necessarily for diagnosis. Other possibilities not shown in the diagram should be considered, including transitional cell carcinoma, metastatic lesions to the kidney, and retroperitoneal and adrenal tumors.

I. Solid Renal Masses

A. **Benign lesions**

1. **Angiomyolipoma (AML)** is a rare parenchymal renal mass accounting for fewer than 0.5% of all renal tumors. A benign renal hamartoma, it is composed histologically of angiomatous, adipose, and smooth-muscle elements. The adipose tissue constitutes up to 80% of the tumor bulk. Most of the adipose tissue is of the “mature” type, giving a negative attenuation coefficient on CT.
   a. **Clinical diagnosis** of AML is often difficult. From 20% to 50% of patients presenting with AML have **tuberous sclerosis**, also called **Bourneville's disease**, which is characterized by epilepsy, mental retardation, adenoma sebaceum, retinal phakomas, and hamartomas of the kidneys, brain, and other viscera. Two genes associated with tuberous sclerosis have been located, TSC1 at 9q34 and TSC2 at 16pl3. In patients with tuberous sclerosis, AMLs tend to be bilateral, multifocal, large, and symptomatic. The retroperitoneal lymph nodes, liver, or spleen may also contain these tumors, indicating multifocality rather than metastases. In the absence of tuberous sclerosis, lesions are usually large, unilateral, and unifocal, and often affect middle-aged women. There are reports of mutation in the TSC2 gene within the lesion of these sporadic cases. AML is most commonly asymptomatic but can present as flank pain or hypotension resulting from hemorrhage into the mass. Other presentations include flank fullness, gastrointestinal symptoms from compression, and hematuria.
   b. **Radiologic diagnosis** is often difficult. US, CT, and MRI are helpful in distinguishing AML from renal cell carcinoma because of the high fat content. A plain abdominal film may demonstrate a soft-tissue mass with radiolucent areas in 10% of instances. Intravenous urogram (IVU) will show unilateral or bilateral space-occupying lesions, occasionally distorting the collecting system. US images areas of increased echogenicity secondary to adipose tissue, hemorrhage, or necrosis within the tumor. Renal arteriography yields a characteristic “onion peel” appearance, although the test cannot reliably distinguish AML from renal adenocarcinoma. In both, there may be a hypervascular mass, tortuous vessels, microaneurysms, and arteriovenous fistulae. CT is currently the most accurate means of diagnosing an AML. The large amount of fat within an AML produces areas of low radiographic density characterized by a negative CT attenuation coefficient as measured in Hounsfield units (HU). AML may rarely be confused with lipoma and liposarcoma. False-negative results of CT may occur if nonadipose tissue or denser, “immature” adipose tissue elements predominate. T_1-weighted MRI will show high signal intensity because of the adipose tissue within the tumor.
   c. **Treatment** of AML diagnosed preoperatively is usually conservative (observation for change in size and new lesions). If hemorrhage occurs, blood transfusion and selective arterial embolization may obviate the need for surgery. Some advocate observation for tumors less than 4 cm. Enucleation or partial nephrectomy should be considered for elective surgical treatment of symptomatic lesions or those greater than 4 cm in diameter. Nephrectomy is indicated for life-threatening hemorrhage that cannot be otherwise controlled.
2. **Renal oncocytoma** is an epithelial neoplasm of intercalated cells of the collecting duct. Oncocytoma rarely metastasizes. It accounts for approximately 3% to 7% of solid renal masses. The lesion is well-circumscribed, encapsulated, and of variable size, with most between 5 and 10 cm in diameter. Grossly, the tumor may contain fibrous bands in a stellate pattern. On a microscopic level, it is characterized by sheets of polygonal cells with finely granular eosinophilic cytoplasm (oncocytes). Ultra-structural analysis demonstrates an overwhelming abundance of mitochondria within each cell. Tumor-suppressor genes have been mapped to 1p, Xq and two loci on 14q.
   a. **Clinical diagnosis.** Nearly 80% of renal oncocytomas are asymptomatic and found incidentally. Others are discovered because of hematuria, a palpable mass, or flank and/or abdominal pain. There is no known association with other diseases. In up to 6% of instances, oncocytoma may occur bilaterally.
   b. **Radiologic diagnosis** is difficult because IVU, renal US, and CT can raise the suspicion of oncocytoma but cannot reliably differentiate oncocytoma from renal adenocarcinoma. Angiographically, there may be suggestive findings, such as the “spoke wheel” pattern, in which vessels radiate toward the center

from a sharp, smooth margin with a lucent rim. CT of large oncocytomas may demonstrate a low-density central area caused by scarring.

c. **Treatment** for renal oncocytoma depends on the size and location of the tumor. If the tumor is very large or located in the hilum of the kidney, radical nephrectomy is indicated because the lesion is not amenable to more conservative excision. If the lesion is small and peripherally located, enucleation or partial nephrectomy may be a reasonable alternative. High-grade elements in the tumor dictate close follow-up to detect local regrowth or metastases.

3. **Xanthogranulomatous pyelonephritis (XGP)** is an atypical chronic bacterial pyelonephritis that can mimic renal carcinoma radiographically. Microscopically, lipid-laden macrophages are the predominant cell in this reactive tissue lesion. In 50% to 80% of instances, obstructing renal or ureteral calculi are found. Positive urine cultures for *Escherichia coli* (40%) and *Proteus mirabilis* (29%) are present in up to 70% of patients. *Klebsiella*, *Pseudomonas*, and *Bacteroides* may also be implicated. The disease not infrequently is also associated with diabetes mellitus and previous urologic surgery. Women, typically middle-aged, are affected three times as frequently as men. Infection proximal to an obstructing calculus presumably stimulates this bizarre inflammatory process. Grossly, diffuse replacement of the entire kidney by lobulated yellow masses occurs, although only focal involvement is found in 17% of instances. Occasionally, XGP penetrates Gerota's fascia into the perinephric space.
   a. **Diagnosis.** It should be noted that patients with XGP have many constitutional symptoms, such as weight loss and anorexia. A syndrome of liver dysfunction may occur in XGP as well as in renal adenocarcinoma. The differential diagnosis rests on the presence of irritative symptoms of the lower tract, leukocytosis, pyuria, and infection in XGP. IVU demonstrates a poorly functioning or nonfunctioning kidney, with hydronephrosis in 75% of patients and calculi in 50% to 80%. Focal lesions may show calyceal distortion only. US shows diffusely enlarged kidneys with obstruction of the collecting system; calculi and purulent collections may be imaged as well. CT with contrast demonstrates an enlarged, nonfunctioning, hydronephrotic kidney with stones and sometimes abscess cavities. Areas of lipid concentration may manifest as a negative attenuation coefficient. The extent of local perinephric extension can be assessed by CT. Angiographically, XGP may mimic many of the features of renal adenocarcinoma, including neovascularity and vessel encasement.
   b. **Treatment** in instances of diffuse involvement requires nephrectomy with excision of any perinephric tissue involved by XGP. Focal disease may be successfully treated by partial nephrectomy in selected patients. Recently, there have been reports of focal XGP being successfully treated nonoperatively.
4. **Congenital mesoblastic nephroma (CMN)** is the most common solid renal mass in neonates. This tumor is thought to arise during development from multipotent blastema. It is usually unilateral, and there tends to be a male predominance in incidence. Histologically, sheets of connective tissue are seen. In contrast to Wilms' tumor, CMN infiltrates the surrounding tissue rather than forming a pseudocapsule.
   a. **Diagnosis.** CMN usually occurs at less than 1 year of age, whereas Wilms' tumor is rare in this age group. The lesion generally presents as a firm abdominal or flank mass at birth or soon thereafter.
   b. **Treatment** is controversial. Total removal is curative, but some advocate enucleation or even observation. The presence of an aggressive cellular element of CMN would dictate more aggressive therapy.
5. **Benign mesenchymal tumors**, including fibromas, lipomas, leiomyomas, and hemangiomas, are extremely rare and usually asymptomatic. Treatment is usually the same as that for renal adenocarcinoma because the diagnosis is unknown preoperatively. Another rarely reported tumor is the **juxtaglomerular tumor**, which is considered benign but causes hypertension because of renin secretion.

B. **Malignant lesions**

1. **Renal adenocarcinoma**, also known as renal cell carcinoma, makes up 85% of primary renal malignancies and 3% of all cancers in the United States. Males predominate by a 2:1 margin, with peak incidence in the fifth to sixth decades of life, although the tumor is known to occur rarely in children and adolescents. There is a strong association with von Hippel-Lindau disease (cerebellar hemagioblastomas, angiomatosis of the retina, and tumors or cysts of the pancreas), and renal adenocarcinoma eventually develops in 40% to 60% of affected persons, often bilaterally. In families afflicted with this disorder, gene analysis has shown loss of heterozygosity at 3p25, the site of the VHL (von Hippel-Lindau) gene. In sporadic cases of renal adenocarcinoma, the tumor cells demonstrate allelic loss at the VHL gene and 3pl2-14. In patients with tuberous sclerosis, a 2% incidence of renal cell carcinoma has been cited. There is also an association with various environmental factors, such as exposure to asbestos, lead, and cadmium, use of tobacco, and a diet high in animal fat.

   Renal adenocarcinoma arises from proximal renal tubular cells and is divided histologically into clear, granular, and spindle or sarcomatoid cell types. Solid, papillary, and cystic forms are recognized. The term **renal adenoma** describes tumors that have the same histology as renal adenocarcinoma but are less than 3 cm in diameter. The malignant potential of such small tumors is debated. Tumors with a papillary histologic pattern tend to be hypovascular and may present problems in diagnosis.

   a. **Clinical diagnosis** is sometimes difficult; in at least one-third of patients, the presentation is nonurologic (e.g., hypertension, hypercalcemia); hence, it is often called the internist's tumor. The classic triad of symptoms—abdominal or flank pain, palpable mass, and hematuria—is now seen in fewer than 10% of patients on presentation. The most common presentation is hematuria (60%), followed by flank mass (45%) and flank pain (40%) (Fig. 8-2).

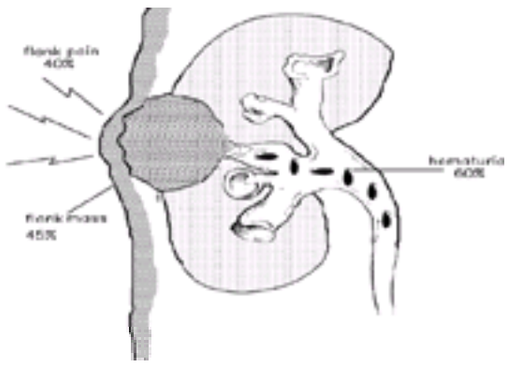

FIG. 8-2. Common presenting symptoms of renal cell carcinoma.

   b. **Radiologic diagnosis**
      1. **Plain film** of the abdomen may show renal enlargement, distortion, or axis shift. Renal adenocarcinoma may contain calcifications in 10% to 20% of cases.
      2. On **IVU**, distortion or obstruction of the urinary collecting system may be seen. Loss of the demarcation between kidney and perirenal fat may also be noted.
      3. **US** has come to play an important role in diagnosis of lesions by virtue of its safety, accuracy, and relatively low cost. Renal US can determine whether a mass is solid or cystic, the patency of the renal vein and inferior vena cava, and the presence of enlarged retroperitoneal nodes. US is also useful as an imaging modality for fine-needle aspiration of cystic renal lesions.
      4. **CT** allows differentiation of cystic from solid masses, determination of the local extent of the tumor, visualization of the renal vein and inferior vena cava, and examination of possible sites of metastatic disease, such as adrenals, liver, contralateral kidney, and lymph nodes. Characteristically, renal tumors show some degree of “enhancement” on CT following injection of contrast, whereas renal cysts do not. Renal tumors can be hypodense or isodense, with an attenuation coefficient similar to that of renal parenchyma (15 to 40 HU), whereas the coefficient of cysts ranges from -5 to 20 HU. Currently, CT is the most efficient examination, as it provides both diagnostic and staging information.
      5. **Angiography.** Since the advent of CT, arteriography is used only in selected patients, showing neovascularity, microaneu-rysms, arteriovenous shunting, and venous pooling of contrast within the tumor. Visualization of tumor vessels is enhanced by intraarterial injection of epinephrine, which constricts normal but not neoplastic vessels. Focal XGP may also manifest neovascularity and present problems in differential diagnosis. Although accuracy approaches 95%, problems arise in the diagnosis of necrotic tumors and the 10% of renal adenocarcinomas that are hypovascular.
      6. **MRI** can be used in patients who have contraindications to the administration of contrast or whose CT findings are indeterminate. The comparison of T_1- and T_2-weighted images usually shows an intense appearance on T_2 and an appearance on T_1 similar to that of normal renal parenchyma.
      7. **Radionuclide scans** may provide information on the function and vascularity of a mass lesion and may be useful in distinguishing between a small renal cell carcinoma and a hypertrophied column of Bertin, for example.
      8. **Fine-needle aspiration** of renal masses guided by fluoroscopy, US, or CT is sometimes necessary to determine the nature of a mass lesion. Fluid that is clear or straw-colored, contains no malignant cells by cytologic examination, and has a low lipid and cholesterol level is consistent with a benign renal cyst. A diagnosis of malignancy can be made if tumor cells are seen in the aspirate, but their absence does not rule out tumor. The presence of inflammatory cells is suggestive of renal abscess or XGP.
   c. **Treatment** is based on stage, size, location in the kidney, number of lesions, and bilaterality. When nephron-sparing surgery is indicated, partial nephrectomy and enucleation of the tumor may be considered. If the location of the tumor renders it amenable to partial nephrectomy, this can be an attractive alternative to radical nephrectomy; however, radical nephrectomy is still the treatment of choice in most situations if the contralateral kidney is

normal. Immunotherapy, chemotherapy, and radiation for metastatic disease have yielded discouraging results to date.

2. **Wilms' tumor (nephroblastoma)** is a malignant renal tumor that occurs predominantly in children and rarely in adolescents and adults. The annual incidence is approximately eight cases per million children, with a peak at 3 years of age. Common presenting signs and symptoms may include the presence of a palpable mass (around 80%), abdominal pain (30%), constitutional symptoms of malaise or fever (50%), and gross or microscopic hematuria. CT and serum neuroendocrine markers help to distinguish Wilms' tumor from other important childhood tumors, such as neuroblastoma. Treatment with a combination of extirpative surgery, chemotherapy, and radiation therapy yield a survival greater than 90%. (See Chapter 19 for further discussion.)
3. **Sarcomas** of the kidney are rare, making up 1% to 3% of all renal tumors. These include liposarcoma (most common), leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, neural sarcoma, and hemangiopericytoma. The **diagnosis** of renal sarcoma is generally not possible preoperatively because the symptoms and signs are indistinguishable from those of renal adenocarcinoma. The **treatment** of localized renal sarcoma is nephrectomy, although the rate of local recurrence, especially with liposarcoma, is high, and the prognosis is extremely poor.
4. **Metastatic lesions** in the kidney are usually asymptomatic and discovered incidentally at autopsy. The most common primary site is lung, followed by breast, stomach, pancreas, colon, and cervix.

II. Cystic Renal Masses

Although most renal cysts are benign, occasionally benign cysts may contain blood or thickened septa that make differentiation from carcinoma difficult.

A. **Benign lesions**
1. **Simple renal cysts** are extremely common and present in 50% of autopsy specimens from patients above 50 years of age. CT studies demonstrate that the prevalence and size increase with age. Renal cysts are most commonly single, unilateral, and located in the cortex in the lower pole of the kidney. Approximately 95% contain clear amber fluid, but 5% contain hemorrhagic fluid. Calcification occurs rarely but is more typical of renal carcinoma.
   a. **Clinical diagnosis** is rarely possible because most cysts are asymptomatic and discovered incidentally. Sudden bleeding into the cyst may produce acute flank pain. Vague gastrointestinal symptoms may be caused by a renal cyst. If infected, renal cysts may manifest with flank pain and fever. Hematuria and hypertension should provoke a thorough workup for renal adenocarcinoma. Rarely, adenocarcinoma arises in the wall of a benign renal cyst.
   b. **Radiologic diagnosis** is usually readily accomplished. Plain abdominal film may show distortion of the renal outline or a change in the renal axis. IVU demonstrates a sharply demarcated, nonfunctioning spherical mass with a thin outer wall. One or more calyces and infundibula may be displaced, obstructed, or obliterated by the mass. A lip of normal parenchyma extending onto the cyst wall constitutes the “beak” sign and is suggestive of a benign renal cyst. **US** demonstrates a space-occupying lesion without internal echoes, increased through echo transmission, and smooth, well-defined walls. The accuracy rate of US in diagnosing benign renal cysts is 95% when all three criteria are present. **CT** shows a sharply demarcated spherical mass with a low attenuation coefficient that does not enhance with IV injection of contrast. Enhancement is defined as an increase of 10 HU after injection of contrast. Bosniak has described a useful classification of renal cystic masses (Table 8-2). Class I and class IV cystic lesions are generally not diagnostic problems. The difficulty usually arises in ruling out carcinoma in class II and especially class III cysts.

Category	Description	Clinical examples
I	Uncomplicated cyst	Simple cyst
II	Wall calcification Thin internal septa Nonenhancing components	Simple cyst Renal abscess
III	Thick, irregular calcification Multiloculated lesions	Multilocular cystic nephroma Necrotic renal carcinoma Cystic renal carcinoma Renal abscess
IV	Thick walls Solid elements Enhancing components	Renal cell carcinoma Xanthogranulomatous pyelonephritis Renal abscess

Table 8-2. Bosniak classification of cystic renal masses

MRI is indicated in patients who are sensitive to iodinated contrast material or have renal insufficiency. Simple cysts have low signal intensity on T_1-weighted images and high signal intensity on T_2-weighted images. Nonenhancement after gadolinium injection is an important feature of benign renal cysts.

Radionuclide studies have little role in differentiating cyst from tumor, but a technetium scan can demonstrate that the mass is avascular and therefore somewhat more likely to be benign.

   c. **Differential diagnosis** of benign renal cyst includes cystic renal carcinoma, polycystic kidney disease, renal abscess, and *Echinococcus* cyst.
2. **Adult polycystic kidney disease** is an inherited autosomal dominant disease. There are two recognized subtypes. Clinically, the first type is more severe in its manifestations than the second type. The two types are also distinguished by their genetic basis. Recently, the PKD1 and PKD2 genes have been located on chromosomes 16 and 4, respectively. Abnormalities found within these genes are responsible for the majority of cases of adult polycystic kidney disease; they manifest by causing a diffuse bilateral renal cystic disease with destruction of normal parenchyma. Presentation is usually between the ages of 30 and 40, when the disease becomes symptomatic with hematuria, flank mass, urinary tract infections, pain from the expanding mass, or clot colic. Diagnosis is aided by a positive family history. Screening for family members is imperative because of the natural history of the disease and the 100% penetrance. Radiologically, IVU, US, and CT all confirm the presence of bilaterally enlarged, poorly functioning kidneys replaced by variably sized cysts. CT may also demonstrate cysts in other organs, such as liver and pancreas.
3. **Multicystic kidney disease,** a form of renal dysplasia, is a common cause of an abdominal mass in the newborn. The disease is usually discovered during prenatal US. The kidney is found to be composed of a lobulated mass of cysts with an atretic or absent ureter. The contralateral kidney is usually normal. Fetuses with bilateral multicystic kidneys are often stillborn or die shortly after birth. IVU and renal scan demonstrate the lack of function. US shows a multicystic structure that may occasionally be difficult to differentiate from severe ureteropelvic junction obstruction. Once the condition is diagnosed, no treatment except observation is required, although some physicians have expressed concern regarding possible eventual malignant degeneration and advocate nephrectomy.
4. **Multilocular cystic nephroma** is a Bosniak class III lesion that is thought to be benign; it is composed of multiple, noncommunicating cysts separated by thick fibrous septa. Approximately 70% of reported cases have been in (mostly white male) patients under the age of 4 years. A second peak incidence occurs in women ages 40 to 70. US will show a large cluster of fluid-filled cysts (most between 5 and 10 cm in diameter) with highly echogenic fibrous septa between them. CT will confirm the US findings, with the septa showing contrast enhancement. In adults, differential diagnosis should include cystic renal carcinoma and chronic renal abscess. As many as 5% of renal cell carcinomas may resemble multilocular cystic nephroma. In children, the differential diagnosis should also include cystic Wilms' tumor. In most cases, it will not be possible to exclude preoperatively cystic Wilms' tumor, cystic or necrotic renal cell carcinoma, or cystic forms of sarcoma; surgical exploration and excision will usually be required.
5. **Calyceal diverticula**, which occur in 0.5% of the population, are small diverticula arising from the tip of the calyx. They are lined with transitional epithelium and communicate with the collecting system. They are usually asymptomatic, but the patient may present with hematuria, pain, infection, or stone within the diverticulum. IVU or CT will show a contrast-filled mass that arises from the tip of a calyx or less commonly the renal pelvis. US can demonstrate a cystic structure with or without debris or calculi. Treatment depends on the size, location, and symptoms associated with the lesion.

B. **Malignant lesions**

Approximately 5% to 10% of instances of renal adenocarcinoma have a cystic appearance (Bosniak class III or IV). Reasons for this include (1) cystic growth pattern (multilocular or unilocular), (2) cystic necrosis of a renal adenocarcinoma, (3) tumor arising in a benign renal cyst, and (4) cyst arising from ductal obstruction by tumor. The most common reason (70%) is an intrinsically cystic growth pattern, sometimes termed **papillary cystadenocarcinoma**. The diagnosis of a malignant cystic lesion is aided by a high degree of suspicion if a cystic lesion cannot be proved to be unequivocally benign. Lesions in which the cyst wall is irregular, thickened, or calcified, internal echoes are seen, or rim enhancement occurs following contrast injection are termed complex cysts and require cyst aspiration, arteriography, or surgical exploration. If the aspirate is bloody, there is a 25% to 50% chance of malignancy. Cytologic studies may be falsely negative because not all tumors shed cells into the cyst fluid. In instances in which malignancy is suspected, arteriography is indicated to look for tumor vessels. If the cyst is diagnosed preoperatively as malignant, radical nephrectomy is the treatment of choice. If the diagnosis is in doubt preoperatively,

exploration of the kidney with biopsy of the cyst wall is recommended.

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Chapter 9 Surgical Disorders of the Adrenal Gland

Caner Dinlenc and Mike B. Siroky

The adrenal glands are small, yellowish, triangular endocrine glands located at the superior and medial aspect of each kidney (Fig. 9-1). In the past, adrenal disease usually became manifest because of systemic symptoms and signs resulting from a change in gland function. Computed axial tomography (CT) has facilitated the discovery of occult asymptomatic adrenal masses. Adrenal masses are noted in approximately 1% of all abdominal CT studies in adults. Although a large number of these are metastatic lesions and benign adenomas, a small number are pheochromocytomas that require surgical removal (Table 9-1). This chapter describes a systematic approach (Fig. 9-2) to the differential diagnosis of adrenal mass lesions (Table 9-2) and surgical considerations in their treatment.

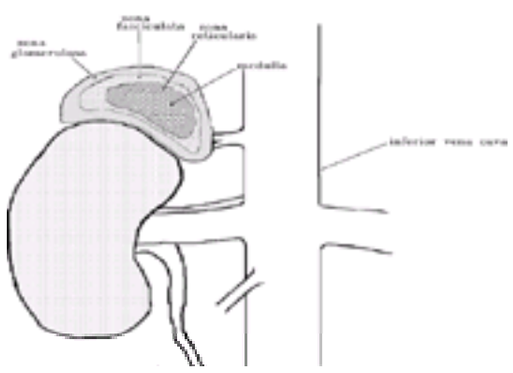

FIG. 9-1. Schematic diagram showing the anatomic relations of the adrenal gland and emphasizing the three zones of the adrenal cortex surrounding the medulla.

Cause	Percentage of cases
Metastases from known malignancies	30
Nonfunctioning adrenal adenomas	24
Adrenal cysts	10
Pheochromocytomas	8
Focal adrenal hyperplasia	2
Myelolipoma	2
Lipoma	2
Undetermined; probably benign	22

Table 9-1. Causes of incidental adrenal masses in adults

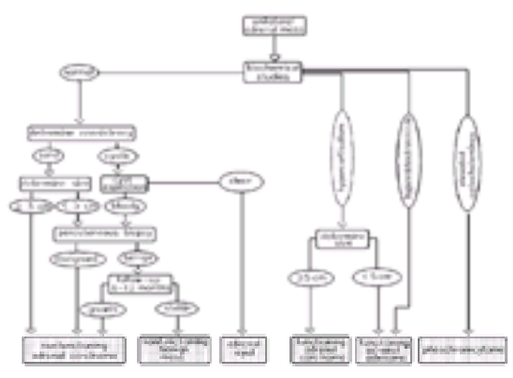

FIG. 9-2. Diagnostic decision tree for evaluation of a unilateral adrenal mass.

Neoplastic	
Primary	
Adrenocortical hyperplasia	
Adenoma	
Carcinoma	
Pheochromocytoma	
Neuroblastoma	
Ganglioneuroma	
Medullary carcinoma	
Secondary	
Breast	
Lymphoma	
Lung	
Colon	
Melanoma	
Leukemia	
Nonneoplastic	
Adrenal cyst and pseudocyst	
Adrenal abscess	
Adrenal hematoma	
Amyloidosis	
Myelolipoma and other hamartomas	
Wolman disease (familial xanthomatosis)	

Table 9-2. Differential diagnosis of adrenal masses

I. Benign Lesions

A. **Adrenal adenoma,** the most common benign adrenal mass, is found in from 1.4% to 8.7% of all autopsies. Many are hormonally active, resulting in primary hyperaldosteronism (Conn's syndrome) or hypercortisolism (Cushing's syndrome).
   1. **Diagnosis.** Size is an important determinant in distinguishing adenoma from carcinoma. The vast majority of adrenal adenomas are less than 6 cm in diameter, although rarely they can be up to 10 cm in diameter. In contrast, more than 90% of adrenal carcinomas are more than 6 cm in diameter. Malignant adrenal masses will demonstrate an increased T_2 signal intensity on magnetic resonance imaging (MRI) when compared with the spleen. CT and MRI may underestimate size, and therefore lesions greater than 5 cm should be explored.
   2. **Conn's syndrome.** Adrenal adenomas causing hypersecretion of aldosterone may be single, multiple, or bilateral. The increased aldosterone production causes sodium retention, potassium loss, extracellular volume expansion, and suppression of plasma renin activity. Most of the symptoms of Conn's syndrome are caused by hypokalemia (muscle weakness, polydipsia, polyuria). Hyperaldosteronism is found in 50% of hypertensive patients with significant hypokalemia. In 80% of patients with Conn's syndrome, a unilateral adrenal adenoma is found that is amenable to adrenalectomy.
   3. **Cushing's syndrome** may be caused by adrenal adenomas, which typically secrete only mildly excessive amounts of glucocorticoids. If there is evidence of virilization or mineralocorticoid excess, adrenal carcinoma should be suspected. The most common manifestations of Cushing's syndrome are obesity, hypertension, muscle weakness, emotional lability, and glucose intolerance.
   4. **Treatment.** All hormonally active adrenal adenomas should be removed surgically. Nonfunctioning adenomas, especially those measuring less than 3 cm in diameter, may be followed by serial CT at 3, 6, and l8 months. Additionally, biopsy specimens can be taken from adenomas 3 to 6 cm in size by CT or ultrasound (US). If any increase in size is noted on follow-up, repeated biochemical assessment and adrenalectomy are indicated.

B. **Hamartomas** include multiple mixed connective-tissue tumors such as myelolipomas, adenolipomas, and lipomas. These benign, nonfunctioning tumors account for fewer than 5% of all adrenal masses. Often, they can be diagnosed on the basis of a high content of fat on CT or MRI.

C. **Ganglioneuromas** are derived from medullary neural crest cells. They are extremely rare nonfunctioning tumors that represent the mature form of neuroblastoma. Ganglioneuromas are diagnosed in the same manner as any adrenal mass. Surgical adrenalectomy is the preferred treatment because the diagnosis cannot be made preoperatively with certainty and because rare instances of degeneration into neuroblastoma have been reported.

D. **Adrenal cysts** may be caused by a variety of unrelated disorders (Table 9-3). The most common cause is an endothelial cyst composed of dilated lymph channels. Calcification may be found in up to 15% of these cysts and does not imply malignancy. The fluid in these cysts may be clear or milky. Hemorrhage is easily identified by MRI. **Pseudocysts** account for approximately 40% of all adrenal cysts and result most commonly from hemorrhage into a normal adrenal gland or an adrenal tumor. Although rare, the potential for cystic degeneration of an adrenal tumor should be kept in mind.

Type	Percentage of cases
Endothelial cysts	45
Pseudocysts (hemorrhage)	40
Cystic adenomas	10
Echinococcus cysts	5

Table 9-3. Differential diagnosis of adrenal cysts

II. Primary Malignant Lesions

A. **Adrenal carcinoma** is a highly malignant tumor, fortunately quite rare (one case per 1.7 million), accounting for only 0.2% of all cancer deaths. Five-year survival rates of approximately 35% are expected. The tumor affects persons ages 20 to 50 years. Although the sexual incidence is approximately equal, female patients tend to be diagnosed somewhat earlier because of virilization. There is no predilection for one side of the body over the other. At least 80% of adrenal carcinomas are hormonally active by clinical evidence, and patients tend to present most commonly with a combination of virilization and Cushing's syndrome. In children, adrenal carcinoma is the most common cause of Cushing's syndrome, whereas in adults adrenal hyperplasia is much more common. However, hormonally active adrenal carcinoma still accounts for 30% of instances of Cushing's syndrome in adults. More than 90% of tumors are greater than 6 cm in size when first discovered. Adrenal carcinoma metastasizes most commonly to the lung, liver, and regional lymph nodes.

1. **Biochemical studies** are important in the initial diagnosis and in providing postoperative tumor markers (Table 9-4). It is important to remember that even in patients without clinical endocrinopathy, elevated levels of steroids such as pregnenolone may be demonstrated in many cases of adrenal carcinoma. The hallmark of this tumor is markedly elevated levels of urinary l7-ketosteroids. Plasma cortisol and urinary free cortisol may also be elevated, whereas plasma levels of adrenocorticotropin (ACTH) are depressed. Even high doses of dexamethasone do not suppress the urinary steroid levels. It is advisable to rule out pheochromocytoma in all patients with adrenal mass to avoid a hypertensive crisis on induction of anesthesia.

Test	Male patients	Female patients
Urine (24 h):		
17-Hydroxysteroid	5–15 mg	3–12 mg
17-Ketosteroid	10–25 mg	8–20 mg
Free cortisol	15–50 μg	10–100 μg
Plasma		
Cortisol 8 a.m.	4–22 μg/dL	4–22 μg/dL
Cortisol 5 p.m.	5–7 μg/dL	3–16 μg/dL

[illegible]

Table 9-4. Adrenal cortex: normal biochemical values[a]

2. **Radiologic diagnosis** is based primarily on CT and MRI with T_2-weighted images. An intravenous urogram (IVU) may show downward displacement and axis change in the ipsilateral kidney, but demonstration of this finding usually requires a mass larger than 2 to 3 cm in diameter. US is a sensitive method for determining the presence of a mass and its fluid content, if any.
3. **Radionuclide studies** based on radiocholesterol labeled with ^{131}I have been used to diagnose adrenal masses. In general, the degree of uptake correlates with the secretory activity of the gland. Radiocholesterol scanning cannot reliably differentiate carcinoma from adenoma, however, because either may have increased uptake or low uptake.
4. **Fine-needle aspiration** is most useful in the evaluation of cystic masses, but even in this case it is of questionable value. A clear aspirate is indicative of a benign cyst, whereas bloody fluid may indicate either a benign or malignant lesion. Even when the aspirate is bloody, however, the lesion is much more likely to be benign than malignant. Unless there is evidence of biochemical abnormality, a small adrenal cyst can be followed in the same manner as small adrenal adenomas. Cytologic examination of adrenal cyst fluid is difficult because there is little published experience.
5. **Percutaneous biopsy** guided by CT or US has recently been reported to be useful in the differential diagnosis of solid adrenal masses. Tissue can be obtained in more than 95% of biopsies, and it is possible to differentiate between benign and malignant disease in better than 85% of these samples. The technique is useful and may obviate the need for surgery. Rare complications include pancreatitis.
6. **Treatment** is surgical removal of lesions that have not metastasized. A thoracoabdominal incision is preferred because, as mentioned previously, adrenal carcinomas tend to be large. If the carcinoma is functioning, perioperative administration of glucocorticoids is essential because the contralateral adrenal is likely to be suppressed (Table 9-5). Complete recovery of contralateral adrenal function generally requires many months, during which time steroid support must be continued. Steroid replacement is not necessary in cases of nonfunctioning adrenal carcinomas. Chemotherapy with the steroid-synthesis blocking agent mitotane (ortho-para-DDD) in doses of 2 to 6 g daily is available in patients with metastatic disease, but the response rate is poor. Cisplatin, etoposide, and ketoconazole have been found to induce regression in some patients. Transarterial embolization may also help induce partial remission. Radiotherapy is

of little use except for palliation of bony metastases.

Cortisone acetate 100 mg IM
1. Evening before surgery
2. Morning of surgery
3. In the recovery room
Cortisone acetate 75 mg IM q8h
1. First postoperative day
2. Second postoperative day
Cortisone acetate 75 mg IM q12h
1. Third postoperative day
2. Fourth postoperative day
Cortisone acetate 25 mg PO bid with fludrocortisone 0.1 mg PO.
Continue for at least 1 month postoperatively.

Table 9-5. Perioperative steriod replacement for adrenalectomy

B. **Pheochromocytoma** is a rare tumor derived from neural crest tissue. There are approximately 400 new instances yearly in the United States. Pheochromocytoma is found in 0.1% to 0.4% of hypertensive patients. Although approximately 90% are adrenal in origin, the tumors can arise wherever chromaffin cells are located, such as the paraaortic sympathetic ganglia and the organs of Zuckerkandl at the aortic bifurcation. Pheochromocytoma is often loosely described as following the “rule of 10s,” which states that 10% are malignant (and metastasize), 10% are multiple, 10% are bilateral, and 10% are extraadrenal; of the ectopic pheochromocytomas, 10% are above the diaphragm. Many cases of bilateral pheochromocytoma are part of multiple endocrine neoplasia type II (Sipple's syndrome), which includes medullary carcinoma of the thyroid and parathyroid hyperplasia. Pheochromocytoma is found in 50% of patients with Sipple's syndrome. An increased incidence of pheochromocytoma is also associated with neurofibromatosis and von Hippel-Lindau disease. Malignant tumors tend to be large and metastasize to bones, lung, liver, and spleen.

1. **Diagnosis** is based on the clinical picture of hypertension (episodic or sustained), severe headaches, palpitations, and sweating found in more than 90% of cases. Paradoxically, orthostatic hypotension is frequently found as a result of diminished plasma volume. An acute hypertensive crisis may be precipitated by almost any stimulus to the sympathetic nervous system, especially induction of anesthesia or administration of contrast media or monoamine oxidase inhibitors, which block the metabolism of catecholamines. A rare phenomenon is “micturition syncope,” which is precipitated by voiding in a patient with pheochromocytoma of the bladder wall.
2. **Biochemical abnormalities** include elevated levels of catecholamines and their metabolites in the plasma and urine (Table 9-6). Because more than 50% of secreted catecholamines appear in the urine as metanephrine, normetanephrine, or vanillylmandelic acid (VMA), these substances may be measured to estimate catecholamine production.

Test	Normal range
Urine (24 h)	
Vanillylmandelic acid (VMA)	2–10 mg
Epinephrine	0–15 µg
Norepinephrine	11–86 µg
Metanephrine	<1.3 mg
Plasma (30 min supine)	
Epinephrine	>50 pg/mL
Norepinephrine	40–410 pg/mL

[a]Values may vary according to method and laboratory.

Table 9-6. Adrenal medulla: normal biochemical values[a]

   a. Measurement of urine and plasma catecholamines is carried out by specific methods such as chromatography or radioimmunoassay. Before collecting urine, obtain specific instructions on diet and drug restrictions from your laboratory.
   b. Although provocative tests are rarely used, the **glucagon test** may be helpful in those patients whose hypertension is paroxysmal. After administration of 1 mg of glucagon subcutaneously (SC), both blood pressure and catecholamine levels will rise markedly within 2 minutes.
   c. The **clonidine test** involves administration of 0.3 mg clonidine; this will produce a drop in norepinephrine and epinephrine levels below 500 pg/mL in patients with neurogenic hypertension but not in those with pheochromocytoma.
   d. In general, a high ratio of VMA to catecholamines in the urine indicates a large tumor, whereas a low ratio indicates a small tumor.
   e. Elevation of only epinephrine—not norepinephrine—in the serum indicates a tumor arising in the adrenal medulla. This is because only medullary tissue can methylate norepinephrine into epinephrine.
3. **Radiologic diagnosis** plays an important role in localizing these tumors. MRI is very useful in identifying pheochromocytomas, as they appear like a “bright light” on T_2 images. MRI is especially useful in identifying extraadrenal tumors. Coronal and sagittal views can bereconstructed to give excellent detail of the surrounding structures and vascular involvement.
4. **Radionuclide studies** include the scanning agent ^{131}I-meta-iodobenzyl guanidine (MIBG), which is concentrated in storage granules of adrenergic cells. It may be used to detect pheochromocytoma in the adrenal as well as in extraadrenal sites.
5. **Treatment** of pheochromocytoma is surgical excision; the operative approach depends on the location and number of tumors.
   a. **Perioperative management** is extremely important in preventing intraoperative malignant hypertension or postoperative hypotension. Preoperative oral **phenoxybenzamine** is titrated (initial dose of 20 to 40 mg/d increased by 10 mg daily) until blood pressure is nearly normalized. As opposed to prazosin, phenoxybenzamine binds irreversibly to a-adrenergic receptors and thus provides stable blood pressure control even in the face of a severe catecholamine surge. In addition, all patients should be well hydrated preoperatively. If tachycardia or arrhythmias are present preoperatively, a b-adrenergic blocking agent such as propranolol may be given orally. If hypertension is a problem intraoperatively despite a-adrenergic blockade, it may be controlled rapidly with sodium nitroprusside. Hypotension is a feared complication in the immediate postoperative period; however, it should not be a problem in patients well prepared and maintained with IV fluids. Finally, blood sugar should be monitored; with removal of the catecholamine stimulus to gluconeogenesis, fatal hypoglycemia may occur.
   b. The **surgical approach** is dictated by the known or suspected location of the tumors. If a tumor has been localized to the adrenal, a thoracoabdominal incision permits exposure of the adrenal and systematic exploration of the abdominal cavity. If an ectopic tumor or bilateral tumors are suspected, a transverse epigastric “chevron” incision is recommended. With either incision, palpation of the obvious tumor mass is kept to a minimum, but careful palpation for other tumors is mandatory. The operative mortality for intraabdominal pheochromocytoma is 1% to 4%. If pheochromocytoma of the bladder wall is present, segmental resection with pelvic lymph node sampling is usually sufficient therapy. Recently, laparoscopic adrenalectomy has been performed to remove incidentally found adenomas and small, single pheochromocytomas. This procedure can be carried out in either transperitoneal or retroperitoneal fashion. As techniques improve, operative times will so diminish.
   c. **Prognosis** in benign pheochromocytoma is very favorable, although local recurrence is possible. Thus, urinary VMA and metanephrine should be measured every 6 months for 3 to 5 years postoperatively. Malignant pheochromocytoma has a 5-year survival of 33% to 44%. Survival after demonstration of metastases is less than 3 years in the vast majority of patients. Prognosis appears worse with extraadrenal than with adrenal tumors. There is no effective chemotherapy, and radiation therapy is only palliative.

C. **Neuroblastoma** is a highly malignant tumor of childhood derived from neural crest cells. Approximately 75% are found in the abdominal cavity, most commonly (50%) in the adrenal gland. The remainder may occur in ectopic locations: the cervical sympathetic chain (4%), thorax (15%), or pelvis (4%). Neuroblastoma accounts for 6% to 8% of all childhood malignancies. Approximately 50% of neuroblastomas are found in children younger than 2 years of age. Seventy percent of patients have metastatic disease at the time of presentation.

1. **Diagnosis.** There are no specific symptoms in neuroblastoma. Approximately 70% of patients present with an abdominal mass, 50% have abdominal or bone pain, 28% have weight loss or failure to thrive, and malaise or weakness is present in 18%. Physical findings may include hepatomegaly or a fixed abdominal mass that often extends across the midline.
   a. **Biochemical and laboratory studies.** Although hypertension is rare, neuroblastoma often produces excess amounts of catecholamines. In more than 80% of patients, the level of VMA or homovanillic acid (HVA) in the urine is elevated and may be used as a tumor marker. Anemia is very common in

disseminated disease. Bone marrow aspirate will reveal tumor cells in up to 70% of cases.

b. **Radiologic studies.** In up to 50% of patients with intraabdominal tumor, neuroblastoma is characteristically calcified in a central, finely stippled pattern. Calcification in neuroblastoma is five times as common as in Wilms' tumor and may be used to differentiate between the two tumors. Typically, neuroblastoma causes a downward and outward displacement of the kidney on IVU. CT is helpful in delineating the mass and documenting extension, especially involvement of the vena cava. Chest roentgenography, skeletal films, and bone scan should be performed to complete the metastatic survey. MIBG has been used to identify primary and metastatic lesions. Staging usually follows the system of Evans:

Stage I. Tumor organ-confined

Stage II. Regional spread but not across midline

Stage III. Tumor extending across midline

Stage IV. Distant metastases

Stage IV-S. Small primary and distant metastases to liver, skin, or bone marrow but negative findings on bone films

2. **Treatment** involves a combination of surgical removal, radiation therapy, and chemotherapy. In stage I, stage II, and some stage III tumors, complete surgical removal is usually possible. The abdominal tumor is explored through a transverse incision. Tumor that cannot be removed totally should be treated by subtotal resection and clipping of the margins for postoperative radiotherapy. Although neuroblastoma is radiosensitive, radiation therapy is mainly a palliative maneuver. In instances of very large tumors thought to be unresectable, preoperative radiation should be given to reduce tumor size and permit a "second look" operation. In unresectable stage III tumors, radiation in doses of 2,500 to 3,000 rads is commonly given. Radiation is also given to palliate painful bone metastases. With residual (stage III) or disseminated disease (except stage IV-S), chemotherapy is indicated with cyclophosphamide, vincristine, and dacarbazine. Infants with stage IV-S disease generally have an excellent prognosis following surgical removal of the primary tumor only. Bone marrow transplantation is still being tested as a part of various chemotherapeutic protocols. Labeled MIBG may also prove helpful with targeted radiation therapy.
3. **Prognosis.** Patients who present at 1 year of age or younger have a much better prognosis (80% cure rate) than do older children (20% cure rate). In addition, one-third of infants present with metastatic disease, compared with two-thirds of older children. The tumor metastasizes to liver most commonly in infants and to bone most commonly in older children. Maturation of neuroblastoma to a more benign tumor (ganglioneuroma) may occur spontaneously in 5% to 10% of patients and implies an excellent prognosis.

III. Metastatic Lesions

Metastases to the adrenal gland from distant sites are found in approximately 12% to 25% of autopsies. As expected, these metastases are more often bilateral and multiple than localized. Common sites of origin are female breast (most common), stomach, large bowel, lung, biliary tract, and kidney. The adrenals may be involved in systemic diseases such as Hodgkin's disease, lymphosarcoma, and leukemia.

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Chapter 10 Urinary Calculi and Endourology

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The occurrence of stones within the urinary tract is a problem that has plagued humans since the beginning of recorded history. Archaeologists have uncovered urinary stones in the mummified remains of Egyptians estimated to be more than 7,000 years old. Many improved methods of dealing with stones have been developed in the past, but none have had as much impact as the development of endourology and extracorporeal shock wave lithotripsy (ESWL) in the last decade. These two innovations have eliminated the need for open surgical removal of urinary calculi in the vast majority of patients.

I. Epidemiology of Stones

In the United States, stone disease accounts for more than 400,000 hospitalizations annually. The peak incidence is in the third to fifth decades. Men are affected three times as commonly as women, and whites four to five times as commonly as blacks. In a patient who has passed one stone, the likelihood of passing another stone is about 15% by 3 years and 30% by 15 years. Urolithiasis is a lifelong disease, with an average of 9 years intervening between episodes.

II. Etiology and Pathogenesis

The development of stones in the urinary tract is a complex, poorly understood, multifactorial process. Some factors related to stone formation are listed in Table 10-1, Table 10-2 and Table 10-3. A number of chemical and physical factors are known to play a role.

Factor	Conditions of increased incidence
Genetics/heredity	Cystinuria—autosomal recessive Renal tubular acidosis—type I Medullary sponge kidney
Geography	High temperature/humidity (southeastern United States)
Diet	Increased intake of calcium or oxalate
Occupation	Sedentary jobs

Table 10-1. Factors associated with urolithiasis

Type of stone	Frequency (%)	Effect of pH on solubility	Radiographic density (water = 1.0)
Calcium stones	75		
Oxalate (monohydrate and dihydrate)	65	Little effect	1.50
Phosphate	10	Increased at pH < 5.5	1.0
Oxalate and phosphate	20	Variable	Variable
Struvite	10	Increased at pH > 6.8	0.20
Uric acid	6	Increased at pH > 6.8	0.06
Cystine	1	Increased at pH > 7.6	0.16
Other types	1		
Triamterene			
Xanthine		Increased at pH > 6.8	0.06
Matrix (noncrystalline)			

Table 10-2. Urinary calculi: composition, frequency, and characteristics

Type of stone	Etiologic factors
Calcium oxalate Calcium phosphate Calcium carbonate	Supersaturation of urine with calcium from (1) renal leak, (2) intestinal absorption, (3) bone resorption; hypercalciuria
Uric acid	Hyperuricosuria, constantly low urine pH
Cystine	Cystinuria
Magnesium ammonium phosphate (struvite)	Alkaline urine produced by urea-splitting organisms
Matrix	Alkaline urine produced by urea-splitting

Table 10-3. Types of urinary calculi and etiologic factors

A. **Supersaturation.** When there is an overabundance of solute in solution, supersaturation is said to be present. This state depends not only on the amount of solute presented to the kidney but also on urine pH and temperature. In the supersaturated state, nucleation and aggregation of solute crystals may occur, leading to stone formation. Supersaturation and crystallization account fairly well for uric acid and cystine stone formation but do not completely explain calcium stone formation. Other stones that may form by supersaturation include xanthine stones. **Epitaxy** is the growth of one type of crystal on a different type of crystal. For example, calcium oxalate stones frequently contain a core of uric acid.
B. **Inhibitors** are substances in the urine that can block crystallization. One theory of stone formation holds that persons who form stones differ from those who do not in their lack of sufficient urinary inhibitors. Substances that are known to act as urinary inhibitors include pyrophosphate, citrate, magnesium, zinc, and macromolecules.
C. **Matrix** is a noncrystalline mucoprotein often associated with urinary calculi. In persons who do not form stones, urinary matrix may act as an inhibitor; however, matrix may act as an initiator in some stone formers and may even provide the framework on which crystal deposition occurs. Pure matrix calculi may be seen in association with *Proteus* infection.
D. **Exogenous substances** may be ingested and become stone components. **Indinavir** is a protease inhibitor recently introduced for the treatment of human immunodeficiency virus (HIV). Renal colic has occasionally been reported to develop in patients taking this drug. Indinavir stones are soft and gelatinous. They

are radiolucent on x-ray examination of the kidney, ureter, and bladder (KUB) as well as on computed axial tomography (CT). **Triamterene**, a component of Dyazide, may also produce radiolucent stones.

III. Stones of the Upper Urinary Tract

A. **Clinical presentation.** Renal calculi are usually silent until the stone moves within the urinary tract and produces either hematuria or some degree of urinary obstruction. This may be accompanied by pain, urinary infection, generalized sepsis, nausea, or vomiting. A urinary calculus should be suspected in a patient who presents with the sudden onset of severely colicky flank or abdominal pain (ureteral colic). Pain may radiate to the groin, testes, or tip of the penis, depending on the location of obstruction. In 25% of cases, patients give a family history of stone disease. Hematuria, gross or microscopic, almost always accompanies an acute episode of stone colic. Careful inspection of the urinary sediment occasionally allows identification of crystals that may suggest the type of stone present.
B. **Diagnosis.** Initial evaluation should include urinalysis, urine culture, and plain film of the abdomen. More than two-thirds of urinary calculi are radiopaque and can be seen on KUB. The initial radiologic investigation should be a renal ultrasonogram (US). This may demonstrate the presence of a stone (US shadowing) in the kidney or ureter as well as any evidence of hydronephrosis. An axial or spiral CT will confirm the presence of calculus in the urinary tract and demonstrate the degree of obstruction. After injection of intravenous (IV) contrast, delayed visualization is not uncommon, and follow-up films up to 24 hours later may be necessary. This is especially true when radiolucent stones (uric acid) are present or when stones overlie bony areas (vertebral transverse process). Oblique films may be required to differentiate phleboliths from ureteral stones. Prone films may be helpful in some instances of severe obstruction. Although still used occasionally, the intravenous urogram (IVU) has gradually been replaced by the spiral CT as the primary imaging modality for acute renal colic. The spiral CT is rapid, does not require a bowel preparation, and avoids the use of IV contrast. It is very accurate at identifying stones in the collecting system and ureter.
C. **Treatment** of the acute episode depends on the size and location of the stone, degree of obstruction, and the patient's clinical status.
    1. **Indications for intervention.** Patients with infection or high-grade obstruction require prompt intervention. This usually requires passage of a retrograde ureteral catheter or percutaneous nephrostomy drainage. Patients with small stones and minimal hydronephrosis may be treated conservatively as outpatients with oral hydration and analgesics. About 90% of ureteral calculi measuring less than 4 mm in diameter pass spontaneously, whereas only 20% of stones greater than 6 mm in diameter pass. Stones are most likely to obstruct the upper urinary tract at one of three locations: (1) the ureteropelvic junction; (2) the pelvic brim, where the ureter crosses the iliac vessels; and (3) the ureterovesical junction, which is the narrowest of the three (Fig. 10-1). Stones located in the proximal ureter are much less likely to pass than those located at the ureterovesical junction.

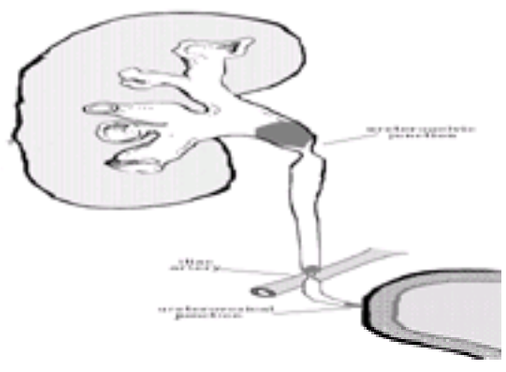

FIG. 10-1. Stones are most likely to obstruct the upper urinary tract at the ureteropelvic junction, iliac vessels, or ureterovesical junction.

    2. **Expectant treatment** is indicated in the asymptomatic, nonobstructed, noninfected patient with a stone less than 4 mm in diameter in the lower third of the ureter. The patient is instructed to drink copious quantities of water, strain the urine, and save for analysis any stone that may be recovered. Plain films of the abdomen should be obtained every week to monitor the progress of the stone as it passes down the ureter. Four to six weeks should be allowed for stone passage.
    3. **Stone extraction** is indicated for lower ureteral stones that do not pass spontaneously. The advent of rigid and, more recently, flexible ureteroscopy has eliminated the need for blind or radiologically guided basket extraction. After passage of a guide wire above the stone, the ureteral orifice seldom requires dilatation if one utilizes the smaller semirigid miniscopes, many of which have an outer diameter of less than 7F (French). Once the stone is visualized, several options are available. Small stones may be grasped directly or engaged in a stone basket and extracted. Larger stones may be fragmented using US, electrohydraulic, pneumatic, or laser lithotripsy. Success rates are approximately 95%.
    4. **Shock wave lithotripsy.** Although its primary use is in the fragmentation of renal calculi, SWL is also advantageous for ureteral stones, especially those less than 8 mm in diameter. SWL may be performed either with or without a stent in place, as long as the stone can be adequately visualized. Patients are often placed in a prone position for distal ureteral stones to focus the stone within the shock path and avoid the bony structures of the pelvis.
    5. **Ureterolithotomy** is rarely necessary, given the high success rate of nonoperative and minimally invasive techniques, such as SWL, ureteroscopy, and laparoscopy.

IV. Bladder Stones

In the Western world, bladder stones are most often found in male patients and are caused by bladder outlet obstruction or foreign bodies (portions of catheters, sutures, or objects inserted through the urethra). Ureteral stones that reach the bladder can also act as a nidus for bladder stone formation. Bladder stones are composed of variable proportions of calcium oxalate, uric acid, and ammonium urate. If uric acid is a major component, bladder stones may be radiolucent. They vary from extremely hard to quite soft. Patients with long-standing bladder stones are at risk for squamous metaplasia or carcinoma.

A. **Clinical presentation** includes pain felt in the hypogastrium or referred to the penis, intermittent stream, dysuria, and hematuria (Fig. 10-2). Patients may also present with recurrent urinary tract infections.

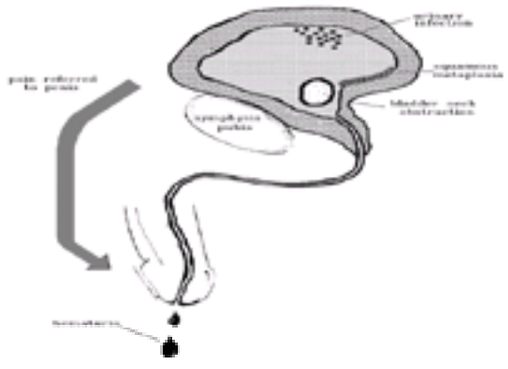

FIG. 10-2. Clinical picture associated with vesical stone.

B. **Diagnosis** includes plain films of the abdomen and bladder US. Cystoscopy is usually performed in conjunction with treatment.
C. **Treatment**
    1. **Lithotrites** are mechanical devices that permit crushing of large, hard bladder stones under direct vision (Hendrikson lithotrite). The lithotrite should be closed only with the bladder partially filled to prevent bladder wall injury. The fragments are then washed out through a resectoscope sheath.
    2. **Electrohydraulic lithotripsy.** Based on the principle of underwater spark generation, the electrohydraulic lithotripsy probe produces a hydraulic shock wave near the stone that usually produces fragmentation after delivery of several shocks. The electrohydraulic lithotripsy probe is flexible and can be passed through both fiberoptic and rigid endoscopes.
    3. **US lithotripsy** is based on US energy delivered through a rigid probe passed through an endoscope. Small fragments are removed by continuous suction

attached to the hollow US probe. Larger fragments can be extracted with grasping forceps or stone baskets.

4. **Cystolithotomy** can be performed through a small suprapubic incision or may be combined with open prostatectomy. Cystolithotomy has the advantage of removing the entire stone rather than leaving fragments in the bladder.

V. Recurrent Stone Disease

A. **Diagnosis.** It is estimated that predisposing factors can be identified in 80% of recurrent stone formers. Passage of a single urinary stone is an indication for screening studies, including determination of serum calcium, phosphorus, and uric acid levels, and measurement of 24-hour urinary creatinine, calcium, phosphorus, uric acid, and oxalate levels. Patients found to have any abnormalities on screening studies should have a more extensive evaluation, described below. Patients with "metabolically active" stone disease should also have a metabolic evaluation. Such patients include any with radiologic evidence of new stone formation, an increase in size of a preexisting stone, or passage of stone in the past year. Metabolic evaluation should be performed at a time far removed from the acute stone episode.

B. **Metabolic evaluation**

1. **Baseline studies.** While on their regular diet, patients collect a 24-hour urine sample for creatinine, calcium, phosphorus, uric acid, oxalate, and citrate (Table 10-4). Screening for cystinuria is performed by the nitroprusside test. The pH of the urine is recorded. Blood is drawn for creatinine, calcium, phosphorus, and uric acid.

Biochemical component	Male patients (mg)	Female patients (mg)
Calcium	<300	<250
Uric acid	<800	<750
Oxalate	<50	<50
Citrate	450–650	650–900

Table 10-4. Normal 24-hour urine values in milligrams

2. **Dietary restriction.** The patient is placed on a diet limited to 400 mg of calcium and 100 mEq of sodium for 1 week. A 24-hour urine specimen is again obtained and serum studies as described previously are repeated.
3. **Calcium loading.** After an overnight fast during which only distilled water is permitted, the patient reports to the office or clinic at 7:00 a.m. After the first urine voided is discarded, a 2-hour pooled specimen is collected from 7:00 a.m to 9:00 p.m. The patient receives 1 g of calcium gluconate orally at 9:00 a.m. and collects a 4-hour urine specimen from 9:00 a.m. to 1:00 p.m.

C. **Hypercalciuria** may be caused by bone resorption (most commonly from hyperparathyroidism), renal leak, or increased absorption from the gastro-intestinal tract. Table 10-5 lists the serum and urinary abnormalities in various types of hypercalciuria.

		Urine calcium	
Type	Serum calcium	Fasting	After loading
Resorptive	Up	Up	Up
Absorptive	Nl	Nl	Up
Renal leak	Nl	Up	Up

Nl, normal

Table 10-5. Classification of hypercalciuria

1. **Resorptive hypercalciuria** is characterized by constant hypercalciuria regardless of dietary restriction.
   a. **Etiology.** Hyperparathyroidism accounts for fewer than 5% of patients with calcium urolithiasis and is a common cause of the resorptive type of hypercalciuria. Stones occur in approximately 50% of patients with hyperparathyroidism. In instances caused by hyperparathyroidism, serum calcium levels are also frequently elevated, but normocalcemic forms of the disease exist. Other causes of resorptive hypercalciuria are neoplasms metastatic to bone, multiple myeloma, immobilization (e.g., spinal cord injury), Cushing's disease, and hyperthyroidism.
   b. **Treatment** of resorptive hypercalciuria consists of treatment of the underlying disorder.
2. **Absorptive hypercalciuria** is the single most common cause of hypercalciuria and is found in more than 50% of patients with stones.
   a. **Etiology.** These patients are felt to have an exaggerated intestinal response to vitamin D, leading to hyperabsorption of ingested calcium. This mechanism explains why the urinary calcium may normalize when oral calcium is restricted and will rise to the abnormal range under calcium loading.
   b. **Treatment**
      1. **Diet and hydration** are important in controlling absorptive hypercalciuria. Patients should be placed on a diet restricted to 400 mg of calcium per day and 100 mEq of sodium per day. The addition of bran to the diet is useful because brain binds calcium in the gastrointestinal tract. Patients should be required to drink 3 to 4 L of water daily to reduce urinary concentration of calcium.
      2. **Cellulose phosphate** is a calcium-binding resin that exchanges sodium for calcium in the gastrointestinal tract. It must be used in conjunction with a calcium-restricted diet. The usual dose is 5 g three times daily with meals. Because cellulose phosphate lowers serum magnesium and elevates urinary oxalate levels, patients should receive oral magnesium supplementation and should restrict oral intake of oxalate.
      3. **Orthophosphates** act by decreasing urinary excretion of calcium and increasing excretion of citrate and pyrophosphate, both of which act to inhibit calcium stone formation. The usual dose is 3 to 6 g daily. The most frequent side effect is diarrhea.
3. **Renal hypercalciuria** accounts for approximately 10% of instances of hypercalciuria.
   a. **Etiology.** The disorder is thought to be caused by the inability of the kidney to resorb calcium from the tubular fluid. Thus, placing the patient on a calcium-restricted diet will not reduce the loss of calcium in the urine. Calcium loading may increase urinary calcium even further.
   b. **Treatment**
      1. **Thiazide diuretics** are the drugs of choice in renal hypercalciuria. The mechanism of action involves increased calcium resorption in the distal tubule and contraction of extracellular volume, thus stimulating calcium resorption in the proximal tubule. The usual dose of hydrochlorothiazide is 50 mg twice daily. Potassium supplementation is necessary in most patients.
      2. **Orthophosphates.** In patients unresponsive to thiazide diuretics alone, orthophosphates may be used in combination with calcium restriction.

D. **Hyperuricosuria.** Pure uric acid stones account for approximately 10% of urinary calculi. The solubility of uric acid is highly pH-dependent; uric acid becomes insoluble in urine at a pH of less than 5.8.

1. **Etiology.** Approximately 25% of patients with uric acid calculi will be found to have gout. Most patients with uric acid calculi, however, have neither hyperuricemia nor hyperuricosuria. The calculi are probably caused by excretion of a constantly acid urine, dehydration, or both. Hyperuricosuria is also found in 20% of patients with recurrent calcium stones. Some investigators feel that uric acid crystals may act as a nidus for calcium stone formation.
2. **Treatment** is based on hydration, alkalinization of the urine, and reduction of uric acid load presented to the kidney.
   a. **Hydration** is achieved by oral intake of at least 3 L of water daily.
   b. **Alkalinization** of the urine is usually achieved by giving 650 mg of sodium bicarbonate (two tablets) orally every 6 hours. Urinary pH should be maintained at no less than 6.5. In patients requiring sodium restriction, potassium bicarbonate or potassium citrate may be used instead. In patients unable to take oral medication, IV hydration with sodium bicarbonate may be used. Alkalinization is usually effective in dissolving even large uric acid stones over a period of weeks.

c. **Reduction of uric acid load** may be achieved by dietary restriction and use of allopurinol. Such measures are indicated in patients who are unresponsive to hydration and alkalinization of urine, who have myeloproliferative disorders, or who are receiving cancer chemotherapy. Dietary protein should be restricted to 90 g daily. Allopurinol is a xanthine oxidase inhibitor that is effective in doses of 200 to 600 mg daily. Xanthine stones may form in patients undergoing long-term allopurinol therapy.

E. **Hyperoxaluria.** Oxalic acid is an extremely insoluble end product of metabolism. Although the diet may contain large amounts of oxalate, less than 10% of ingested oxalate is absorbed from the gastrointestinal tract and most is derived from metabolism.
   1. **Primary hyperoxaluria** is a rare autosomal recessive disorder characterized by early onset of nephrocalcinosis. There are two types, distinguished by their specific enzymatic defect, but the clinical picture is similar in both. Urinary levels of oxalate may exceed 100 mg/d. Widespread deposition of oxalate in the kidneys and other soft tissues (oxalosis) eventually occurs. Medical treatment with 100 to 400 mg of pyridoxine daily has been reported to reduce oxalate excretion in some patients. General measures should also be employed, including adequate hydration and reduction of dietary oxalate.
   2. **Enteric hyperoxaluria** may occur in patients with malabsorption from any cause (inflammatory bowel disease, small-bowel bypass surgery). The increased amount of fatty acids in the bowel binds calcium, leaving increased oxalate for absorption. Treatment includes a low-oxalate, low-fat diet; oral fluid hydration; and calcium supplementation. Cholestyramine has been found to bind oxalate and may be useful in patients with malabsorption.
   3. **Exogenous hyperoxaluria** occurs when substances metabolized to oxalate are ingested in large quantities, such as ethylene glycol (a component of antifreeze), ascorbic acid in amounts greater than 5 g/d, and the anesthetic methoxyflurane.

F. **Struvite stones** are composed of magnesium ammonium phosphate and carbonate apatite ("triple-phosphate stones"). They may grow to fill the entire renal pelvis and collecting system ("staghorn calculus"). These stones form only when urinary pH is markedly elevated and increased concentrations of ammonia, bicarbonate, and carbonate are present in the urine. Such conditions may be caused by organisms that produce the enzyme urease, which splits urea into ammonia and carbon dioxide. *Proteus* species are the most common “urea-splitting” organisms and are identified in more than 75% of patients with struvite stones. Other organisms may produce urease also, including *Klebsiella*, *Pseudomonas*, *Providencia*, and *Staphylococcus*. *Ureaplasma urealyticum* has recently been shown to be a urea-splitting organism. Female patients are affected about twice as often as male patients. Approximately 10% of spinal cord-injured patients have struvite calculi. Other populations at risk are patients with indwelling catheters for many years and persons with ileal conduit or other supravesical diversions.
   1. **Diagnosis.** Struvite stones should be suspected in any patient with high urinary pH caused by infection. The organisms cultured from the urine may not correspond to the organisms within the stone itself. Plain film of the abdomen will usually demonstrate the stones, but they may be poorly mineralized and relatively radiolucent. IVU should be performed to determine whether obstruction is present and causing persistence of infection. Radionuclide studies should be performed to assess renal perfusion and function. Voiding cystourethrogram (VCUG) and urodynamic studies may be indicated if bladder dysfunction is suspected.
   2. **Treatment.** Successful treatment depends on complete elimination of the stones, correction of any obstruction that may be present, and eradication of infection. Selection of the best treatment method is still controversial, and each instance presents unique problems. For example, patients with obstruction or areas of stasis in the upper urinary tract are poor candidates for treatment by ESWL alone. Another consideration is that percutaneous techniques often require multiple treatments.
      a. **Surgical techniques.** Surgical nephrolithotomy—“anatrophic nephrolithotomy”—can render approximately 80% of patients permanently stone-free. Nephrectomy should be performed when there is little or no renal function. In instances of partial staghorn calculi with renal parenchymal damage, partial nephrectomy should be considered.
      b. **Percutaneous lithotripsy** recently has replaced open surgery in many patients with dendritic or large staghorn calculi. When rigid and flexible nephroscopes and a variety of fragmenting tools are used, approximately 85% of patients can be rendered stone-free at 3 months; long-term results are comparable with those of open surgery, although many large stones will require staged procedures.
      c. **ESWL.** As mentioned previously, ESWL alone can be used in patients without obstruction or stasis; however, stone-free rates are in the range of 40% to 60%, and multiple treatments are usually required. One of the most effective techniques is the so-called sandwich technique, involving percutaneous lithotripsy followed by ESWL, followed by secondary percutaneous lithotripsy, extraction, or chemolysis.
      d. **Chemolysis.** Chemolysis is generally ineffective in calcium stones but can be used very effectively to dissolve uric acid, cystine, struvite, and carbonate apatite stones.
         1. **Uric acid and cystine stones** occasionally require local irrigation through a urethral catheter, ureteral catheter, or nephrostomy tube. These stones are readily soluble in alkaline solutions. Uric acid stones can be treated with a solution of sodium bicarbonate in normal saline solution to bring the PH to 7.5. Oral alkalinizing agents such as potassium citrate may be better tolerated for long-term maintenance of an alkaline pH. Cystine stones may be treated with a solution of 60 mL of 20% acetylcysteine and 300 mg of sodium bicarbonate per liter of normal saline solution. An alternative agent is tromethamine B, an organic buffer with a pH of 10.2.
         2. **Struvite and carbonate apatite calculi** are amenable to dissolution by acidic solutions with pH of less than 5.5. The most widely used solution is 10% hemiacidrin (Renacidin), which has a pH of 4.0. The solution is delivered to the stone via nephrostomy tube or ureteral catheter. Normal saline solution should be infused at 30 mL/h initially to determine the response of the collecting system. The saline infusion rate is increased over 24 hours to the maximal rate tolerated without flank pain or rise in pressure above 30 cm H_2O. Hemiacidrin is then infused at half the maximal rate achieved with normal saline solution.

         When chemolysis is used, several important precautions must be observed: (1) Care must be taken to avoid excessive pressure in the collecting system. A manometer must be placed in the infusion line to monitor pressure and provide a blow-off valve in case of obstruction. Intrapelvic pressure must be below 30 cm H_2O. Treatment should be discontinued if the patient reports any flank pain. (2) The infusate must have adequate egress, which may be a problem when infusion is through a single ureteral catheter. (3) Chemolysis is contraindicated in the presence of active urinary tract infection. The urine must be cultured daily during chemolysis, and treatment should be stopped if urinary infection is found or a fever develops. (4) Hemiacidrin contains magnesium that can be absorbed to cause hypermagnesemia. Serum magnesium levels should be monitored three times weekly during treatment. Success rates of 85% have been reported for complete dissolution of struvite calculi. Hemiacidrin may be used as primary therapy given through a nephrostomy tube, or as an adjunct to percutaneous lithotripsy, surgical lithotomy, or ESWL.
   3. **Prevention** of struvite calculi depends on elimination of infection with urea-splitting organisms. When chronic infection cannot be eradicated, urease inhibitors such as **acetohydroxamic acid** may be used to decrease urinary pH and ammonia levels. This drug has been shown to be effective in preventing struvite calculi in spinal cord-injured patients, although it may be difficult to tolerate.

G. **Renal tubular acidosis** is characterized by metabolic acidosis caused by defects of the renal tubule. Although several types of renal tubular acidosis are recognized, urinary lithiasis occurs only in type I, a disorder in which the distal tubule is unable to maintain adequate hydrogen ion gradients. Renal tubular acidosis accounts for approximately 1% of calcium stone-forming patients. Patients with renal tubular acidosis may form calcium phosphate, calcium oxalate, or mixed stones. Treatment involves alkalinizing the urine with sodium bicarbonate or potassium citrate.

VI. Endourologic Techniques

Percutaneous access to the upper urinary tract is the cornerstone of endourologic technique. The first “nephroscopes” were actually cystoscopes modified to avoid trauma to the renal pelvis. In the early 1980s, specially designed rigid nephroscopes were produced with offset lenses and straight instrumentation ports to allow passage of alligator forceps and stone graspers. Flexible fiberoptic endoscopes intended for the biliary and bronchial tracts were used in the upper urinary tract until specially designed instruments became available. Percutaneous stone retrieval was initially limited by the size of the nephrostomy tract. This limitation was addressed by the development of US probes that could be passed through the nephroscope and used to fragment large calculi. The combination of rigid and flexible endoscopes with US or electrohydraulic lithotripsy allows virtually all stones to be treated by percutaneous means. In comparison with open surgery, percutaneous treatment offers a reduction in cost, discomfort, and recovery time.

A. **Percutaneous puncture techniques.** The patient is placed on the fluoroscopy table in the prone position, and imaging of the kidney is carried out by fluoroscopy or US. The puncture site is most commonly on the posterior axillary line midway between the 12th rib and the iliac crest. In general, the nephrostomy tube should be placed through a renal pyramid into a posterior calyx. Direct pyelostomy is not recommended because it is difficult to stabilize the nephrostomy tube. Once the collecting system is entered, a 0.038-in. guide is inserted through the needle or introducer sheath and advanced into the renal pelvis or down the ureter. The nephrostomy tract can then be dilated with either fascial dilators or a high-pressure balloon. Depending on the clinical indication, one can pass a nephrostomy catheter over the guide wire or introduce a 28F or 30F Amplatz sheath into the kidney for nephroscopic stone manipulation. A second guide wire—“safety” guide wire—is necessary before nephroscopic stone extraction begins to permit reentry should the primary guide wire become dislodged.
B. **US lithotripsy** is based on the ability of high-frequency sound waves to fragment stones. The US energy is delivered through a rigid probe passed through the nephroscope. Small fragments are removed by continuous suction attached to the hollow US probe. Larger fragments can be extracted with grasping forceps or stone baskets passed under direct vision through the nephroscope.
C. **Electrohydraulic lithotripsy.** Stones resistant to US lithotripsy can be fragmented by means of electrohydraulic lithotripsy. Based on the principle of spark generation, the electrohydraulic lithotripsy probe produces a hydraulic shock wave near the stone that readily leads to fragmentation. Unlike the US probe, the

electrohydraulic lithotripsy probe is flexible and can be passed through both fiberoptic and rigid endoscopes. The disadvantage is that the fragments produced by electrohydraulic lithotripsy discharge tend to scatter widely, and retrieval is not as easy as with US lithotripsy.

D. **Pneumatic lithotripsy.** The introduction of the Swiss lithoclast has offered yet another alternative to stone fragmentation. This device delivers a “jackhammer” effect; compressed air is used to cause stone fragmentation. It can be passed through all rigid scopes in the kidney, ureter, and bladder.

E. **Laser lithotripsy.** The coumarin green pulsed dye laser has largely been replaced by the Holmium laser, which is both more efficient and versatile. In addition to excellent stone fragmentation, the Holmium laser is an effective incisor of tissue and may be used to cut scars and ureteral strictures.

VII. Extracorporeal Shock Wave Lithotripsy

ESWL was developed in Germany in the early 1980s and has already had an enormous impact on the treatment of stones. The treatment is based on the propagation of focused shock waves through the body, which fragment the stones. The shock may be produced by discharging a high voltage (spark gap), deforming a piezoelectric crystal, or moving a membrane by electromagnetic energy (Table 10-6). The “third-generation” machines are characterized by more compact designs, with lower pressures and narrower focusing, allowing anesthesia-free lithotripsy. Depending on the energy source, many of the newer lithotripters need not be gated to the electrocardiogram, and shocks may be produced at a rate of two per second; the average patient requires 1,000 to 4,000 shocks to fragment stones completely. The fragments usually pass through the ureter without a problem. In some cases, these fragments may cause obstruction of the ureter (*steinstrasse*). A combination of percutaneous techniques may be required to reduce large staghorn calculi to smaller fragments ("stone debulking") before ESWL is performed. Experimental and clinical work has failed to demonstrate significant long-term tissue damage to the kidney or surrounding tissues by ESWL. The question of hypertension developing after ESWL is currently being investigated in prospective studies. Contraindications include infundibular obstruction, obstruction of the ureter, and active urinary tract infection.

Manufacturer/model	Localization	Energy source	Anesthesia
Mobile			
Dornier Compact S	x-ray and US	Electromagnetic	IV sedation
Medirex Tripter X	mobile C-arm	Spark gap	IV sedation
Medispec Econolith	mobile C-arm	Spark gap	IV sedation
Fixed			
Siemens Lithostar	x-ray, US	Electromagnetic	IV sedation
Medstone STS	x-ray, US	Spark gap	IV sedation
Storz Modulith	x-ray, US	Electromagnetic	IV sedation
Dornier (DoLi)	x-ray +/- US	Electromagnetic	IV sedation

US, ultrasound.

Table 10-6. Characteristics of “third-generation” shock wave lithotriptors

Suggested Reading

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Chapter 11 Management of Urinary Incontinence

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The patient complaining of wetness presents a challenging problem, and an orderly approach to diagnosis and treatment is required. **Urinary incontinence**, the involuntary loss of urine, is a symptom or sign of urinary tract dysfunction; it is not a disease (Table 11-1). The presence of even minor degrees of urinary incontinence may be a devastating problem for patients, preventing them from leaving home or enjoying normal activities. The clinician must determine (a) whether it is urine that is leaking, (b) the source of the urinary loss, (c) the underlying pathophysiologic mechanism, and (d) the appropriate therapy.

Detrusor	Urethra	Nonurinary causes
Instability	Incompetence	Impaired mobility
Hyperreflexia	Hypermobility	Impaired mentation
Impaired contractility	Trauma (surgery)	Medications
Low compliance	Denervation	Psychiatric disease
Low capacity	Radiation	
	Diverticulum	

Table 11-1. Causes of urinary incontinence

I. Nonurinary Wetness

As a first step, the type of fluid actually leaking should be identified. Nonurinary perineal wetness may easily be confused with incontinence. Urine may be identified by measuring the creatinine level of the fluid, which will be markedly elevated in urine. Agents that color the urine, such as indigo carmine or phenazopyridine, can also be used. If the perineal fluid does not obviously stain with these agents, it is not urine. A perineal pad is helpful in collecting the perineal fluid, and it can be weighed to quantify the leakage. Nonurinary perineal wetness can occur from various sources.

A. **Gastrointestinal tract:** diarrhea, fistula, or leakage from a colostomy or ileostomy
B. **Vagina:** vaginal discharge, exudate, or transudate
C. **Serous or purulent drainage** from perineal infection or hidradenitis
D. **Perspiration**
E. **Subjective wetness:** a complaint of wetness when no wetness is demonstrated

II. Nonurethral Wetness

A. **Fistulae.** Wetness caused by fistulae may follow hysterectomy, radiation to the pelvis, or birth trauma. The most common type of fistula is vesicovaginal. A fistula may develop years after radiation therapy has been completed. The patient typically will complain of constant urinary wetness. Urinary fistulae are generally easy to diagnose on physical examination or cystoscopy. If the fistula is not obvious but is suspected on clinical grounds, the patient may be given a urinary coloring agent and instructed to wear a vaginal tampon and perineal pad. In the case of a urinary fistula to the vagina, the tampon will be stained but the perineal pad will not. Vesicovaginal and urethrovaginal fistulae may be repaired by a transvaginal or transvesical approach, depending on the location of the fistula and the experience and preference of the surgeon. Ureterovaginal fistulae require an abdominal approach because reimplantation of the ureter into the bladder is usually necessary.
B. **Ureteral ectopia**, in which the ureter congenitally inserts into a location other than the normal bladder trigone, may cause incontinence in female patients if the insertion is distal to the external urethral sphincter. Although ureteral ectopia is usually associated with a duplex renal collecting system in female patients, single ectopic ureters are encountered on rare occasions. The ectopic orifice usually drains the upper pole of a duplex system and may insert in the urethra, vagina, or perineum. Male patients with ureteral ectopia are generally not incontinent because ureteral insertion will always be proximal to the external sphincter; however, they may present with epididymitis. Ectopic ureter is almost always discovered in childhood. The patient or parents may note continuous urinary incontinence despite a normal voiding pattern. In the case of a duplicated system with a poorly functioning upper pole segment, treatment may consist of excision of the upper pole and a varying length of its draining ureter. In the case of a single collecting system or a duplex system with good function of the upper pole moiety, treatment is reimplantation of the ureter into the bladder.
C. **Vaginal reflux of urine** during voiding may result in postvoiding wetness. This condition may occur with vaginal stenosis or atrophy, congenital urethral “female hypospadias,” or repositioning of the urethra intravaginally following incontinence surgery.

III. Urethral Incontinence

See Table 11-1.

A. **Pathophysiology of continence.** Urinary continence requires that the bladder store an adequate volume of urine at low pressure, efficient urethral sphincteric function, and integrity of the neurologic control mechanisms to coordinate voiding and continence. The bladder neck must remain closed at all times, except during voiding, and must be able to withstand momentary increases in intraabdominal pressure. The prostatic and membranous portions of the male urethra act as the primary continence mechanism; the entire female urethra performs this function. In both sexes, the urethra prevents leakage by several important mechanisms.
   1. **Smooth-muscle tone** is the single most important factor in maintaining minute-to-minute continence.
   2. **Striated muscle fibers** are found within the urethral wall and in the periurethral area. The striated muscle constitutes the second line of defense against incontinence. The striated muscle within the urethral wall consists of “slow-twitch” fibers specialized to maintain constant tone. The periurethral fibers consist of “fast-twitch” fibers that can be rapidly activated to provide auxiliary compression, such as might be required during coughing. The periurethral striated muscle, innervated by the pudendal nerve, is much stronger in males than in females.
   3. **Coaptation of the mucosa** acts as a seal and reduces the urethral muscular tone required to prevent leakage. Female estrogens cause the urethral mucosa to proliferate and mature. It has been suggested that this factor may partially explain the increased incidence of stress incontinence in postmenopausal women. Urethral scarring, such as after multiple incisions for recurrent urethral strictures, may affect the ability of the urethra to coapt effectively.
B. The **classification of incontinence** is traditionally based on clinical symptoms rather than the pathophysiology.
   1. **Stress incontinence** is defined as the involuntary loss of urine during physical effort that is not caused by a bladder contraction. Terms such as **genuine stress incontinence** and **urethral incompetence** are sometimes used as synonyms. As a symptom or sign, stress incontinence does not indicate any

particular disease. It may be seen in both male and female patients but is much more common in women. Most commonly, this type of incontinence occurs in the upright position. Maneuvers that commonly elicit stress incontinence include coughing, lifting, straining, and laughing. The amount of urine lost is usually small, unless a bladder contraction is precipitated at the same time. Minimal or occasional stress incontinence probably occurs in all women at some point in their lives; however, significant stress incontinence (defined as occurring two or more times a month) affects 5% to 10% of women between the ages of 35 and 64. Stress incontinence is unusual in nulliparous women and becomes more prevalent as parity increases. In women, most instances of stress incontinence result from a defect in the pelvic support of the bladder neck (type I stress incontinence) or both the bladder neck and urethra (type II). In both of these types, increased intraabdominal pressure causes **hypermobility** of the bladder neck or urethra. In type III stress incontinence, there is no urethral hypermobility, but an intrinsic urethral defect is the cause of incontinence. Type III incontinence (**sphincteric insufficiency**) may be caused by trauma, denervation, multiple surgical procedures, radiation therapy, or postmenopausal atrophy.

In men, the most common cause of stress incontinence is prostatic surgery, especially radical prostatectomy. The incidence of permanent incontinence following transurethral resection of the prostate (TURP) is approximately 0.5%. After radical prostatectomy, the incidence of significant and permanent incontinence is 5%, although up to 30% of patients suffer some degree of leakage and require protection.

2. **Urge incontinence** is loss of urine associated with marked urinary urgency. Other storage symptoms are typically also present, such as frequency, urgency without incontinence, nocturia, and enuresis. By definition, involuntary bladder contractions that are idiopathic are referred to as detrusor instability, whereas those that occur in conjunction with a known neurologic disease (e.g., stroke, multiple sclerosis, spinal cord injury) are known as detrusor hyperreflexia. Typically, the patient reports the loss of considerable amounts of urine under specific circumstances, such as during cold weather, hand washing, or emotional upsets. In about one-third of patients with detrusor instability, there is a history of enuresis in childhood. In contrast to genuine stress incontinence, urge incontinence becomes increasingly likely as the bladder fills to capacity. Coughing or other stressful episodes may provoke bladder contractions (stress hyperreflexia of the bladder), making this type of incontinence difficult to differentiate from genuine stress incontinence.

   In men, urge incontinence may be a manifestation of outflow obstruction, idiopathic detrusor instability, or neurologic disease. In addition, idiopathic loss of bladder capacity or radiation therapy may be factors.
3. **Overflow incontinence** is sometimes called paradoxical incontinence because it results from chronic urinary retention. The patient leaks urine episodically and never voids normally. Leakage may be worsened by any increase in intraabdominal pressure. This type of incontinence may be caused by neurogenic impairment of bladder contractility or by outflow obstruction, especially in men.
4. **Total incontinence** refers to **constant** diurnal and nocturnal incontinence without normal voiding. The symptoms may be similar to those of overflow incontinence, but total incontinence may be differentiated from overflow incontinence in that little or no urine is obtained on catheterization of the bladder. This type of incontinence may be seen in neuropathic bladder dysfunction (especially peripheral neuropathy), after obstetric or surgical injury to the female urethra, with epispadias in children, and following radical prostatectomy in male patients.
5. In **functional incontinence**, the urinary organs are normal but the patient voids without regard to the social norms of time and place. This may be seen in patients with organic dementia, psychiatric disease, or physical problems of mobility or dexterity.
6. **Mixed incontinence** is frequently encountered in clinical practice. For example, an elderly male diabetic may have impaired detrusor contractility leading to increased postvoid residual as well as detrusor hyperreflexia resulting from small cerebral lacunar infarcts.
7. **Postvoid dribbling** may be caused by collection of urine in the urethral bulb or in a urethral diverticulum.

C. The major **mechanisms of incontinence** are classified below.

1. **Detrusor abnormalities** may cause incontinence by interfering with the ability of the bladder to store urine.
   a. **Loss of compliance.** A bladder that cannot maintain a low intra-vesical pressure during filling is said to have low compliance. Once the intravesical pressure exceeds that of the urethra, incontinence occurs even without a bladder contraction. This sequence of events can be seen in cases of myelodysplasia or other forms of neurogenic bladder dysfunction, and after bladder operations or pelvic irradiation.
   b. **Overactivity.** This term denotes an involuntary detrusor contraction (pressure >15 cm H_2O) that occurs during filling, either spontaneously or with provocative maneuvers such as standing upright. As mentioned before, when a specific neurologic cause such as cerebrovascular disease exists, the term **detrusor hyperreflexia** is used. Detrusor instability in men is most often associated with outflow obstruction. In women, the cause of detrusor instability is most often idiopathic. Detrusor instability can be demonstrated in approximately one-third of all women presenting with incontinence. If severe urgency is present, inflammatory or malignant conditions of the bladder (such as carcinoma *in situ*) should be ruled out with cystoscopy and urinary cytology.
2. **Urethral sphincter incompetence** may result from various causes.
   a. **Loss of anatomic support** is by far the most common and most important cause of urethral incompetence in female patients (see Table 11-3). Anatomic support of the female bladder neck and urethra results from the combined action of the pubourethral and urethropelvic ligaments and the supportive elements of the pelvic diaphragm. Loss of pelvic support may result from age-related loss of elasticity or multiparity. Of patients with urethral incompetence, about 50% have an associated cystocele or cystourethrocele and 25% have a rectocele. These manifestations of pelvic floor prolapse should be corrected at the time of surgery for stress urinary incontinence. With lesser degrees of pelvic floor laxity, there may be no obvious prolapse of pelvic organs, but abdominal straining may displace the urethra and bladder neck downward into the vagina--"hypermobility of the urethra." Why displacement of the urethra is associated with stress incontinence is not clearly understood, but several hypotheses have been put forward:

Grade 1	Minimal bladder descent with stress
Grade 2	Bladder descent to vaginal introitus with stress
Grade 3	Bladder descent to vaginal introitus without stress
Grade 4	Bladder prolapse with or without stress

Table 11-3. Clinical grading of cystoceles

   1. **Unequal transmission of pressure** occurs as the urethra is displaced from an intraabdominal position. During episodes of increased intraabdominal pressure (stress), more pressure is transmitted to the bladder than to the urethra, and urine is forced out.
   2. **Mechanical disadvantage** to the periurethral muscles results when the urethra is excessively mobile. These muscles cannot efficiently occlude the urethra during stress became their anatomic relation to the urethra is no longer normal.
   3. **Slow sphincter contraction** in women with stress incontinence has been documented. In some women with stress incontinence, the ability of the urethra to compress rapidly enough to prevent leakage during episodes of stress is decreased. The relation of this finding to urethral hypermobility is not understood.

   b. **Estrogen deficiency** leading to loss of urethral mucosal coaptation has been suggested as a factor in urethral incompetence.
   c. **Denervation** of the urethra may occur in conjunction with peripheral neuropathy, such as that found in diabetes mellitus.
   d. **Urethral scarring** may result from interference with the urethral blood supply. Multiple surgical operations or trauma may result in a urethra that is noncompliant and unable to coapt, frequently producing total incontinence.
   e. **Prostatectomy** is the most common cause of incontinence in male patients.
      1. After **transurethral prostatectomy**, continence depends on the presence of a stable bladder as well as the remaining distal smooth-muscle sphincter. The striated sphincter, as always, provides additional continence during periods of increased abdominal pressure, such as coughing or laughing, as well as during periods of increased bladder activity. Urodynamic studies in patients who are incontinent following transurethral prostatectomy have revealed that sphincteric insufficiency alone accounts for approximately 25% of cases. About 60% to 75% of patients had detrusor instability, although this was usually not the sole cause, as it was commonly combined with sphincteric insufficiency.
      2. **Radical prostatectomy**, whether performed by the retropubic or the perineal route, leads to incontinence much more commonly than transurethral prostatectomy. Despite the fact that the entire prostatic urethra is removed in this type of surgery, most studies have indicated—somewhat surprisingly—that urethral insufficiency alone is present in only about one-third of cases. Detrusor instability alone accounts for 20%, and the remainder represent a combination of these two factors. Patients who undergo a nerve-sparing radical prostatectomy appear to have a better chance of achieving continence than those undergoing standard radical prostatectomy. This may be because the nerves supplying the urethra are spared or because the blood supply of the urethra is preserved.

3. **Risk factors** for incontinence after prostatectomy include neurologic disease (cerebrovascular disease, Parkinson's disease, peripheral neuropathy), increased age, and prior radiation therapy to the pelvis.

IV. Evaluation of Incontinence

A. **Initial evaluation** of the incontinent patient is outlined in Table 11-2. The history is very helpful in determining the nature, duration, and severity of incontinence. Physical examination in female patients should include a speculum examination, bimanual pelvic and rectal examination, and occasionally cystoscopy (particularly if prior incontinence surgery has been performed). The presence of cystocele and rectocele on straining should be noted and graded (Table 11-3). In male patients, the rectum and prostate should be examined. In most cases, the diagnosis can be made reliably on the basis of history, physical examination, and a few specialized tests.

History		Physical Examination	
Duration:	Recent onset, long-standing	Pelvis:	Masses, cystocele, rectocele
Pattern:	Diurnal, nocturnal, occasional, constant	Rectum:	Resting tone, voluntary control, fecal impaction
Type:	Stress, urge, overflow, fatal	Urethra:	Marshall-Bonney test, "Q-tip" test
Voiding:	Normal, straining, frequency/urgency	Bladder:	Postvoid residual urine
Medications:	Anticholinergic agents, adrenolytic agents, diuretics, sedatives, hypnotics, opiates	Neurologic:	Perineal sensation, sacral reflexes
Surgery:	Previous anti-incontinence procedures, hysterectomy, prostatectomy		
Obstetric:	Parity, weight of babies, birth trauma		

Table 11-2. Clinical evaluation of urinary incontinence

1. **Pad tests** may be used to quantify the amount of urine lost during a 24-hour period. The wet pads are weighed and the weight of the dry pads subtracted, leaving the weight of urine lost.
2. **Postvoid residual urine** should be determined after the patient has voided. A low voided volume may reflect diminished bladder capacity. If there is little postvoid residual urine, overflow incontinence can be ruled out. The postvoid residual can be determined by catheterization. Alternatively, the use of small, portable ultrasound (US) postvoid bladder scanners can obviate the need for catheterization.
3. The **Marshall-Bonney test** is performed during the pelvic examination by asking the patient to bear down or cough with a full bladder. If incontinence is observed, the test is repeated after the urethra is gently elevated (but not obstructed) by two fingers placed inside the vagina. If incontinence is corrected by this maneuver—a positive test result—it indicates that a urethropexy or colposuspension should be successful. Although many authorities place little credence in this aspect of the Marshall-Bonney test, the objective demonstration of stress incontinence is valuable.
4. The **Q-tip test** is used to diagnose urethral hypermobility. After a sterile Q-tip is placed within the urethra, the patient is asked to cough or bear down. The normal urethra allows little movement of the shaft of the Q-tip during this maneuver. With urethral hypermobility, there is obvious movement.

B. **Urodynamic tests** are designed to measure pressure or flow during bladder filling or voiding. See Chapter 20 for details of urodynamic testing techniques.
1. **Cystometrogram.** The intravesical pressure is measured during bladder filling and during contraction to assess bladder function. The most common abnormality found is detrusor instability. Because detrusor instability and urinary incontinence may coexist, the presence of detrusor instability is not a contraindication to surgical therapy of incontinence; however, the patient should be forewarned that irritative symptoms may persist even after successful surgery. Conversely, the finding of detrusor areflexia, especially if associated with diminished bladder sensation, indicates the possibility of neuropathic incontinence. In patients with detrusor areflexia, there is a high likelihood that intermittent catheterization will be required after surgery for incontinence.
2. **Long-term ambulatory monitoring** of bladder pressure is performed with solid-state transducers and portable data storage devices. This technique monitors bladder pressure over an extended period (24 to 72 hours) and is much more sensitive than conventional cystometry in detecting detrusor instability.
3. **Abdominal leak point pressure** is measured during a conventional cystometrogram and is useful in both men and women with incontinence. The bladder is gradually filled with contrast and monitored fluoroscopically. After a volume of at least 200 mL is reached, the patient is placed in a sitting or upright position and asked to perform the Valsalva maneuver gradually. The lowest total bladder pressure at which leakage is detected is the abdominal leak point pressure. If no leakage occurs with the Valsalva maneuver, the patient is asked to cough several times, with repeated fluoroscopic observation for the presence of leakage. The abdominal leak point pressure of female patients with type I stress incontinence typically is above 120 cm H_2O; among those with type II incontinence, it is usually between 60 and 120 cm H_2O; and among those with type III incontinence, it is usually below 60 cm H_2O.
4. **Urethral pressure profile.** This test, which measures pressures generated along the length of the urethra, is occasionally useful in the evaluation of incontinence. Although patients with urethral incompetence tend to have lower values than healthy persons, there is so much overlap that static measurement of the urethral pressure profile is of little diagnostic use. The stress urethral pressure profile is more useful; it requires simultaneous measurement of intravesical and urethral pressure. In women with urethral incompetence, urethral pressure falls below bladder pressure during coughing or stress and allows leakage of urine. This abnormality is corrected by successful surgery.
5. **Uroflow measurements** in patients with incontinence are used to detect outflow obstruction. In female patients, this is an extremely rare cause of incontinence. It is much more common in male patients and may be the cause of detrusor instability. The uroflow pattern in detrusor instability is one of rapid attainment of high peak flow rates, whereas obstructed voiding is characterized by a low maximal flow rate and prolonged duration of voiding.
6. **Voiding cystourethrography** is often a useful test in the diagnosis of incontinence and may be combined with simultaneous urodynamic studies. Voiding cystourethrography is performed by filling the bladder with radiographic contrast and allowing voiding to occur. Fluoroscopic visualization of the bladder and urethra may give valuable information about vesicoureteral reflux, trabeculation of the bladder, sphincteric function, and outflow obstruction. In the upright position, contrast should not leak below the bladder neck. Intrinsic urethral dysfunction (caused by neuropathy or trauma) is possible if an open bladder neck exists at rest. With urethral incompetence, increased intraabdominal pressure will cause the bladder base and urethra to move inferiorly and the urethra to fill with contrast.
7. **The pressure-flow video study** is a urodynamic study combined with simultaneous voiding cystourethrography. It is useful when it is difficult to determine whether or not a bladder neck opening is a result of detrusor contraction. This technique permits accurate diagnosis of detrusor instability, detrusor-sphincter dyssynergia, and intrinsic urethral dysfunction. It is indicated in patients with neurogenic incontinence, those who have failed surgery, or patients with combined incontinence and obstruction.
8. **Sphincter electromyography** is occasionally useful in the diagnosis of incontinence. Proper innervation and function of the striated muscle (external) sphincter is important for coordinated micturition. Electromyography can therefore be used to demonstrate neuropathic involvement of the striated perineal muscles in peripheral neuropathies associated with diabetes mellitus, alcoholism, multiple sclerosis, and myelodysplasia. Electromyography is often performed simultaneously with a cystometrogram.

C. **Endoscopy** may be useful in either sex to rule out bladder trabeculation, stones, tumor, or diverticulum. In men with postprostatectomy incontinence, endoscopy may be used to assess the presence of strictures or bladder neck contractures.

V. Pharmacologic Treatment

An authoritative drug reference should be consulted before any medications are prescribed. The following sections contain guidelines only and describe many, but not all, of the drugs used in treating incontinence.

A. **Detrusor instability** may be treated effectively in many instances with anticholinergic agents or related compounds. Most of the drugs in this class produce dry mouth, blurred vision, mild tachycardia, drowsiness, and constipation. Dryness of the mouth is so common with most anticholinergic agents that it can be used to monitor for adequacy of drug effect. In general, if no effect on the bladder is noted, the dosage can be increased until significant dryness of the mouth is reported by the patient. Dryness of the mouth tends to become less prominent after several weeks of therapy. This class of agents is contraindicated in patients with narrow-angle glaucoma because mydriasis may cause acute intraocular hypertension. In addition, all the medications listed below have prominent anticholinergic effects and should therefore be used with caution in the elderly and in all patients with autonomic neuropathies, hepatic or renal disease, hyperthyroidism, coronary artery disease, congestive heart failure, cardiac tachyarrhythmias, hypertension, or hiatal hernia associated with reflux esophagitis. In patients with detrusor instability resulting from outlet obstruction, the use of these medications may lead to urinary retention.
1. **Oxybutynin chloride** is widely prescribed for detrusor overactivity. It has anticholinergic, antispasmodic, and local anesthetic actions. The recommended dose is 5 mg orally two to four times daily. It is available in liquid form for children. A slow-release form (Ditropan XL) is now available.

2. **Tolterodine tartrate** is a new anticholinergic agent with a significantly lower profile of side effects. In particular, dry mouth is less prominent, so that patient compliance is improved. It is given in doses of 2 mg twice daily.
3. **Hyoscyamine sulfate** is an anticholinergic agent available in tablet or liquid forms. The dose is one tablet orally every 4 hours or one teaspoon orally every 4 hours.
4. **Dicyclomine hydrochloride** has both antispasmodic and anticholinergic actions. It is given in doses of 20 mg orally three or four times daily, but higher doses are often required to obtain a good clinical effect.
5. **Flavoxate hydrochloride** is similar to dicyclomine in its pharmacologic properties. The recommended dose is 100 to 200 mg orally three or four times daily.
6. **Imipramine hydrochloride** is a tricyclic antidepressant that blocks reuptake of norepinephrine by peripheral adrenergic nerves. Clinically, it suppresses bladder contractions and increases urethral pressure, but the mechanisms involved are unclear. The usual adult dose is 25 to 50 mg orally four times daily, reduced in elderly patients. Caution should be used when treating any patient with underlying cardiac disease. The drug can be combined with an anticholinergic agent such as oxybutynin, which permits a lower dose of these agents to be effective. The side effects of imipramine and the precautions regarding its use are similar to those for the other drugs listed above, but when it is combined with anticholinergic agents, its anticholinergic side effects may be additive. Other important side effects include obstructive jaundice, abnormal liver function, skin rash, and agranulocytosis. Central nervous system effects include parkinsonism, sedation, irritability, and fine tremor. A baseline electrocardiogram should be obtained in elderly patients or in those with underlying cardiac disease.

B. **Urethral incompetence.** Drug therapy should be considered for patients who have intrinsic urethral incompetence without hypermobility, those who refuse or are not well enough for surgery, and those for whom surgical procedures have failed.
1. **Pseudoephedrine hydrochloride** is a sympathomimetic agent that is available alone or as a component in cold and allergy preparations. The usual dose is 30 to 60 mg orally up to four times daily. All sympathomimetic agents should be used with caution in the elderly and in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure, and bladder outlet obstruction from prostatic hyperplasia.
2. **Phenylpropanolamine hydrochloride** is an a-adrenergic agonist used in doses of 50 mg orally three times daily. Like pseudoephedrine, this drugs works by increasing the muscular tone at the bladder neck and in the urethra. If detrusor instability is present, an anticholinergic agent may be used concurrently. Phenylpropanolamine is contraindicated in patients receiving monoamine oxidase inhibitors.
3. **Estrogens** have been reported to produce subjective improvement in postmenopausal women with stress incontinence, apparently by enhancing the mucosal quality (and therefore coaptation potential) of the urethra. Various preparations have been used, including 0.3- to 1.25-mg Premarin tablets daily, one applicator full of Premarin vaginal cream daily, and 1 mg of estradiol orally three times daily. Because estrogens have been reported to increase the risk for endometrial carcinoma and thromboembolic events, patients should receive the lowest effective dose and should be monitored every 3 to 6 months during therapy for vaginal bleeding.

VI. Surgical Treatment

A. **Fistulae.** Small vesicovaginal fistulae sometimes respond to endoscopic fulguration of the fistula tract. Most, however, require some type of surgical procedure. Repair may be either by the transvaginal or transabdominal route, depending on the preference and experience of the surgeon. Basic principles of fistula repair include (a) complete separation of the involved organs around the area of the fistulous tract; (b) watertight closure of each organ, preferably with nonoverlapping suture lines; (c) interposition of another tissue, if possible, such as omentum or peritoneum. Approximately 80% of traumatic fistulae are closed successfully with one operation, although in patients who have had radiation therapy, the success rate is only 50%.
B. **Ureteral ectopia.** Usually, the ectopic ureter is draining the upper pole of a duplicated renal unit. See Chapter 19 for a further discussion of this problem.
C. **Sphincteric incompetence**
1. **Intraurethral** and **bladder neck injections** should be considered in female patients with a well-supported urethra and urinary incontinence. Male patients with postprostatectomy incontinence are also candidates. Various materials have been described for this purpose.
a. **Cross-linked bovine collagen** elicits a minimal foreign-body reaction and has not been associated with particle migration. It has recently gained popularity for use as a urethral bulking agent in both male and female patients with incontinence. It is injected through a special needle into the submucosal space of the urethra near the bladder neck. This can be done either transurethrally or periurethrally. The material begins to degrade in 3 months and is completely resorbed within 1 year. The procedure may need to be repeated but has a reasonable success rate (25% to 50%) and very low morbidity in well-selected patients. In men with incontinence after transurethral prostatic resection (post-TURP incontinence), moderate success rates have been reported. In patients who have had radical prostatectomy or pelvic irradiation, success rates are significantly lower because of tissue fibrosis.
b. **PTFE paste** is a mixture of polytetrafluoroethylene micropolymer particles, glycerin, and polysorbate. PTFE particles elicit a foreign-body reaction at the injection site and produce a tissue-bulking effect. Because of concern about particle migration to other organs, PTFE has been largely replaced by bovine collagen injection.
c. **Autologous fat** is easily harvested and elicits little reaction after injection. The material is prepared by passing it several times through an 18-gauge needle to emulsify and soften it before injection.
d. The **technique of injection** is relatively straightforward but requires attention to detail. In male patients, the selected material is injected cystoscopically in four quadrants just proximal to the striated sphincter. In patients who have undergone radical prostatectomy, the material is injected into the anastomotic area. In female patients, a 22-gauge needle is placed lateral to the urethral meatus at 4 and 8 o'clock or 3 and 9 o'clock. It is advanced under endoscopic visualization until it is near the bladder neck and the injection is made. Injections may also be made in an antegrade fashion through an existing cystotomy tract or by flexible cystoscope.

2. **Retropubic suspension procedures**
a. **Marshall-Marchetti-Krantz procedure.** The retropubic space is developed, allowing placement of absorbable sutures adjacent to the urethra and at the bladder neck. The sutures are tied to the periosteum of the pubis, so that the urethra and bladder neck are elevated toward the pubis. The operation has a success rate of about 85% and rarely causes outflow obstruction. Its major disadvantage is that it cannot repair coexistent cystocele or urethrocele. The major complication is osteitis pubis (3%).
b. **Burch colposuspension.** Nonabsorbable sutures are placed in the anterior wall lateral to the urethra and bladder neck and are tied to the iliopectineal (Cooper's) ligaments. The success rate is reported to be more than 80%. The procedure can be used to correct coexistent mild-to-moderate cystoceles. Complications include detrusor instability, bladder trauma, postoperative retention, and osteitis pubis.
c. **Sling procedures** are usually reserved for patients with type III incontinence or in whom a previous operation has failed. The urethra is dissected out to permit placement of various materials, such as rectus fascia, Marlex, Mersilene, or Silastic, around it. The tension of the sling is adjusted to allow elevation of the bladder neck. Voiding difficulties are common, and most patients must use intermittent self-catheterization for an average of 30 days. Success rates vary from 75% to 95%. The major complications are operative injury to the urethra or bladder and delayed erosion of the sling into the urethra.

3. **Vaginal procedures**
a. **Anterior colporrhaphy** is commonly used to repair mild stress incontinence, especially when associated with cystocele or rectocele. Through a vaginal incision, the bladder neck and urethra are exposed. The pubocervical fascia is sutured in the midline to provide support for the bladder neck. Although the success rate of anterior colporrhaphy (65%) is not as high as that of suprapubic procedures, anterior colporrhaphy can correct coexistent prolapse, is very well tolerated, and has a low morbidity rate.
b. The **Stamey procedure** is a vaginal sling procedure performed both vaginally and through a small suprapubic incision. A nylon bolster suture is used bilaterally to suspend the urethra. Endoscopy is performed to make sure no injury to the urethra or bladder has occurred. The procedure is simple to perform and has a success rate of approximately 90%. The complications include infection of the suture material, which requires its removal.
c. The **Raz procedure** is similar to the Stamey procedure except that the sutures are not placed near the urethra but are situated well laterally into the anterior vaginal wall. It is thus a colposuspension from below. Success rates are similar to those for the Stamey procedure.
d. **Pubovaginal sling procedures**, as stated above, are usually reserved for patients with type III incontinence or in whom a previous operation has failed. The urethra is dissected vaginally to permit placement of a sling, usually a strip of rectus fascia. The sling is then brought out through a suprapubic incision and tied loosely. Voiding difficulties are common, and most patients must use intermittent self-catheterization for an average of 30 days but occasionally longer. Success rates are reported to be above 90%. The major complications are operative injury to the bladder, erosion of the sling, wound infection, and prolonged retention.

4. **Artificial urinary sphincter.** This device consists of a periurethral cuff, a pressure-regulating balloon inflated in the prevesical space, and a control valve implanted into the labia (or scrotum if used in men) (Fig. 11-1). When the control valve is activated (with a gentle squeeze), the periurethral cuff pressure lowers for several minutes to allow voiding, then automatically repressurizes. To prevent erosion into the urethra, the device is activated 6 weeks after implantation, when healing has progressed. The device should be used only in complicated instances of incontinence in which the standard procedures previously described have failed. Like all prosthetics, these devices may be complicated by mechanical failure or infection. In male patients, the cuff can be placed around the urethra or around the bladder neck. The control valve is then implanted into the scrotum. Patients with good manual dexterity who are highly motivated are candidates for this procedure. Detrusor instability or poor bladder compliance are relative contraindications. Approximately one-third of patients require revision of the device at some point. Nevertheless, the overall success rate is reported to be as high as 95% (including reoperations).

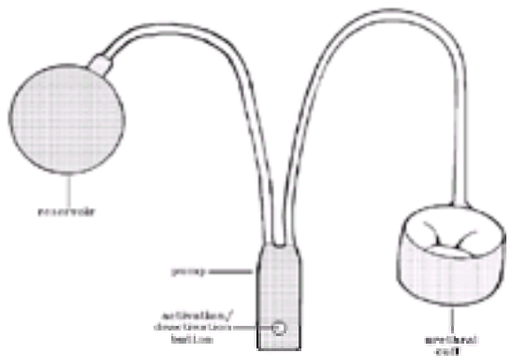

FIG. 11-1. Artificial urinary sphincter (American Medical Systems AMS-800).

D. **Diminished bladder capacity** leading to incontinence may be managed by augmenting the native bladder with a detubularized segment of bowel. The goal of this surgery is to produce a compliant, low-pressure reservoir without contractions that cannot be inhibited.
   1. **Augmentation cystoplasty** may be accomplished by a variety of techniques with an isolated segment of bowel, such as ileum, cecum, stomach, or ileocecal segment, to improve the bladder capacity and lower the intravesical pressure.
   2. **Urinary diversion.** Supravesical diversion is generally applied as a last resort in incontinent patients. The simplest method is an ileal conduit, in which the ureters are implanted into an isolated segment of small bowel. A cutaneous ostomy is then created, and the urine collected in a bag. Continent supravesical diversions have also been designed, in which detubularized bowel is used to fashion a urinary reservoir. The patient then empties this “substitute bladder” several times a day by catheterizing a small stoma brought up to the skin. Because the stoma is continent, no external appliance is needed. Supravesical diversion is indicated when incontinence is unmanageable by other means or when serious upper urinary tract deterioration is caused by high intravesical pressure or vesicoureteral reflux.

VII. Use of Catheters

Many patients, because of age or associated disabilities, cannot be treated by the surgical or pharmacologic means described above or simply fail to respond.

A. **Indwelling urethral catheters**, including urethral Foley catheters and suprapubic catheters (see Chapter 3), may be responsible for considerable morbidity if used improperly. The incidence of catheter-associated bacteriuria ranges from 3% to 10% per day of catheterization. The incidence of febrile episodes related to indwelling catheters is about 1 per 100 days of catheterization. Therefore, most episodes of bacteriuria are asymptomatic, representing only colonization and not pathogenic infection. Consideration should always be given to not treating asymptomatic bacteriuria, as growth of resistant organisms may be promoted. In addition to bacteriuria, indwelling catheters may produce epididymitis/orchitis, periurethral abscess, and urethral erosion in both male and female patients. Patients with indwelling catheters also have an increased incidence of bladder stones and bladder carcinoma. To reduce the incidence of sepsis, the catheter should drain into a closed system with a one-way valve to prevent reflux of urine and a port to permit collection of urine samples without opening the system. The two major sites for bacterial growth in a closed system are the drainage bag and the space around the catheter within the urethra. To prevent bacterial ascent around the catheter, hospitalized male patients should have the meatus cleansed with an antiseptic solution such as povidone-iodine (Betadine) twice a day. For patients at home, the use of mild soap and water is usually sufficient.
   1. **Catheter fixation** is important to prevent trauma to the bladder and urethra resulting from traction on the catheter. The balloon is not sufficient to keep the catheter in place; many patients have pulled out Foley catheters with balloons fully inflated, occasionally causing significant urethral trauma. The catheter should be firmly fixed to the upper thigh with a Velcro band or tape.
   2. **Catheter changes.** All catheters tend to deteriorate over time as they are exposed to urine. When the lumen becomes obstructed, the catheter should be exchanged for one of the same size and type. There are no hard data to support a particular schedule of catheter changes, but once a month is a commonly used schedule.
   3. **Leakage** around an indwelling catheter is a common problem, especially in female patients. It is caused most commonly by the presence of uninhibited bladder contractions, loss of urethral tone, or both. The new onset of this symptom may indicate infection, bladder stones, or bladder carcinoma. It is generally futile to insert a larger catheter because this merely results in further urethral stretching. The patient should have a complete urologic evaluation to ascertain the cause. Pharmacologic therapy to decrease bladder contractions or increase urethral tone may be required to control leakage around a catheter.

B. **Intermittent catheterization** may be performed with sterile or clean technique and may be carried out by the patient or by others (see also Chapter 3). Sterile (aseptic) technique requires the use of sterile gloves and a sterile catheter each time. Clean technique does not require the wearing of gloves, and the catheter is washed with soap and water after each use. Intermittent catheterization has many advantages over indwelling catheterization, including (a) significant reduction in bacteriuria and other complications, (b) reduced trauma to the urinary tract, and (c) greater patient independence. The only true contraindications to intermittent catheterization are structural obstruction of the urethra, severe urethritis, and possibly low-pressure vesicoureteral reflux. Almost any patient with manual dexterity, including the very young and very old, can successfully learn the technique. Although the incidence of bacteriuria is somewhat lower when the aseptic technique is used, this may be offset by the expense and time required. Thus, aseptic technique is almost always used in hospitalized patients, but clean technique is taught to patients who must use the technique at home.

VIII. External Collecting Devices

A. The **condom catheter** is one of the most effective techniques for managing incontinence in male patients. It consists of a penile sheath, a collecting tube, and a drainage bag (Fig. 11-2). The penile sheath is held in place by an adhesive band or by adhesive inside the sheath. The drainage bag is held in place by belts or straps around the leg. Some men have difficulty keeping the sheath in place because the penis is short or redundant penile skin is present. Such problems may occasionally require circumcision or penile prosthetic implants to increase the shaft length. Another problem is penile skin breakdown or necrosis from overzealous application of the adhesive band. Although it is difficult to estimate the extent, the incidence of bacteriuria is increased in patients treated with condom catheters.

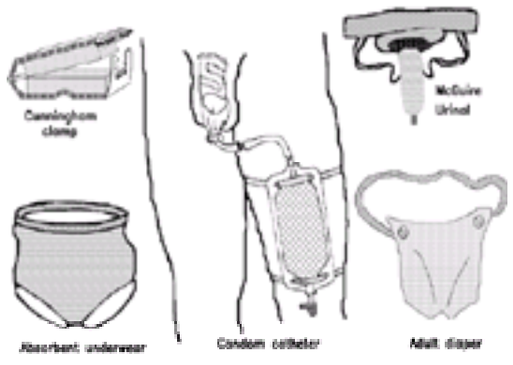

FIG. 11-2. Various external collecting devices in the male patient.

B. The **McGuire urinal** consists of a heavy rubber collecting pouch incorporated into an athletic supporter (Fig. 11-2). The patient places the penis into the pouch, obviating the need for adhesive bands around the penis. The McGuire urinal is best suited for moderately incontinent patients. With severe incontinence, the McGuire urinal can be attached to a leg bag. This device is not intended for nocturnal use.
C. The **Cunningham clamp** is a device placed around the penis to occlude the urethra (Fig. 11-2). The outside is made of metal, and the inside is cushioned. Although continence can be achieved with minimal urethral compression, the clamp nevertheless should be released every 4 hours. Complications include penile necrosis and urethral erosion, but in most patients the device continues to be very successful.
D. The **vaginal pessary** is in some ways the female counterpart of the Cunningham clamp. Available in various sizes, a vaginal pessary is a hard, rubber, doughnut-shaped device placed in the vagina to compress the urethra. It is generally fitted by a gynecologist.
E. **Absorbent aids** are usually made of disposable material with a waterproof backing.

1. **Pads** are commonly used by both women and men for mild-to-moderate incontinence. It has been estimated that 10% to 20% of sanitary napkins sold in the United States are purchased for incontinence rather than menstruation. The pads can be worn under the patient's usual underwear or under absorbent underwear.
2. **Diapers** for adults are available in both disposable and reusable forms (Fig. 11-2).
3. **Absorbent underpants** can absorb much more urine than pads and are less bulky than diapers (Fig. 2). Newer systems lock in fluid in gel form and contain agents to counteract urine odor. Examples are the Tranquility system and Attends disposable briefs.
4. **Male drip collectors** are designed to control minimal degrees of incontinence. They are disposable absorbent pouches fixed to the penis by an adhesive strip and worn inside the underwear.

F. **Care of the urinary stoma**

1. **Site selection.** Ideally, the urinary stoma is located over the lateral aspect of the rectus abdominis, away from bony prominences, scar tissue, skin folds, and the umbilicus. The patient should be able to see the stoma from both sitting and standing positions. The prospective stoma site is marked, and the patient wears a stoma appliance for 1 or 2 days to determine if the site is appropriate.
2. **Changing the flange.** Wash the skin around the stoma with soap and water and allow to air dry. After drying is complete, apply an adhesive skin preparation to the skin around the stoma. The flange should be cut to a size that is 1/8 in. larger than the stoma. If the flange is cut too large, urine will cause skin irritation (urea dermatitis). If the flange is cut too small, the flange will leak. If properly applied, a flange can remain in place for 3 to 7 days. Use hypoallergenic tape around the flange to reinforce the seal if needed.
3. **Changing the drainage bag.** The change interval depends on urine production. It is best to empty the bag when it is one-third full to prevent urea dermatitis. Reusable bags should be washed out and dried thoroughly between uses. At night, use a larger-capacity drainage bag to prevent urine leakage from interrupting sleep.

Suggested Reading

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Chapter 12 Male Erectile Dysfunction

Hossein Sadeghi-Nejad and Irwin Goldstein

I. Definitions

Erectile dysfunction is defined as the persistent inability to obtain and maintain an erection sufficient for sexual intercourse. It is estimated that between 18 and 30 million men in the United States are affected. Erectile dysfunction is more prevalent among patients with atherosclerotic peripheral vascular disease, hypertension, diabetes mellitus, hypercholesterolemia, and heart disease, and among men who smoke cigarettes.

Primary impotence refers to impotence that is lifelong, whereas **secondary impotence** implies the loss of previously normal potency. Impotence caused exclusively by emotional stress or psychiatric disease is termed **psychogenic impotence** and accounts for an estimated 10% to 50% of all cases of impotence. **Organic impotence**, which is erectile dysfunction caused exclusively by vascular, neurologic, endocrine, or other physical disease, accounts for an estimated 50% to 80% of cases. In the majority of impotent men, erectile impairment has both a psychological and an organic basis, and a complete management program will take this into account. **Priapism** is persistent erection that is not associated with sexual desire; it may be venoocclusive (associated with arterial ischemia and usually painful) or arteriogenic (occurring in high-flow states and painless; see Chapter 4).

Erectile function must be differentiated from libido, ejaculation, orgasm, and fertility. **Libido** is a psychological concept that describes the desire for sexual intercourse. **Ejaculation**, which is neurophysiologically distinct from penile erection, consists of three events: (a) seminal emission (delivery of semen to the posterior urethra), (b) bladder neck closure, and (c) propulsion of semen to the external meatus. **Orgasm** is the cerebral and psychological appreciation of release of sexual tension. **Infertility** is the inability to produce offspring, which is usually not caused by impotence.

II. Physiology of Erection

The penis is composed of paired erectile bodies (the corpora cavernosa) and the corpus spongiosum, which surrounds the urethra (Fig. 12-1). The fibrous tissue surrounding the outer covering of the corpus cavernosum is the tunica albuginea. The interior of the corpus cavernosum contains specialized, widely communicating, endothelium-lined vascular spaces that consist of connective tissue (50% to 55%) and corporal smooth muscle (45% to 50%) (Fig. 12-2).

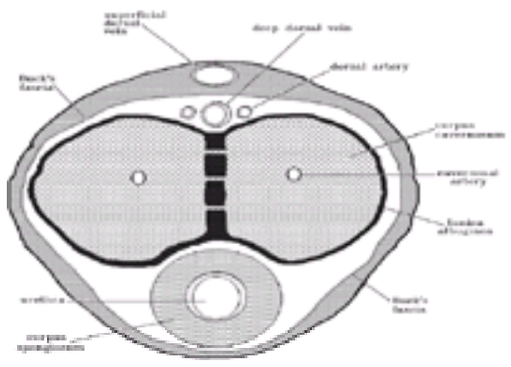

FIG. 12-1. Cross-sectional anatomy of the penis.

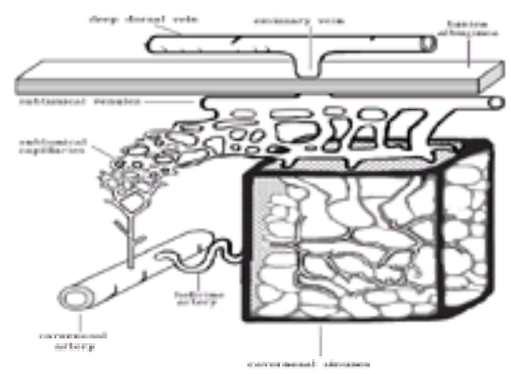

FIG. 12-2. Microcirculation of the penis. During erection, the subtunical venules are compressed against the rigid tunica albuginea, impeding venous outflow from the cavernosal sinuses.

A. **Blood supply** to the penis is from the internal pudendal artery, which divides into three terminal branches: (a) bulbourethral, (b) cavernosal, and (c) dorsal penile. Within the corpora, the cavernosal artery branches into the helicine arterioles. These arterial resistance vessels open into the lacunar spaces.
B. **Venous drainage**
   1. **Intracavernosal drainage** from the peripheral lacunar spaces passes into subtunical venules, which lie between the peripheral erectile tissue and the tunica albuginea (Fig. 12-2). A series of subtunical venules coalesce into emissary veins, which pierce the tunica albuginea to join extratunical veins. In the flaccid state, lacunar venous blood passes unimpeded from the subtunical to the emissary to the extratunical veins. In the erect state, however, the subtunical venules become stretched and compressed, thus forming the primary site of resistance to venous outflow during penile erection.
   2. **Extracavernosal drainage.** The three routes of extratunical venous drainage are the (a) deep dorsal veins, (b) cavernosal and crural veins, and (c) superficial dorsal vein. The deep dorsal veins accept most of the venous flow from the distal corpora by way of emissary and circumflex veins. The deep dorsal veins empty into Santorini's vesicoprostatic plexus. The proximal corporal bodies are drained by the cavernosal and crural veins, which drain into both Santorini's vesicoprostatic plexus and the internal pudendal vein. The superficial dorsal vein drains blood from the pendulous penile skin and glans and communicates with the deep dorsal vein.
C. **Vascular physiology**
   1. **Nitric oxide.** The corporal smooth muscle is contracted in the flaccid state and relaxed in the erect state. Following sexual stimulation, initially contracted helicine arteriolar smooth muscle undergoes relaxation through release of neuronal nitric oxide, arterial inflow increases, and nitric oxide is released from endothelial cells. Nitric oxide is a gas that diffuses into the corporal smooth muscle and induces smooth-muscle relaxation. This latter process can occur only if the partial pressure of oxygen in the lacunar spaces is above 50 mm Hg, a situation that occurs only after exposure of the lacunar space to systemic arterial blood.
   2. **Venous outflow resistance.** Filling of the lacunar spaces stretches the subtunical venules to create venous outflow resistance and a further increase in intracavernosal pressure.
   3. **Detumescence** is brought about by neuronally mediated smooth-muscle contraction, with restoration of corporal venous drainage.

D. **Neurophysiology.** Most cerebral regulatory functions for erection occur in the hypothalamus and limbic system (Table 12-1). The efferent pathway is via the pelvic nerves, which are preganglionic parasympathetic nerves originating from S-2 through S-4. The pelvic nerves join the pelvic plexus, which gives rise to the cavernous nerve of the penis. Stimulation of the pelvic nerves causes a marked increase in flow through the pudendal arteries and entrance of blood into the cavernosal spaces. The afferent limb of the erection response is mediated by the dorsal penile nerve (a branch of the pudendal nerve), which transmits sensory impulses to the spinal cord. The role of the sympathetic nervous system in penile erection is not clear, but its activation is generally associated with contraction of corpus cavernosal smooth muscle and penile detumescence.

Response	Afferent	Spinal Cord	Efferent
Erection			
Reflexogenic	Pudendal nerve	S2-4 sacral	Pelvic nerves
Psychogenic	Cerebral	Suprasacral	Pelvic nerves
Emission	Pudendal nerve	Lumbosacral	Sympathetic nerves
Ejaculation	Pudendal nerve	S2-4 sacral	Pudendal nerve

Table 12-1. Neurologic pathways of the sexual response

III. Causes of Impotence

The causes of impotence are summarized in Table 12-2.

I. Psychogenic
II. Organic
  a. Inflammatory: prostatitis, urethritis, stricture
  b. Mechanical: chordee, Peyronie's disease, phimosis
  c. Postoperative: iatrogenic
  d. Occlusive: arteriogenic
  e. Traumatic: pelvic fracture, urethral rupture
  f. Endurance: chronic and systemic diseases
  g. Neurologic: neuropathy, temporal lobe epilepsy, multiple sclerosis
  h. Chemical: alcohol, marijuana, prescription drugs
  i. Endocrine: testicular failure, pituitary failure, hyperprolactinemia

From A. D. Smith, personal communication.

Table 12-2. Etiology of impotence

A. **Vasculogenic impotence**
   1. **Arterial disease.** Atherosclerosis is a common cause of organic impotence. Arterial impotence is characterized clinically by erections that take longer than usual to develop (diminished spontaneity), diminished rigidity, and failure to maintain the erection. Arterial erectile dysfunction may be associated with general vascular risk factors such as, hypertension, cigarette smoking, diabetes mellitus, and hypercholesterolemia. The incidence of impotence in atheromatous aortoiliac and peripheral vascular disease is about 50%. Blunt trauma to the perineum related to falls, sporting accidents, or bicycle injuries and blunt trauma to the pelvis (pelvic fractures) related to motor vehicle accidents may cause site-specific, nondiffuse arterial occlusive disease in the common penile or cavernosal artery.
   2. **Venogenic impotence.** The venous outflow regulatory mechanism depends on the completeness of trabecular smooth-muscle relaxation and the expandable mechanical properties of erectile tissue, defined as the ability to achieve maximal corporal volumes at low intracavernosal pressures. An increase in corporal smooth-muscle tone during stress or anxiety may induce a functional venous leak. An increase in the trabecular connective tissue content, which can be secondary to chronic ischemia-induced abnormal collagen metabolism, plays a central role in the pathogenesis of organic venous leak impotence. Ultimately, fibrosis of the erectile tissue causes a decreased expandability of erectile tissue, with subsequent poor stretching of the subtunical venules, poor venous outflow resistance, and failure to maintain erection. Ischemia may be secondary to atherosclerosis, pelvic or perineal injuries, or injuries to the penis that occur while the person is erect (fractured penis).

B. **Diabetes mellitus.** Diabetes mellitus is a common cause of organic impotence. Impotence is reported in up to 75% of diabetic patients and occurs in these persons 10 to 15 years earlier than in the general population. Patients with insulin-dependent juvenile diabetes commonly have peripheral neuropathic impotence. Those with non–insulin-dependent, adult-onset diabetes usually have vasculogenic impotence, but a combination of the neuropathic and angiopathic effects of diabetes is probably responsible in most cases.

C. **Renal failure.** Approximately 50% of dialysis-dependent uremic patients suffer from erectile dysfunction, but improvement after transplantation occurs in many patients—presumably because of reversal of the anemia associated with chronic renal failure or improvement in uremic neuropathy. Correction of abnormalities in zinc metabolism may also contribute to restoration of potency following renal transplantation. Hyperprolactinemia secondary to decreased clearance and increased production seen in end-stage renal disease has also been associated with erectile dysfunction.

D. **Neurologic lesions** can affect erectile function at many levels:
   1. **Intracerebral** (Parkinson's disease, cerebrovascular accident). Efferent pathways from the medial preoptic area or the hypothalamic center may be affected in addition to higher cortical functions affecting sexual response.
   2. **Spinal cord** (spinal cord trauma, multiple sclerosis, myelodysplasia). Approximately 30% of patients with cervical spinal cord lesions, 70% with thoracic lesions, and 50% with lumbar lesions are able to have reflex erections. In those with lesions of the upper cord, however, erections are short-lived and nonejaculatory and do not involve the corpus spongiosum. Psychogenic erections may occur in approximately 25% of patients whose spinal cord injury or lesion is below T-12. Psychogenic erections are not possible in patients with complete lesions above T-12. Erectile dysfunction may, in rare cases, be the sole presenting symptom of multiple sclerosis. Sexual dysfunction may be seen in up to 75% of patients with multiple sclerosis.
   3. **Peripheral nerves** [alcoholic neuropathy, diabetic neuropathy (see above), after surgery or trauma]. Damage to the cavernous nerves during radical pelvic surgery, such as radical prostatectomy, is not uncommon. Diabetic neuropathy is the most frequent cause of peripheral neurogenic impotence.

E. **Endocrine disorders** are responsible for fewer than 5% of instances of impotence. Isolated testosterone deficiency is rare and is usually accompanied by a marked loss of libido. Testosterone is not directly involved in the vascular and neurologic events associated with penile erection.
   1. **Hypogonadotropic hypogonadism** (Prader-Willi and Laurence-Moon-Biedl syndromes). These syndromes are rare, and patients usually present to the pediatrician or internist with delayed puberty.
   2. **Hypergonadotropic hypogonadism** (Klinefelter's syndrome, mumps orchitis, surgical orchiectomy). These are all conditions in which the pituitary secretes excess gonadotropins in an attempt to overcome underlying testicular pathology. Potency may persist despite decreased libido.
   3. **Hyperprolactinemia** (pituitary adenoma, craniopharyngioma, drug therapy). Although prolactin promotes the action of androgens, at pharmacologic doses it may inhibit luteinizing hormone and testosterone release as well as the peripheral conversion of testosterone to dihydro-testosterone. Hyperprolactinemia is associated with low or low-normal levels of serum testosterone. Androgen replacement therapy without restoration of normal prolactin levels will not restore potency. The effects of hyperprolactinemia on erectile function appear to be centrally mediated. Serum prolactin may be lowered by administering bromocriptine, l-dopa, or cyproheptadine.

F. **Trauma**
   1. **Pelvic fracture** with ruptured posterior urethra. Suprapubic cystostomy, primary realignment, and primary realignment with immediate suturing are associated with a high incidence of impotence or decreased rigidity, ranging from 13% to 56%. Primary realignment with immediate suturing of the defect is associated with the highest incidence of impotence, likely secondary to disruption of the cavernous nerves during manipulation of the hematoma. Damage to the neurovascular bundle or to the internal pudendal or common penile artery at the time of injury is predominantly responsible for most of the erectile pathology seen in these injuries.

2. **Perineal trauma.** Many patients previously thought to have primary psychogenic impotence are found to have occlusion of the common penile or cavernosal artery secondary to perineal trauma that occurred before puberty. Bicycle accidents account for a significant portion of these blunt perineal injuries.

G. **Postoperative or iatrogenic impotence.**
   1. **Aortic or peripheral vascular surgery** may impair blood flow through the hypogastric arteries and thus cause arterial erectile impotence.
   2. **Renal transplantation** may cause impotence, especially if a second, contralateral transplantation is performed with end-to-end hypogastric artery anastomosis. In most instances, however, renal transplantation improves sexual function by reversing the anemia and uremic neuropathy associated with chronic renal failure.
   3. **Pelvic irradiation** may cause an accelerated occlusive atherosclerosis of the pelvic vessels leading to erectile impotence. Fibrosis of cavernosal erectile tissue secondary to irradiation of the crural region is also likely to contribute to postirradiation erectile dysfunction.
   4. **Cavernosal-spongiosal shunts** performed for the emergency treatment of priapism (Winter, Quackles, and El Ghorab procedures) can rarely produce a permanent corporal leak impotence.
   5. **Neurosurgical procedures.** Surgery such as lumbar laminectomy, sacral rhizotomy, and pudendal neurectomy can produce neurogenic impotence, especially if the sacral roots at S-2, S-3, and S-4 are injured.
   6. **Abdominoperineal resection of the rectum.** The incidence of impotence is higher if this operation is performed for malignant disease.
   7. **Radical prostatectomy or cystoprostatectomy.** The incidence of impotence approaches 100%, but this figure can be lowered to 40% to 60% if "nerve-sparing" techniques are used. Recent studies have implicated injury to the accessory pudendal artery and other perineal vessels during the course of the operation as one cause of postoperative impotence.
   8. **Transurethral sphincterotomy** may lead to impotence in rare instances. One should avoid incision at 3 o'clock and 9 o'clock to prevent thermal injury to the cavernosal arteries.

H. **Drugs.** Various medications are associated with erectile dysfunction. Please refer to Table 12-3 for a partial list of these agents.

Table 12-3. Partial list of medications that can cause impotence

IV. Evaluation

A. **Sexual history.** The onset, duration, and circumstances of the erection problem are all important. One can distinguish three different types of erections: partner-induced, nocturnal, and self-induced (masturbation). Three important qualities are hardness, maintenance, and spontaneity. It is useful to ask the patient questions concerning the qualities of all three types of erection. The degree of axial penile rigidity (hardness) can be quantified by using a scale of 1 to 10 in which 1 denotes the rigidity of a marshmallow and 10 the rigidity of a steel rod. Questions about the degree of maintenance should be asked in regard to previous capabilities. Questions concerning the degree of spontaneity should relate to the work, effort, and concentration required to achieve an erection compared with previous capabilities. Other questions include the following: Are there associated abnormalities in ejaculation, libido, or orgasm? Some symptoms suggest psychogenic impotence, and others suggest organic disease. A psychogenic cause is suggested by sudden onset of impotence or the presence of impotence under some circumstances but complete erection at other times. In contrast, gradual deterioration of erectile quality with preservation of libido suggests organic disease. Most patients with impotence can ejaculate despite poor or absent erections.

B. **Medical history.** Inquiries should be made about diabetes mellitus, hypertension, smoking, and hyperlipidemia, and about liver, renal, vascular, neurologic, psychiatric, or endocrine disease. Is there any history of abdominal, pelvic, or perineal surgery or trauma? The possible use of androgenic substances by athletes mandates inquiries about these agents, as they are associated with decreased serum testosterone levels and decreased libido.

C. **Psychological evaluation.** A psychological interview with a psychologist or sex therapist is used to assess the presence of personality disorders and anxiety. If possible, the couple should be present for the evaluation to assess their expectations from the planned therapy.

D. **Physical examination.** The general body habitus and status of **secondary sexual characteristics** should be assessed. Gynecomastia may be present in patients with androgen deficiency or estrogen excess. Absence of the peripheral pulses in the lower extremities may indicate vascular insufficiency. The penis should be examined carefully for adequacy of length, fibrotic regions of the tunica albuginea (Peyronie's disease), or deformity of the corporal bodies. It is important to stretch the penis to examine for tunical pathology. The dorsal penile pulse should be easily palpable. The presence, size, and consistency of the testes should be determined by palpation. The sensory function of the pudendal nerve can be assessed by pinprick testing of the penile and perineal skin. The integrity of the sacral reflexes is determined by eliciting the bulbocavernosus reflex.

E. **Laboratory tests** should routinely include a complete blood cell count, determination of blood sugar and serum creatinine, and liver function tests. In many cases, these data may have been recently obtained from the referring physician. Hormonal status is adequately assessed by serum testosterone, luteinizing hormone, and serum prolactin levels. Diurnal variations in testosterone levels do occur, and one abnormal value may not be reliable. An early morning determination of the serum testosterone level usually represents the peak value for the day. If both luteinizing hormone and testosterone levels are decreased, hypogonadotropic hypogonadism is suspected and warrants consultation with an endocrinologist.

F. **Specialized tests**
   1. **Nocturnal penile tumescence (NPT)** refers to the assessment of changes in penile circumference that occur during sleep. Such testing may be used to distinguish organic from psychogenic impotence, but its validity remains controversial. In the normal postpubertal male, three to five erections occur each night during rapid eye movement (REM stage) sleep. Each erection lasts approximately 30 minutes, and these episodes occur every 90 minutes. The number and duration of tumescence episodes decrease gradually with age. The use of NPT testing in the differential diagnosis of impotence is based on two major assumptions: (a) the mechanism of nocturnal erection is identical to that of erotic stimulation (unproven), and (b) the psychogenically impotent patient will have normal erections during sleep (mostly true). With any technique one may see false-positive results (lack of erection the first night of monitoring because of abnormal sleep pattern) and false-negative results (change in full circumference but poor rigidity in organic impotence). Overall, the accuracy of NPT in distinguishing organic from psychogenic impotence is approximately 80%. Formal NPT testing is usually performed in a sleep laboratory and is thus somewhat impractical and costly. Various types of NPT techniques are as follows:
      a. **Penile strain gauge.** A circular strain gauge is placed at the base and tip of the penis. Penile erection results in stretching of the strain gauge, which is recorded. This technique measures only change in circumference, not rigidity.
      b. **Snap gauge.** A disposable band is placed around the penis; the band contains three plastic strips that snap on stretching. Each strip has a different tensile strength (approximately 80, 100, and 120 mm Hg). The snap gauge provides a rough measure of rigidity and circumferential change but not a written record.
      c. **Rigiscan** is an ambulatory device consisting of two loops placed around the base and tip of the penis that send information to a microcomputer to measure penile circumference and radial rigidity. Radial rigidity does not predict axial buckling forces in a patient, and thus the value of the Rigiscan is questionable.
   2. **Neurologic testing.** Penile biothesiometry (vibration testing) is used to assess the threshold for vibratory sensation. This is a very limited test because it is not neurophysiologic. The following tests should be considered in the presence of neurologic disease or abnormalities detected during physical examination, but they should not be used for screening: (a) dorsal nerve conduction time—for peripheral sensory neuropathy; (b) sacral evoked response—for pudendal nerve and sacral cord lesions; (c) dorsal nerve somatosensory evoked potential testing—for peripheral and central nervous system lesions in the sensory (afferent) pudendal pathway.
   3. **Vascular testing**
      a. **Penile-brachial index testing.** A Doppler stethoscope and a 1.2-cm penile cuff are used to determine penile artery systolic pressures. This value is expressed as a ratio, with the systemic blood pressure measured in the arm, and the result is considered abnormal if the ratio is less than 0.60. This test is now rarely performed, as it is not possible to distinguish which penile artery is being assessed or the location of the vascular lesion.
      b. **Duplex ultrasonography.** B-mode images and Doppler values are obtained with a 7.5-MHz transducer during a pharmacologically induced penile erection. This test is performed to assess cavernosal artery diameter and flow velocity; simultaneous functional and anatomic information are thereby

obtained. Peak flow velocity, acceleration time, diastolic flow velocity, and resistive index are some of the parameters that can be measured to gather information about the relative status of penile inflow and outflow mechanisms in a minimally invasive fashion.

c. **Dynamic infusion cavernosometry and cavernosography.** The intracavernosal pressure and volume are measured following injection of intracavernosal vasoactive agents. In healthy persons, the equilibrium intracavernosal pressure is recorded after 10 minutes to approximate the mean systemic arterial blood pressure (90 mm Hg). Subsequently, infusion of saline solution into the corpora is begun through a separate intracavernosal needle. Flow rates for maintenance of various intracavernosal pressures are recorded. Generally, an infusion rate of less than 5 mL/min is required to maintain a series of intracavernosal pressure values. Once a pressure of 150 mm Hg is reached, the infusion is stopped and the "pressure decay" is noted after 30 seconds. Normally, the pressure should not drop more than 45 mm Hg in 30 seconds. Patients suspected of having venous leak impotence, based on abnormalities of the flow-to-maintain and pressure decay studies, undergo infusion of x-ray contrast into their corpora to confirm the diagnosis. Radiographic demonstration of contrast outside the corpora following administration of intracavernosal papaverine, combined with the inability to sustain intracavernosal pressure, indicates impotence caused by "corporal venous leak." Arterial integrity is assessed in this study by recording the cavernosal artery systolic occlusion pressure and comparing this value with the systemic brachial artery systolic occlusion pressure.

d. **Selective internal pudendal arteriography.** Arteriography is a more invasive test that is indicated if arteriogenic impotence is suspected in a candidate for microvascular arterial bypass surgery for impotence. Arteriography is usually performed with intravascular and intracavernosal vasodilators and patient sedation to optimize visualization of the cavernosal vessels.

V. Treatment

A. **Sex therapy.** Patients with evidence of psychogenic impotence and no discernible organic cause should be encouraged to undergo a short course (6 to 12 weeks) of sex therapy. The details of this therapy are beyond the scope of this chapter. In organic impotence, behavioral sex therapy may be combined with various other forms of therapy in selected cases to optimize patient response. Because performance anxiety may continue to play a significant role in a couple's sexual life after medical or surgical treatment, behavioral sex therapy must not be routinely abandoned in the presence of organic pathology.

B. **Nonsurgical therapy**

1. The **vacuum erection device (VED)** is considered as one of the three main forms of therapy for erectile dysfunction by the American Urological Association (AUA). The VED is best suited to the patient who wants noninvasive treatment. It consists of a cylindrical component and a suction device that the patient places around the penis to create negative pressure and achieve an erection. Maintenance of erection is then accomplished with a constriction ring. The advantages of VED include simplicity of use, low cost, relative safety, and the ability to start treatment immediately. Patient compliance with the recommended guidelines for use is mandatory because serious problems may be encountered if the VED is left in place for a long period. Patients with significant peripheral vascular disease and diabetics are generally not good candidates for the VED.
2. **Intracavernous pharmacotherapy.** Most patients suffering from erectile dysfunction, both organic and mixed, may potentially be treated with intracavernous pharmacotherapy. Safety and efficacy have been established in multiple studies, including those associated with the 1995 Food and Drug Administration approval of alprostadil (prostaglandin E_1) as therapy for erectile dysfunction. Intracavernosal pharmacotherapy with vasoactive medications is contraindicated in patients taking monoamine oxidase (MAO) inhibitors, patients with hypersensitivity to these agents, and those prone to secondary priapism (e.g., sickle cell disease or trait, leukemia, or multiple myeloma). Alprostadil alone (usually 1 to 40 µg) or in combination with papaverine and/or phentolamine mesylate may be injected intracavernosally. Most studies show increased efficacy for the three-drug combination regimen compared with monotherapy. Lower doses of vasoactive agents are typically given to spinal cord-injured patients, whereas diabetics usually require higher doses. Onset of erection is usually around 10 minutes from the time of injection, and duration may range from 30 minutes to 6 hours.

   Before intracavernosal pharmacotherapy is instituted as a long-term form of therapy, a diagnostic and therapeutic trial must be performed in the office so that the patient is fully comfortable with the technique of injection and the dosage. Patients are usually advised to inject a maximum of three times per week. The initial acceptance rate for intracavernosal pharmacotherapy is between 65% to 85% in most studies, but there is a nearly 50% 1-year dropout rate. Loss of interest in sexual activity, complications of intracavernosal pharmacotherapy (e.g., pain, recovery of spontaneous erections, other medical conditions) are some of the reasons for the high dropout rate.

   The **complications** of intracavernosal pharmacotherapy are summarized in Table 12-4. Local hematoma can be prevented by instructing the patient to compress the injection site manually for at least 3 minutes. Local induration may be reduced by alternating injection sites and limiting the injections to no more than two or three per week. **Priapism** is a potentially serious complication that can lead to permanent corporal fibrosis. Priapism of less than 24 hours' duration can usually be managed without surgery by corporal aspiration and intracavernosal injection of a-adrenergic agents (see Chapter 4). The patient on intracavernosal pharmacotherapy may experience local pain at the injection site for a short time after injection, but diffuse penile "ache" is more common. Prolonged pain may be experienced in the penile shaft or the perineum in approximately 20% of patients on prostaglandin E_1 monotherapy, but this is rare with papaverine or phentolamine.

Local hematoma	11%
Pain at injection site	8%
Priapism (>8 h)	3%
Penile induration	3%

Table 12-4. Complications of intracavernosal pharmacotherapy

Corporal fibrosis is the most significant long-term complication of intracavernosal pharmacotherapy and may be related to a number of factors, including drug effect, genetic predisposition, local trauma during intercourse, injection frequency, or a combination of these. It may resolve spontaneously in nearly 35% of patients, and intracavernosal pharmacotherapy may be reinstituted. Persistence of corporal fibrosis is not necessarily a reason to stop intracavernosal pharmacotherapy if the degree of fibrosis and deformity is not severe and is not interfering with intercourse. Insertion of a penile prosthesis and penile straightening will be required in refractory cases.

C. **Transurethral, oral, and topical therapy**

1. **Transurethral alprostadil.** A medicated pellet containing alprostadil is inserted intraurethrally with an applicator. Dissolved medication in the corpus spongiosum must pass into the corpus cavernosum to initiate the hemodynamic events leading to erection. Although most patients experience penile tumescence, a satisfactory rigid erection is produced in about one-third of patients. Recent studies suggest that placement of a penile ring may enhance intracavernosal drug delivery. Advantages include ease of delivery compared with intracavernosal injections. Penile pain is experienced by nearly one-third of patients.
2. **Oral sildenafil citrate.** Recently released, sildenafil acts by inhibiting the cGMP (cyclic guanosine monophosphate)-specific phosphodiesterase type V. The result is an increase in the intracellular concentration of cGMP and amplification of corporal smooth-muscle relaxation and erection. The drug is generally well tolerated and efficacious. Mild side effects such as headaches, dyspepsia, and subtle alteration in color perception cause drug discontinuation in fewer than 5% to 10% of patients.
3. **Oral phentolamine** is a direct smooth-muscle relaxant as well as an a_1- and a_2-adrenergic blocker. Preliminary studies have shown this oral medication to be effective and safe in the treatment of erectile dysfunction. The oral form of phentolamine is currently undergoing clinical trials. It has an excellent pharmacokinetic profile, with rapid peak levels and early clearance. It has also been shown to be free of major side effects to date.
4. **Apomorphine.** This is a dopamine receptor agonist that is currently undergoing clinical trials. Early studies seem to indicate that the drug may be most effective in persons with psychogenic erectile dysfunction.
5. **Androgen replacement** is indicated only in patients with documented androgen deficiency; it should not be used empirically. The cause of androgen deficiency should be thoroughly investigated. Older men should be followed regularly for prostatic enlargement or nodularity while receiving androgen

therapy. Prostate-specific antigen (PSA) must be checked annually.

a. **Parenteral testosterone** is the drug of choice. Testosterone enanthate or testosterone cypionate is given in a dosage of 200 to 400 mg intramuscularly every 2 to 4 weeks.
b. **Oral testosterone** may be given as 10 to 30 mg of methyltestosterone daily or 5 to 20 mg of fluoxymesterone daily but is generally less effective than parenteral therapy. Oral testosterone therapy is associated with cholestatic jaundice (reversible on withdrawal of drug therapy) and hepatocarcinoma. Liver toxicity is caused by 17a-methyl preparations of testosterone.
c. **Transdermal testosterone** therapy is now available, with the same benefits and side effects, although compliance may be significantly improved because of the ease of application.

D. **Surgical therapy**

1. **Vascular surgery.** Microvascular arterial bypass surgery for impotence is still considered “experimental” in the AUA guidelines for the therapy of erectile dysfunction. The recommendation is for this procedure to be performed only at centers with a large experience where the procedure is undergoing further evaluation. Patients with “failure-to-fill” erectile dysfunction and focal arteriogenic pathology are candidates for penile revascularization. Most ideal candidates are young men with a history of perineal or pelvic trauma in whom arteriography reveals a localized common penile artery lesion. Those with generalized vascular pathology are poor candidates for this operation, as the same disease will likely affect the revascularized segment in the years following surgery. Revascularization is achieved by microsurgical anastomosis of the inferior epigastric artery to the dorsal penile artery. The donor artery is carefully dissected from its origin at the femoral artery to a more distal point near the umbilicus, where it is transected. The cut artery is then brought through the inguinal ring into the scrotum for microvascular anastomosis to the right or left dorsal artery. Adherence to strict patient selection criteria will yield excellent long-term patency and patient satisfaction.
2. **Inflatable prostheses.** Excellent functional and cosmetic results are achieved with multicomponent penile prostheses. Inflatable prostheses consist of a pair of inflatable cylinders, a reservoir, a pump, and tubing to connect these components. The cylinders are implanted within the corpora, the pump within the scrotum, and the reservoir behind the rectus abdominis muscle in the prevesical space. Compressing the pump achieves active transfer of fluid from the reservoir into the cylinders. Pressing a release valve on the pump allows passive flow of fluid back to the reservoir and achieves detumescence. Significant alterations in design during the years since these devices were first introduced have reduced mechanical failures and improved safety and efficacy such that they now compare favorably with noninflatable rod-type devices. Recent multiinstitutional 2-year follow-up studies have shown an approximately 9% risk for morbidity, 7% risk for revision or explantation, and 2.5% risk for mechanical failure for one brand of the inflatable three-piece prostheses. Satisfaction rates of 80% or higher in terms of confidence and ability to have intercourse as well as function and rigidity of the prosthesis were reported in the same study.
3. **Noninflatable prostheses.** In general, these devices do not provide the cosmetic results achieved with the multicomponent inflatable devices, but the lower cost and relative ease of insertion make them desirable in selected cases. Infection rates range from 0.6% to 8.9%; infection is more likely to occur in the first 3 months (same as for the inflatable devices).

Suggested Reading

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Chapter 13 Male Reproductive Dysfunction

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I. Definition and Incidence

Infertility is defined as the inability to achieve a pregnancy resulting in live birth after 1 year of unprotected intercourse (primary infertility). Couples by whom fewer than the desired number of children are produced have secondary infertility. Fifteen percent of couples in the United States cannot achieve an unassisted pregnancy. A male factor can be identified in nearly 50% of these couples (one-third male factor only and 20% joint subfertility.)

II. Normal Hypothalamic-Pituitary-Gonadal Axis

Please refer to Fig. 13-1.

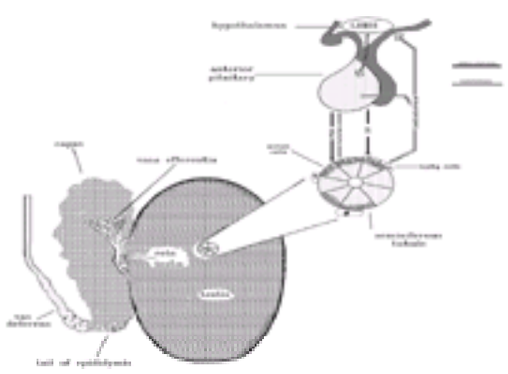

FIG. 13-1. Hypothalamic-pituitary-gonadal (HPG) axis. *LHRH*, leuteinizing hormone-releasing hormone. *FSH*, follicle-stimulating hormone. *LH*, luteinizing hormone.

A. The **hypothalamus** is the site of production of gonadotropin-releasing hormone (GnRH), which reaches the anterior pituitary via the portal system. GnRH is produced in the basal medial hypothalamus and the arcuate nucleus. The pulsatile release of GnRH depends on multiple stimuli, including catecholamines, dopamine, and serotonin. Endorphins, estrogen, and androgen can inhibit GnRH release.
B. **Pituitary.** The anterior pituitary secretes two important hormones (gonadotropins) that control testicular function—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Pituitary function and gonadotropin release depend on the pulsatile stimulation of GnRH at nearly 60-minute intervals. LH and FSH are glycoproteins with a- and b-subunits that are linked by noncovalent bonds. The biologic properties of each hormone are determined by its hormone-specific b-subunit. Conversely, the a-subunits are identical in LH and FSH as well as in other human glycoprotein hormones.
    1. **Luteinizing hormone.** Stored LH is released into the systemic circulation in a pulsatile fashion after GnRH binds the cell surface receptor. LH is the major stimulus to testosterone production by the **Leydig's cells**; testosterone exerts a negative feedback on pituitary LH release.
    2. **Follicle-stimulating hormone.** FSH is responsible for the initiation and maintenance of spermatogenesis and acts on the **Sertoli's cells**. It also causes increased production of müllerian-inhibiting factor, aromatase, and inhibin. The latter is a polypeptide secreted by the Sertoli's cells that has a negative inhibitory effect on pituitary FSH release. The negative feedback of testosterone and other steroids such as estradiol on the release of pituitary gonadotropins is mediated primarily via the hypothalamus and GnRH rather than by direct inhibition of the pituitary.
C. **Testis.** The testis is responsible for sperm production as well as testosterone synthesis and secretion.
    1. **Germ cells**, contained within the seminiferous tubules, constitute approximately 66% of the mass of the testis (Fig. 13-1). Spermatogenesis proceeds by the production of increasingly mature and differentiated germ cells (Fig. 13-2). Fully formed spermatozoa are finally extruded into the lumen of the seminiferous tubule. Mature spermatozoa are produced in about 71 days. FSH and high intratesticular concentrations of testosterone are required for germinal epithelium maturation.

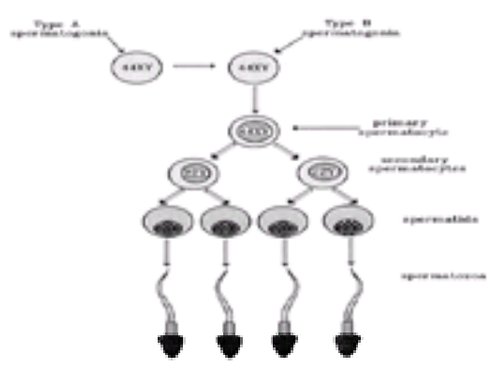

FIG. 13-2. Schematic representation of the sequential stages of spermatogenesis.

    2. **Leydig's cells** are located in the interstitium between the seminiferous tubules and produce testosterone in response to pituitary LH stimulation. The mean adult serum level of testosterone is 600 ng/dL (range, 250 to 1,000 ng/dL). Approximately 7.0 mg of testosterone is produced daily in a normal adult male. Most of the plasma testosterone (60%) is bound to sex hormone-binding globulin, and some (38%) is bound to serum albumin. The remaining 2% (free testosterone) is the physiologically active portion. A small amount of estradiol is also produced by the Leydig's cells.
    3. **Sertoli's cells**, also contained within the seminiferous tubules, lie slightly offset from the inside surface of the basement membrane. They surround the developing germ cells and have a nutritive and supportive role. Tight junctions between adjacent Sertoli's cells create an effective blood-testis barrier. The polypeptide inhibin, which suppresses FSH, is secreted by the Sertoli's cells. FSH action in the testis appears to be targeted toward the Sertoli's cells, which act as an intermediary between the germinal epithelium and pituitary gland.

III. Normal Testicular and Ductal Anatomy

A. **Testis.** Located in a dependent position in the scrotum, the human testes are paired oval structures weighing approximately 15 to 20 g in the male adult. They are covered by the tunica albuginea, a dense and fibrous capsule. Fibrous septa divide the testis into many lobules and segregate the seminiferous tubules. These long, V-shaped tubules terminate in the rete testis toward the posterior and central superior segments of the testis. They are composed of supporting cells (Sertoli's cells and peritubular cells) as well as the germinal elements that differentiate to form mature spermatozoa. The epithelium of the rete testis is flat

cuboidal. Efferent ductules emerge from the rete in the superior testis and end in the caput epididymis to form a single epididymal tubule. Blood supply is via the internal spermatic artery as well as the cremasteric and vasal arteries. Venous return is via the veins of the pampiniform plexus; these eventually join to form a single gonadal vein. The latter then empties into the renal vein on the left side and into the inferior vena cava on the right. The veins of the pampiniform plexus are intimately associated with the testicular (internal spermatic) artery.

B. The **epididymis** is divided into three segments (Fig. 13-1): the head (caput), body (corpus), and tail (cauda). Progressive motility and fertility are acquired by the spermatozoa during epididymal transit. Spermatozoa exit the testis via six to eight tiny tubules, collectively called the efferent ducts. These tubules quickly merge into a single tubule in the head of the epididymis (globus major). Pseudostratified columnar epithelium lines the epididymal tubule. Sperm in the caput region of the epididymis have limited fertilization ability and are relatively immotile. As they travel through the epididymis, their motility and capacity to penetrate through the egg membrane increase progressively. Blood supply is via the deferential artery and branches of the testicular vessels.
C. The **vas deferens** is a thick-walled structure that is embryologically derived from the mesonephric duct. Starting at the level of cauda epididymis and terminating at the ejaculatory duct, where it joins the ipsilateral seminal vesicle, each vas deferens is 25 to 45 cm long. The outer adventitial layer contains a rich neurovascular network. The lumen of the vas deferens is the continuation of the convoluted epididymal ductule in the tail (globus minor) of the epididymis and is lined with pseudostratified columnar epithelium. Roughly one-third of the sperm in the ejaculate comes from the tail of the epididymis and the remainder from the vasal ampulla, the dilated segment of each vas deferens located at its junction with the ejaculatory duct.
D. The **seminal vesicles** are lobulated structures, approximately 5 to 10 cm long and 2 to 5 cm wide, found lateral to the vasal ampullae on each side. The seminal vesicles do not store sperm, but rather produce a fluid rich in fructose and coagulation factors. Seminal vesicle fluid accounts for approximately 70% of the ejaculate volume, prostatic secretions contribute 20%, and vasal fluid containing sperm accounts for only 10%. Recent reports of seminal vesicle aspiration immediately after ejaculation document very few residual sperm in normal unobstructed male subjects. The luminal epithelium is of the pseudostratified columnar type.
E. The **ejaculatory duct** is the confluence of the seminal vesicle duct and the ampulla of the vas. It courses through the prostate to terminate at the verumontanum.
F. The **prostate** is a glandular structure situated between the bladder neck and external sphincter. Fibromuscular stroma surrounds the gland. Prostatic ducts empty into the urethra through the verumontanum.

IV. Neurophysiology of Ejaculation

Ejaculation consists of three distinct phases:

A. **Emission.** This is the initial deposition of the seminal fluid components from the vasa, vasal ampullae, prostate, and seminal vesicles into the posterior urethra. It is mediated by efferent sympathetic fibers emanating from T-10 through L-2.
B. **Bladder neck closure.** Coaptation of the circular smooth-muscle fibers of the bladder neck occurs during ejaculation to prevent reflux of seminal fluid into the bladder.
C. **Antegrade propulsion** is mediated by somatic efferents arising from S-2 through S-4 and results in forceful expulsion of seminal components through the urethra. This is the result of rhythmic contractions of the bulbocavernosus, ischiocavernosus, and pelvic floor muscles. Pelvic splanchnic nerves relay afferent sensory stimuli from the prostate, vas deferens, and seminal vesicles to the cord, whereas the sensory division of the pudendal nerve is responsible for the transmission of information coming from the genital skin afferents. The ejaculatory reflex center, located between T-12 and L-2, is thought to integrate higher cerebral neural inputs, the sensory fiber afferents from the genital region, and the sympathetic and somatic efferent motor outflow to coordinate temporally the various components of the ejaculatory reflex.

V. Spermatogenesis

Spermatogenesis is the series of events leading to the production of mature spermatozoa from spermatogonia (Fig. 13-2). It occurs in the seminiferous tubule. Forward motility is acquired during epididymal transport. The three major phases of spermatogenesis are as follows:

1. Spermatocytogenesis Spermatogonia type A ® type B ® primary spermatocytes (2N)
2. Meiosis I and II Primary spermatocytes ® secondary spermatocytes (1N) ® spermatids (haploid)
3. Spermiogenesis Spermatids ® spermatozoa (transformation with nuclear elongation and flattening, acrosome formation, and shedding of residual cytoplasm)

VI. Clinical Evaluation of the Infertile Couple

In treating infertile couples, the physician generally deals with young, healthy persons who are nevertheless faced with a profound organic dysfunction: the inability to procreate. The best approach is direct, factual, and sensitive to the psychological implications of infertility. In most instances, successful treatment of infertility requires that the urologist work closely with a gynecologist and occasionally an endocrinologist. The proper treatment of infertile couples often involves counseling and psychological support in addition to surgical or medical therapy.

A. **History.** Information regarding the duration of the marriage and attempts to conceive is essential in establishing that infertility exists. If either partner has been previously married, it is important to determine whether one or more pregnancies resulted, and if not, what the reasons were. One should take a survey of the sexual development of the male partner during childhood and puberty, including information about undescended testicles, hypospadias, gynecomastia, mumps, herniorrhaphy or scrotal surgery, and the onset of pubertal changes. A history of **cryptorchidism** is particularly important because the incidence of bilateral abnormalities is high even in unilateral cryptorchidism. The development and maintenance of libido, potency, and ejaculatory function should be noted. **Retrograde** or **absent ejaculation** is most often caused by diabetic autonomic neuropathy, sympatholytic drugs, or retroperitoneal surgery. A history of urethritis or epididymitis may suggest genital tract obstruction as the cause of infertility. Some **prescription medications** and **spermatotoxins** may adversely affect spermatogenesis or sperm motility (Table 13-1). Self-administered agents may also be detrimental to spermatogenesis, especially marijuana (reversible depression of spermatogenesis, likely secondary to alterations in the hypothalamic-pituitary-gonadal axis) and alcohol (probably a direct effect at the testicular level). Cigarette smoking has adverse effects on sperm count, motility, and morphology. The spermatogenic function of the testis is extremely sensitive to radiation and may be completely destroyed by as little as 80 cGy.

Dilantin
Valproic acid
Alcohol
Anabolic steroids
Cannabis (marijuana)
Cimetidine
Colchicine
Spironolactone
Nicotine
Nitrofurantoin
Sulfasalazine
Calcium-channel blockers

Table 13-1. Partial list of spermatotoxins

B. **Physical examination** in infertile male patients may provide a specific diagnosis or suggest the focus for the ensuing workup. The examination is best performed with the patient standing in a warm room.
   1. **Testes.** The size and consistency of the testes should be assessed, as spermatogenesis is often reduced or absent in small testes with an abnormal consistency. The normal testis is about 4.5 cm long and 2.5 cm wide, with a volume greater than 20 mL. Because the seminiferous tubules account for approximately two-thirds of the mass of the testis, patients with diminished spermatogenesis have a decreased testicular volume. Even in markedly atrophic testes, the Leydig's cells may be preserved and testosterone production may be relatively normal.
   2. **Spermatic cord.** Any asymmetry of the spermatic cords should be noted. The vas deferens and epididymis should be palpated for areas of tenderness or induration, which may be indicative of obstruction. The presence of both vasa must be clearly documented. **Bilateral absence of the vasa** is rare but may occur in up to 2% of infertile male patients. Both spermatic cords should be palpated for the presence of varicoceles (see below). The body habitus and the presence of gynecomastia or galactorrhea (possible indicators of excess circulating estrogens) must be noted. Abnormalities of the urethral meatus or any

penile anatomic features that could interfere with normal intercourse and delivery of ejaculate to the vagina should be evaluated.

C. **Laboratory evaluation**

1. **Semen analysis** is the single most important component of the laboratory evaluation of the infertile male patient. The semen should be collected after 3 days of abstinence from ejaculation. The specimen should be kept at room temperature and delivered to the laboratory within 1 hour. Three separate samples should be collected within a period of 4 to 6 weeks. Minimum adequate parameters of semen analysis found in fertile men are summarized in Table 13-2 and Table 13-3.

Ejaculate volume	>2.0 mL
Sperm density	>20 million per milliliter
Percent motility	>60%
Forward progression	>2 (scale 1–4)
Morphology	>30% normal forms

From *WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction*, 3rd ed. Cambridge, UK: Cambridge University Press, 1992.

Table 13-2. Semen analysis: standards of adequacy

Normozoospermia	Sperm density >20 million per milliliter
Oligozoospermia	Sperm density <20 million per milliliter
Azoospermia	Sperm density = 0
Asthenozoospermia	Motility <50%
Teratozoospermia	Morphology <30% normal forms
Oligoasthenoteratozoospermia (OAT)	Density, motility, morphology less than the minimal standards of adequacy
Aspermia	Absence of ejaculate

Table 13-3. Semen analysis nomenclature

a. **Seminal fluid** comprises the combined secretions of the prostate, seminal vesicles, and bulbourethral glands. Seminal volume normally varies from 1 to 5 mL, of which the prostate contributes one-third and the seminal vesicles two-thirds. If the seminal vesicles are absent, atrophic, or nonfunctional, or if bilateral obstruction of the ejaculatory ducts is present, the volume of the semen will be low (<1 mL) and the pH will be acidic (<7.0), the semen consisting mostly of prostatic fluid. The initial portion of the ejaculate contains most of the spermatozoa and secretions of the prostatic glands, Cowper's glands, and epididymis. The seminal vesicles contribute most of the final portion of the ejaculate. Following ejaculation, **coagulation** occurs secondary to seminal vesicle factors. Within 5 to 20 minutes, **liquifaction** of the coagulum by proteolytic enzymes in the secretions of Cowper's glands, the prostate, or both results in the formation of a semiviscous fluid. In some instances, delayed liquifaction (>1 hour) is observed; its significance is unknown.

b. The **fructose assay** is a technique to measure the amount of fructose in the semen semiquantitatively. Fructose is secreted by the seminal vesicles, and an absence of fructose in the azoospermic patient indicates either bilateral seminal vesicle aplasia or bilateral ejaculatory duct obstruction. If the seminal fluid volume is normal and the pH alkaline in an azoospermic patient, seminal vesicle fluid and therefore fructose will be present, and there is no need to perform the test. Conversely, if the semen volume is low (<1 mL) and the pH is acidic (<7.0) in an azoospermic patient, then one of those two diagnoses will represent the underlying etiology and the evaluation of fructose will not be helpful.

c. **Sperm density** varies over a wide range in fertile men (Table 13-2 and Table 13-3) and is poorly correlated with the conception rate. Thus, it is difficult to define a “normal” sperm density. Although 20 million spermatozoa per milliliter is commonly accepted as the lower limit of normal, as many as 10% of fertile men have a sperm density of less than 20 million per milliliter. The conception rate decreases with decreasing sperm density, but only azoospermia is absolutely associated with sterility.

d. **Sperm motility, morphology, and function** are perhaps more important than sperm density, although this is difficult to determine because poor motility and low density usually coexist. Sperm are said to have normal motility if at least 60% are moving in a straight line at a good speed. The forward progression score is a characterization of the direction and speed of the motile sperm fraction and is as important a parameter as the overall percentage of motile sperm. Asthenospermia (poor motility) may be secondary to improper collection methods and other artifacts, inherent factors, or morphologic abnormalities. Varicoceles, chromosomal abnormalities, and hematospermia are some of the other factors associated with abnormal motility. The spermatozoa must rapidly penetrate the cervical mucus and gain access to the cervical canal because the acidic vaginal secretions are able to immobilize spermatozoa within 1 to 2 hours. In contrast, spermatozoa may remain motile within the crypts of the uterine cervix for a period of 2 to 8 days, forming a sperm reservoir from which sperm may be constantly transported to the fallopian tubes. Fertilization of the ovum also requires that the spermatozoa undergo a final process of maturation in the female genital tract, called **capacitation**. Because of the complexity of this process, it is not surprising that estimates of sperm motility as commonly performed are a very crude index of fertilizing capacity. Sperm of normal morphology have smooth and oval heads with an acrosome that is well defined and comprises 40% to 70% of the total surface area of the sperm head. There should be no defects in the tail, midsection, and neck, nor any cytoplasmic droplets larger than half the size of the sperm head.

2. **Analysis of sperm function** is accomplished by looking at how sperm actually “work” in a biologic system. *In vitro* and *in vivo* assays of mucus define how the sperm penetrate and move in cervical mucus, which may be quite different from the motility they exhibit in a semen analysis. Fertilizing ability is the most critical attribute of sperm, and a sense of potential capability can be gained with the zona-free and human zona pellucida assays.

a. ***In vitro* mucus penetration tests**, commercially available in kit form, are designed to assess the ability of sperm to cross cervical mucus. The patient's sperm are mixed with either human or bovine cervical mucus in a capillary tube to determine how far they can travel within a standardized period of time.

b. ***In vivo* penetration testing**, called the **postcoital test** or **Sims-Huhner test**, is performed at the time of ovulation, when the partner's cervical mucus is most receptive to sperm penetration. The cervical mucus is examined under the microscope for motile spermatozoa within several hours of intercourse. The presence of 10 to 20 actively motile sperm per high-power field is considered normal. It is important to realize that an abnormal test result may indicate a deficiency of sperm motility as well as abnormalities of cervical mucus. Infections, presence of antisperm antibodies, and poor timing of the test may contribute to abnormal test results.

c. ***In vitro* fertilization testing** has become possible with the development of the **sperm penetration assay**, which measures the percentage of zona-free hamster eggs (eggs stripped of their zona pellucida) penetrated by the patient's sperm and the number of sperm that have gained entry into each oocyte. Although each laboratory has its own normal values, the sperm penetration assay can be quite predictive of the ability of a subject's sperm to fertilize oocytes, both in natural and *in vitro* environments. The hemizona assay measures the ability of the patient's spermatozoa to bind to receptors on the human zona pellucida. This test is currently under further investigation and refinement and is not widely available.

d. The **antisperm antibody assay** is used to detect antibodies directed against sperm surface antigens in the semen. Antisperm antibodies detected in the serum are thought to be less significant clinically. Testicular trauma, previous genital infections, or genital tract obstruction may predispose to elevated antisperm antibody levels. The immunobead test is one of the most precise antisperm antibody tests currently in use; it can detect immunoglobulin A or immunoglobulin G binding to sperm and is considered clinically relevant if more than 20% to 50% of sperm demonstrate binding to the polyacrylamide beads.

3. **Hormonal assays**

a. **FSH, LH, and testosterone** are routinely measured to detect abnormalities in the hypothalamic-pituitary-testicular axis, which account for a small percentage of patients with infertility. Interpretation of these tests is complicated by the wide range of normal values and by the considerable overlap between normal and abnormal. In men with mild oligospermia or motility deficiencies, hormonal abnormalities are rarely striking and often require provocative tests before they become manifest. No significant difference in levels of testosterone or estradiol exists between normal and oligospermic men. FSH may be elevated in both azoospermia and oligospermia. In general, only the severely oligospermic or azoospermic patient benefits from hormonal assessment.

b. **Elevation of prolactin** secondary to a pituitary microadenoma may result in suppression of FSH and LH output and is usually suspected when symptoms

and signs of testosterone deficiency are noted.

D. **Genetic assessment**
   1. **Azoospermia.** The azoospermic or severely oligospermic patient with spermatogenic deficiency may have an underlying genetic defect. A karyotype may reveal aberrations in chromosome number (e.g., Klinefelter's syndrome, 47,XXY; mosaic Klinefelter's syndrome, 46,XY/47,XXY) or chromosome structure (e.g., abnormal Y chromosomes, translocations). Spermatogenesis is controlled by at least one gene cluster (DAZ) located on the long arm of the Y chromosome. Approximately 13% of men with azoospermia and cytologically normal Y chromosomes have a deletion involving this region. Genetic defects of the androgen receptor, androgen synthesis, and intracellular androgen function may have variable indirect effects on spermatogenesis and fertility.
   2. **Syndromes of vasal aplasia** are predominantly a consequence of mutations in both alleles of the cystic fibrosis transmembrane conductance regulator genes. If the combination of the two abnormalities is “severe,” clinical cystic fibrosis will be present. However, if the phenotypic manifestation of the two anomalies is “less severe,” the patient may present clinically with one of the vasal aplasia syndromes but no recognizable pulmonary or pancreatic pathology.

E. **Radiologic evaluation**
   1. **Transrectal ultrasonography (TRUS)** is now the initial diagnostic modality for documenting ejaculatory duct obstruction and seminal vesicle/vasal absence or aplasia, including congenital bilateral absence of the vas deferens (CBAVD). Ejaculatory duct obstruction should be suspected in azoospermic or severely oligoasthenospermic patients with a low or low-normal semen volume. A previous history of recurrent prostatitis, perineal pain, hematospermia, epididymal pain, or pain with ejaculation is not infrequently present. It is important to note that the diagnosis is not excluded if the volume is normal. TRUS will demonstrate dilated seminal vesicles and ejaculatory ducts and occasionally a midline prostatic cyst in cases of ejaculatory duct obstruction. TRUS also helps define the depth of resection that may be necessary as treatment of ejaculatory duct obstruction. In cases of CBAVD, TRUS is clearly able to demonstrate the anatomic deficiencies of the vasal ampullae and seminal vesicles. Because the intrarenal collecting system, ureters, seminal vesicles, vasa, and distal two-thirds of the epididymis share a common embryologic precursor, renal US should be obtained in patients with syndromes of vasal aplasia to rule out ipsilateral renal anomalies.
   2. **Vasography**, now infrequently performed, permits radiologic visualization of the entire vas deferens from the most proximal straight portion to the ejaculatory duct and is indicated only in patients with vasal obstruction in the inguinal or pelvic area. It is not required in the patient with spermatogenic dysfunction at the time of testis biopsy nor in the patient with suspected ejaculatory duct obstruction. TRUS is the diagnostic step of choice in this latter circumstance. Retrograde contrast injection toward the epididymis should never be performed. There is no need for scrotal US in the routine evaluation of male infertility.

VII. Male Reproductive Abnormalities

A. **Low-volume azoospermia.** When no sperm are found in the ejaculate of the patient with a semen volume of less than 1 mL, either ejaculatory duct obstruction or one of the syndromes of vasal aplasia will usually be the cause.
   1. **Ejaculatory duct obstruction** may be of both acquired and congenital causes. Congenital midline prostatic cysts may be of müllerian origin and can outwardly compress the terminal portions of the ejaculatory ducts as they course through the prostate. These are easily seen with TRUS. Prior prostatic inflammation may result in scarring and occlusion of the ejaculatory ducts. In this circumstance, no intraprostatic dilation of the ducts will be seen, although there will be vasal ampullary and seminal vesicle dilation. Complete ejaculatory duct occlusion is manifested by low-volume azoospermia, but partial ejaculatory duct obstruction may present as severe oligoasthenospermia out of proportion to what might be expected from the testis size and consistency coupled with the hormonal data.
   2. **Congenital bilateral absence of the vas deferens (CBAVD)** and congenital unilateral absence of the vas deferens (CUAVD) are clinically mild forms of a phenotypic spectrum that includes cystic fibrosis. The presence of abnormalities (e.g., mutations, deletions of base pairs) in both the maternal and paternal copies of the cystic fibrosis transmembrane conductance regulator (CFTR) gene leads to defective protein action. Pulmonary and pancreatic ductal secretions are thick and tenacious as a consequence, and disease becomes manifest. In addition, nearly all male patients with cystic fibrosis have bilateral vasal aplasia and are infertile. CBAVD and CUAVD are limited, “mild” clinical expressions of CFTR dysfunction in which no pulmonary or pancreatic pathology is evident but vasal absence is still present. Cystic fibrosis mutation analysis is critical before commencement of infertility treatment for both partners to define and refine their risk, as a couple, of transmitting maternal and paternal CFTR gene anomalies. TRUS images seminal vesicle anatomic abnormalities, including aplasia, hypoplasia, or cystic dysplasia. The vasal ampullae are typically absent.

B. **Normal-volume azoospermia.** When the semen volume is normal, ejaculatory duct obstruction and CBAVD are not likely causes of azoospermia. Either an obstruction exists to sperm flow between the testis and vasal ampullae (implying normal spermatogenesis), or the ductal system is patent but spermatogenesis is markedly deficient.
   1. **Vasal or epididymal occlusion** may be congenital or acquired. The seminal fluid volume will be of normal quantity because so little of it is contributed by the vasal and epididymal component. Congenital epididymal obstruction is typically located at the vasal-epididymal junction. Acquired causes are numerous, the most common being vasectomy. Inflammation of the vas and epididymis may lead to scarring and point occlusions, most commonly in the epididymis. Tuberculous vasitis and epididymitis may completely obliterate large luminal sections, making reconstruction impossible. Young's syndrome is characterized by bronchiectasis and gradual epididymal obstruction by inspissated epididymal secretions. It is unclear whether Young's syndrome is also a mild form of cystic fibrosis. The testis size and consistency are normal, as spermatogenesis is unaffected. Serum FSH, LH, and testosterone are all within an adequate range, reflecting an uncompromised spermatogenic and androgenic axis. The epididymis may be firm and full, which can be appreciated only with careful and thoughtful physical examination.
   2. **Spermatogenic failure** that is sufficiently severe will lead to azoospermia. As explained above, the semen volume is relatively unaffected. Clinical clues to this diagnosis include small testes, reflective of a lack of spermatogenic cell mass. The consistency may be soft or firm, depending on the level of interstitial fibrosis that exists. In most instances, Leydig's cells are unaffected and testosterone production remains normal. If serum FSH is elevated, the problem is within the seminiferous tubules, and the pituitary is responding appropriately with a compensatory increase in its output of FSH (hypergonadotropic hypogonadism). If the FSH is undetectable, then a hypothalamic or pituitary anomaly is present in which testicular stimulation is absent (hypogonadotropic hypogonadism).

C. **Hypergonadotropic hypogonadism** is the end result of multiple conditions that limit spermatogenesis.
   1. **Klinefelter's syndrome** occurs in 1 in 500 live births. The karyotype reveals an extra X chromosome (47,XXY). Testes are small and firm. Gynecomastia may be present. Hormonal evaluation reveals elevated LH and FSH, whereas testosterone may be low.
   2. **XX male syndrome** is seen in 1 in 10,000 males and is the result of translocation of the sex-determining gene from the Y chromosome to either an autosome or one of the X chromosomes. Occasionally, an abnormality in one of the other genes is involved in the testis-determination cascade. These patients are phenotypically male with absent spermatogenesis. They are missing the “spermatogenesis” genes located on the long arm of Y that are required for optimal spermatogenesis.
   3. **DAZ gene cluster deletions** are found in approximately 13% of azoospermic men and in a lesser, but undefined, number of patients with oligospermia. Testing is not yet clinically available on a routine basis. Other spermatogenesis genes are actively being searched for and will likely help explain the remainder of the azoospermic population, for whose condition there is presently no recognizable etiology.
   4. **Bilateral mumps or viral orchitis**, radiation, chemotherapy, and other toxic/inflammatory insults may temporarily or even permanently suppress spermatogenesis. A proper history will elicit these causes.

D. **Hypogonadotropic hypogonadism** results from both pituitary and hypothalamic disorders. Serum testosterone and gonadotropin levels are typically very low, often undetectable. Panhypopituitarism may result from pituitary tumors and the treatment regimens employed.
   1. **Kallmann's syndrome** is the consequence of failure of GnRH neurons to migrate from the olfactory area to the hypothalamus during fetal brain development. Clinical findings include anosmia, infertility, and deficient virilization.
   2. **Prader-Willi syndrome** is also a form of hypogonadotropic hypogonadism resulting from hypothalamic dysfunction. In addition to the clinical signs mentioned above for Kallmann's syndrome, obesity, mental retardation, cryptorchidism, and diabetes mellitus may be found in Prader-Willi syndrome. Genetically, deletion of a region on chromosome 15 is often found.
   3. **Anabolic and androgenic steroid abuse** suppresses pituitary LH release, leading to decreased intratesticular testosterone production. The end result is severe oligospermia or azoospermia. Although the effects are thought to be reversible, long-term pituitary suppression has been reported. Extremely low, even undetectable FSH and LH levels in a well-virilized patient are the keys to diagnosis.

E. **Oligoasthenospermia.** Low sperm density and poor sperm motility often coexist; the term oligoasthenospermia is descriptive of the semen analysis only and is not sufficient for etiologic diagnosis. **Varicocele**, the most common cause of oligospermia, refers to the dilated, tortuous veins of the pampiniform plexus in the spermatic cord. It occurs unilaterally on the left in 80% of patients and bilaterally in 18%. The diagnosis is best made after the patient has been standing upright in a warm room for several minutes. Varicoceles have been reported in about 15% of the fertile male population. Although varicocele may be found more frequently in infertile male patients (40%), the pathophysiology of infertility in association with varicocele is unclear. Testicular arterial blood flow and temperature elevation with decreased Leydig's cell function have been demonstrated and may affect the contralateral testis as well. Partial ejaculatory duct obstruction and various toxins are two of the other possible causes of oligospermia in the infertile male patient. Finally, the etiology of oligoasthenospermia is often not apparent from the history and/or physical examination. In this regard, its cause is “idiopathic,” but it is more than likely that genetic and environmental mechanisms will soon be found to explain the most severe cases. Immunologic infertility may be suspected in the presence of considerable sperm clumping or agglutination; poor or absent motility with relatively normal sperm density; an abnormal postcoital test result; an unexpectedly poor result in the hamster egg

penetration test; or a history predisposing to the development of antisperm antibodies (e.g., vasectomy). The patient's semen should be tested for antibodies against sperm by the techniques described above.

VIII. Therapy of Male Reproductive Dysfunction

A. **Low-semen-volume azoospermia** (<1.0 mL)
   1. **Ejaculatory duct obstruction** is clearly defined with TRUS. Transurethral resection is carried out if TRUS has defined a midline cystic structure or intraprostatic dilation of the ejaculatory ducts. Excision of the roof of the cyst at the level of the verumontanum allows decompression of the cyst and relieves obstruction of the ducts. If there is no midline cyst, incision into the surface of the ejaculatory duct itself on the floor of the prostate is carried out. If the ejaculatory ducts are not dilated and are affected by fibrosis, transurethral resection will not be helpful. Direct ductal sperm aspiration will be the treatment of choice (see below).
   2. **Vasal aplasia** coexists with absence or aplasia of the seminal vesicles as a consequence of improper mesonephric duct development. No reconstruction is possible in these cases. As spermatogenesis is adequate and at least the caput epididymis is always present, it is possible to achieve pregnancy through a combination of microsurgical sperm aspiration (MESA) and intracytoplasmic sperm injection (ICSI). ICSI involves microinjection of a single sperm into an oocyte. Sperm that are surgically harvested from the epididymis have little capacity to fertilize but can readily participate in all the postfertilization events required for embryo development. When ICSI is used for fertilization of oocytes with sperm obtained by MESA, the results are superior to those obtained with conventional *in vitro* fertilization techniques (which require the sperm to fertilize the oocyte), and ICSI is now the preferred treatment for these patients. Sperm can be retrieved on the day of oocyte harvesting or can be obtained at a time remote from ICSI and cryopreserved. This type of specimen can be subdivided into many cryovials, each serving as the sperm source for a future ICSI cycle. With this approach, MESA needs to be carried out only once. Percutaneous epididymal sperm aspiration (PESA) is an alternative approach but is limited in terms of amount of sperm recovery and ability to cryopreserve several specimens.

B. **Normal-semen-volume azoospermia**
   1. **Primary spermatogenic failure** is not a surgically correctable lesion. FSH levels are typically elevated. Although testicular biopsy has traditionally been advocated, a thorough physical examination and review of relevant laboratory values will usually be enough for diagnosis. Testicular sperm extraction (TESE) is a form of excisional therapeutic biopsy of the testis. Sperm are obtained with microscopic assistance from the excised specimen, and ICSI is performed with those individual spermatozoa. Approximately 50% to 75% of azoospermic men will have some sperm within their testis tissue that can be used in conjunction with ICSI. Both frozen-thawed and fresh tissue can be employed. The obvious worry is that if the etiology of the patient's azoospermia is genetic (e.g., deletion of the DAZ region on the Y chromosome), transmission to his offspring may occur. There is no correlation between the results of the testis biopsy histologic pattern and whether sperm will be found in the retrieved tissue. This new therapy has dramatically changed the approach to the nonobstructive azoospermic patient, as no diagnostic biopsy is therefore necessary. Fertilization and pregnancy rates with testicular sperm extraction have been lower than those obtained with ejaculated or epididymal sperm in most studies, but biologic paternity can be realized in a population that had very little chance until recently.
   2. **Secondary spermatogenic failure** occurs as the result of pituitary or hypothalamic dysfunction, which may be of congenital or acquired causes, as elucidated above. Medical therapy in these instances depends primarily on manipulation or replacement of the gonadotropins FSH and LH. To induce virilization, human chorionic gonadotropin (hCG) can be administered. This will stimulate Leydig's cell production of testosterone. If fertility is also a goal of therapy, pure FSH or a combination of FSH and LH also needs to be administered to induce spermatogenesis. Once a steady state has been reached (often after 12 months of continuous therapy), hCG may be all that is required to maintain ongoing spermatogenesis.
   3. **Epididymal and vasal obstruction** may be amenable to reconstructive microsurgery. A combination of history, physical examination, and laboratory results often point to an obstructive pathology, and there is no need for a testis biopsy before definitive reconstruction. At this initial surgery, the level of obstruction is determined. Obviously, if the patient had a prior vasectomy, that will be the likely site of blockage. Microsurgical expertise is required to optimize the patient's chances for a successful outcome.
      a. **Vasectomy reversal** is carried out in those men who wish to restore their fertility potential. Postoperative patency rates are excellent but do depend on the number of years since the vasectomy (Fig. 13-3). The longer the duration, the more likely it is that a secondary site of obstruction has developed in the epididymis. Although some surgeons will always perform an anastomosis of one end of the vas to the other (vasovasostomy), others will move back to the epididymis if no sperm are found in the testicular end of the vas and create a vasal-epididymal tubule connection (vasoepididymostomy). This is performed at a location where the epididymal tubule contains sperm, thus ensuring that the anastomosis is proximal to any secondary obstructive site and that the epididymal tubule is patent from the testis to that point. Pregnancy rates do not equal patency rates, as female factors and poor sperm activity may limit the chances of conception.

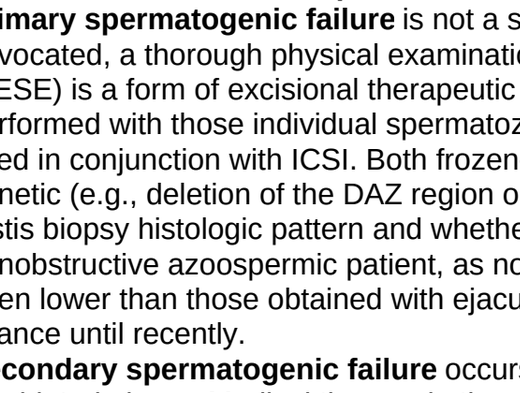

FIG. 13-3. Patency and pregnancy rates following vasovasostomy. (Adapted from Belker AM, et al. *J Urol* 1991;145:505–511.)

      b. **Microsurgical reconstruction** of congenital or postinflammatory occlusions almost always involves vasoepididymostomy. Patency and pregnancy rates depend on the microsurgical experience of the surgeon and the level at which the anastomosis occurs. There appears to be little difference between the cauda and corpus of the epididymis in regard to these rates, but there is a definite decrease in both when the anastomosis is to the caput region.
      c. **Microsurgical sperm aspiration (MESA)** is carried out when reconstruction is not possible. MESA should also be considered at the time of reconstruction, so that if the attempt does not lead to sperm in the ejaculate, at least a cryopreserved specimen can be used as the sperm source for ICSI. Obviously, before vasal or epididymal sperm are extracted and frozen, the couple must have decided that they would indeed carry out an ICSI cycle with any cryopreserved sperm if that was their only option.

C. **Ejaculatory dysfunction.** Anejaculation is a common result of spinal cord injury. Ejaculatory dysfunction and infertility will occur in almost all of those so injured. In addition to the difficulties with ejaculation, testicular spermatogenic function may also be compromised. Possible etiologies for this suppression are numerous and include chronic infection of the urinary tract, debilitating associated illnesses (e.g., decubitus ulcers, respiratory infections), disruption of the normal thermoregulatory mechanisms, infrequency of ejaculation, and hormonal derangements. This is an important aspect of the total evaluation of these patients, because once a semen specimen has been obtained (see below), the need for advanced reproductive therapies such as *in vitro* fertilization may arise. The therapy of these couples, therefore, includes two main considerations: (a) How do we best obtain the semen specimen? (b) Once we have it, how do we most efficiently use it to help the couple achieve pregnancy?
   1. **Spinal cord injuries above the T-10 level.** If the neurologic injury has occurred at T-10 or above and the lower cord is alive and reflexive, the sympathetic innervation of the vasal ampullae, seminal vesicles, bladder neck, and prostate should be intact, the putative integration center at T-12 and L-1 should be functional, the sensory afferents reaching the cord at S-2 through S-4 and the efferents exiting the cord at this same level to innervate the periurethral musculature should all be uninjured, and the tracts leading to and from the integration center should be complete. Therefore, because the entire ejaculatory reflex arc is in place, all that is missing are the influences from the cortical regions and other higher centers.
      a. **Penile vibratory stimulation (PVS).** By placing a vibrator on the frenular surface of the glans penis, a tremendous sensory stimulus is delivered to the ejaculatory integration center. This will activate the center, and if a certain threshold is exceeded, a normal ejaculatory reflex will be initiated and lead to antegrade ejaculation. PVS is the first line of therapy for the anejaculate spinal cord-injured patient. The vibrator initially tried does not have to be fancy or expensive. A simple massage unit will suffice. The key element is the tip that is used. Ideally, it must be conical in shape so that the vibratory stimulus is focused on a small surface point and not diffuse, as occurs with the round-headed units. Of men with cervical cord injuries, approximately 60% to 75% will ejaculate with PVS, and approximately 50% of patients with injuries at the thoracic level will do so (Fig. 13-4). Obviously, the lower cord segment must be active and able to generate reflex responses. If the lower extremities are flaccid and the bladder atonic, PVS is unlikely to be effective, as these signs demonstrate a lack of activity in the lower cord and it is unlikely that any sensory stimulus from the sacral area will actually reach the integration center. Why all patients with active lower cords do not respond to PVS is unknown. It could be that in the incompletely cord-injured patient, inhibitory impulses from the cortical regions still repress the ejaculatory reflex. In addition, we may not recognize patchy damage to the lower cord that interferes with one or

more of the reflex limbs.

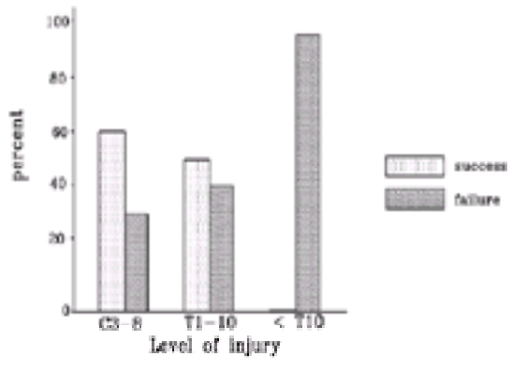

FIG. 13-4. Penile vibratory stimulation success and failure rates according to level of spinal cord injury.

b. **Technique.** In general, an erection occurs immediately. An increase in penile tumescence and rigidity heralds impending ejaculation. Immediately following emission, the periurethral musculature contracts and semen is rhythmically discharged. If PVS is effective in inducing antegrade ejaculation, the couple can easily be taught how to perform it. In this way, a semen specimen is obtained by the patient at home. This substantially eases the financial burden without increasing inconvenience. In the periovulatory period, PVS is carried out and the collected seminal fluid is inseminated onto the cervical area. In this way, the couple may be able to achieve conception naturally without the need for medical intervention. If the semen specimen is poor or if the couple is unsuccessful after 6 to 12 months of home insemination, more advanced strategies can be employed, such as intrauterine insemination, *in vitro* fertilization, or ICSI.

c. **Autonomic dysreflexia.** Patients with lesions above neurologic level T-6 may experience autonomic dysreflexia when ejaculating because the sympathetic nervous system is being activated. Either giving sublingual calcium-channel blockers 10 minutes before PVS is begun or simply stopping the stimulation and raising the patient's head is usually all that is needed to abort the dysreflexia. It is important, however, always to have the first trial in the clinician's office to ward off any potential severe dysreflexic side effects.

2. **Spinal cord injuries below the T-10 level.** If the damage to the spinal cord has occurred to segments below neurologic level T-10, it is unlikely that a full ejaculatory reflex loop is still intact. There is interruption of the pathway from the integration center to the sympathetic nuclei (a lesion just above the integration center but below the sympathetic outflow tract at T-10 through L-2) or somewhere below the integration center, which impairs the transmission of sensory impulses from the afferents or motor impulses through the efferents. In this case, PVS will not be effective in eliciting an antegrade ejaculation. Two options are available at this point: rectal probe electroejaculation and direct sperm harvesting.

a. **Rectal probe electroejaculation** should be thought of as the next most appropriate maneuver, as it involves no incisions, can be performed repeatedly in an office setting if the patient has no sensation in the rectal area, and provides a semen specimen that can possibly be used for less complicated adjunctive reproductive techniques, such as intrauterine insemination. Direct retrieval of sperm from the ductal system is an invasive operative intervention that provides smaller numbers of sperm. In general, it is used only in conjunction with *in vitro* fertilization or ICSI. In rectal probe electroejaculation (Fig. 13-5), contraction of the vasal ampullae and seminal vesicles is electrically induced with a probe so that “emission” occurs. Typically, semen simply drips from the urethral meatus. Most often, the bladder neck also tightens to prevent retrograde flow of semen. If seminal fluid does travel in a retrograde direction (e.g., following transurethral resection of the bladder neck), it can be recovered after completion of the stimulations. In all cases, the bladder is emptied before the initiation of electric stimulation, and 20 to 30 mL of an appropriate buffer is left indwelling. This optimizes the environment in which the sperm will be should they move in a retrograde direction. Once the semen is collected, the various sperm parameters (count, motility, forward progression) determine what reproductive technique will be used to try to achieve pregnancy. Because it is somewhat intensive to retrieve specimens in this fashion, the approach is usually more aggressive at the outset than it would be if the method to obtain a semen specimen were uncomplicated (e.g., masturbation or PVS). Overall, approximately 10% of spinal cord-injured patients will have extremely poor semen parameters. With the availability of ICSI, however, these men may also be able to achieve biologic paternity. With the combination of intrauterine insemination and *in vitro* fertilization, approximately 50% of couples will achieve pregnancy (Table 13-4). It is most important in interpreting the reports of success rates to understand that concomitant female factors do exist in a fair number of couples that may prevent conception.

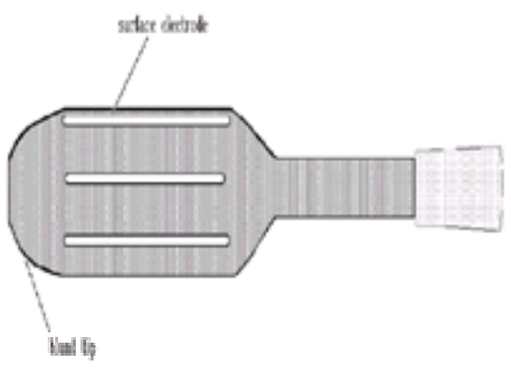

FIG. 13-5. Seager model 11 rectal probe (1.25-in. diameter). Note surface electrodes and blunt tip to prevent rectal injury.

Technique	Total No. Cycles	No. successful couples per total	Pregnancy rate per cycle (%)
Self-insemination	—	5/8	—
Intrauterine insemination			
Natural cycle	11	0/6	0
Clomiphene citrate	6	1/4	17
Human menopausal gonadotropin	19	4/8	21
Gamete intrafallopian transfer	9	5/6	56
In vitro fertilization	5	2/7	29

From Nahoul K., et al. *J Urol* 1996; 155:554–559.

Table 13-4. Adjunctive reproductive techniques in spinal cord-injured men

3. **Retroperitoneal lymph node dissection**, a type of surgery for testis cancer, may cause anejaculation in a small percentage of men. In a male patient who has had a unilateral orchiectomy, the baseline level of sperm production in the remaining testis may be significantly impaired. Approximately 25% of men in this situation will have an exceedingly poor production potential in that gonad, and adjuvant therapy, such as chemotherapy, may be additionally detrimental. This factor must always be kept in mind during determination of how best to achieve pregnancy once semen has been retrieved. Nerve-sparing retroperitoneal lymph node dissection often leaves the sympathetic chain intact, and no deficit in ejaculatory ability is noticed. However, if the retroperitoneal lymph mode dissection was performed before the development of modifications that maintain the integrity of the sympathetic nerves, or if the nerves had to be sacrificed, a failure of emission may occur. Most patients will sense a fairly normal orgasmic experience, but there will be no antegrade flow of semen. In contrast to what occurs in the spinal cord-injured patient, the afferent sensory impulses and the augmentative cortical stimuli will activate the ejaculatory integration center. The normal temporal sequence of events is preserved, and the patient “feels” the “buildup” and “release” sensations associated with ejaculation and the rhythmic contractions of the periurethral musculature. PVS is obviously ineffective in these men, as the entire problem is the interruption of the efferent motor outflow via the sympathetic nerves to the seminal structures; it is not failure of initiation or control of the ejaculatory reflex, as it is in the spinal cord-injured male patient. Rectal probe electroejaculation is the treatment of choice for these men, as semen specimens can be easily obtained.

Because rectal sensation is completely intact, a general or spinal anesthetic is required. As in the spinal cord-injured patient, the determination of which adjunctive reproductive technique will be used to achieve conception is based in part on the semen parameters. If they are particularly poor, *in vitro* fertilization or ICSI may be the most efficient option. However, if the sperm count and motility are excellent, several cycles of intrauterine insemination may be carried out. It is important to consider that each cycle of sperm retrieval involves anesthesia for the patient, and each specimen obtained should therefore be cryopreserved at the very least. A good overall approach is to cryopreserve the first trial specimen recovered and make plans based on the results. If the counts are low, one of the thawed vials will suffice as the sperm source for ICSI. If the specimen is adequate, one of the vials may be used for intrauterine insemination. In addition, this subdivided specimen can be considered as a backup if a fresh sample is to be collected on the day of ovulation (intrauterine insemination) or oocyte harvesting (*in vitro* fertilization or ICSI). For both the spinal cord-injured patient and the patient left anejaculate secondary to pelvic or retroperitoneal surgery that inadvertently interrupted the sympathetic outflow to the seminal structures, PVS or rectal probe electroejaculation can be quite easy and successful in retrieving sperm to be used in a variety of ways. Depending on a number of factors, including sperm density, motility, forward progression, technique required to obtain the semen, and female factors, an appropriate therapeutic strategy can be outlined for the couple. Unfortunately, many will be limited in their choices by financial constraints.

4. **Retrograde ejaculation** may be of neurologic or anatomic causes (Table 13-5). It occurs when the bladder neck does not coapt tightly during emission, so that the path of least resistance is into the bladder instead of the urethral meatus. It is a common misconception that retrograde ejaculation is present in spinal cord-injured patients and patients who have undergone retroperitoneal lymph node dissection. Occasionally this is true, but most often anejaculation and failure of emission are the predominant outcomes of these two situations. The etiologies of retrograde ejaculation can be divided into two main groups, neurologic and anatomic. The history of the patient will be most revealing. If the patient has never noticed an antegrade ejaculate, it is likely that the reason is idiopathic or "occurred" before puberty. Many patients, such as those with diabetes mellitus, may describe a gradual onset of failure of antegrade ejaculation, whereas others can pinpoint an exact temporal onset, such as following an extensive retroperitoneal lymph node dissection. It is important to ask whether the patient has noticed whitish fluid admixed with urine during the first void subsequent to intercourse. In addition, it is interesting to note whether there have been times when the patient actually has had an antegrade flow of semen, and in what particular situations that might occur. It has been reported that ejaculation with a full bladder may lead to antegrade semen flow, perhaps through a different reflex mechanism that leads to closure of the internal sphincter.

Neurologic
Spinal cord injury
S/P retroperitoneal
Lymph node dissection
Diabetes mellitus
Transverse myelitis
Multiple sclerosis
Pharmacologic
α-Sympatholytic medications
Anatomic
Bladder neck revision
Transurethral prostatic resection
Transurethral bladder neck resection.

Table 13-5. Etiologies of retrograde ejaculation

a. **Diagnosis of retrograde ejaculation.** The simplest way to diagnose retrograde ejaculation is through examination of the postejaculate urine specimen. The steps the patient and clinician should follow are listed below. It is critical to have the patient empty his bladder before ejaculation so that the volume of the postejaculate mixture of urine and semen is small, which makes analysis and processing far easier. There is no reason to catheterize the patient after ejaculation if his voiding pattern is normal, as he will be able to discharge whatever is in the bladder himself—usually 10 to 15 minutes after ejaculation. The final volume of this second urination is typically 30 to 40 mL.

   Patient instructions: (a) Void to completion. (b) Ejaculate and capture any antegrade material. (c) Void to completion immediately afterward. (d) Label the specimen "postejaculate urine."

   Clinician instructions: (a) Grossly examine the specimen and note the presence of seminal fluid, and measure and record pH. (b) Centrifuge specimen for 5 minutes. (c) Reconstitute the pellet to 1 cc. (d) Calculate the concentration (millions per milliliter) and motility parameters. In this fashion, an accurate estimation of the number of sperm released into the posterior urethra (the sperm count) can be made. If there is a relatively large number of sperm in the postejaculate urine with no antegrade ejaculate produced, then the diagnosis of retrograde ejaculation is secure. If the specimen is azoospermic, it may indicate either failure of emission (no seminal fluid will be noticed in the postejaculate urine specimen) or a combination of retrograde ejaculation and testicular failure or obstruction of the proximal ductal system (seminal fluid present indicating emission but no sperm seen in the postejaculate urine). This is not an uncommon occurrence in a patient after retroperitoneal lymph node dissection who may also have a spermatogenic failure in the remaining gonad.

b. **Treatment of retrograde ejaculation.** Treatment objectives depend in part on the etiology. If the cause is anatomic, the bladder neck is fixed in an open position, and closure with medical therapy will not be successful. In this case, the mixture of urine and semen must be optimized for use with intrauterine insemination. This is best done by adjusting the pH, both before and during processing. The patient should be instructed to ingest bicarbonate (four 650-mg tablets) 1 hour before anticipated ejaculation. This will usually alkalinize the urine component of the mixture. The ideal pH is between 7.5 and 8.5. The patient should also ingest two full glasses of water at that time so that the urine portion is dilute. The specimen should be immediately processed with standard sperm media and prepared for intrauterine insemination as per the laboratory protocol. Only in the rare circumstance of inadequate motility (most affected by a suboptimal milieu) is catheterization with instillation of 30 mL of sperm media into the bladder necessary before ejaculation. If intrauterine insemination is unsuccessful, then more aggressive therapies should be considered. If the etiology is neuropathic, an attempt at pharmacologically inducing bladder neck coaptation is worthwhile. This involves stimulation of the circular fibers with a-sympathomimetic agents, such as 60 mg of pseudoephedrine every 6 hours beginning 24 to 48 hours before expected ejaculation. This technique is successful in approximately 30% of cases of retrograde ejaculation following retroperitoneal lymph node dissection. Occasionally, the patient will mention that he noticed antegrade semen flow while on "cold medications" that probably contain agents such as pseudoephedrine. If antegrade semen flow is restored, medication is begun 1 to 2 days before ovulation, and intercourse is often all that is required to achieve pregnancy. If medical therapy fails to reverse the direction of seminal flow, processing of the postejaculate urine sample for use with adjunctive techniques is carried out as described above.

D. **Oligoasthenoteratospermia**

1. **Elimination of spermatotoxin.** The first step in the treatment of oligoasthenoteratospermia is identification and possible elimination of spermatotoxins. Semen analysis should be repeated 2 to 3 months after discontinuation of any identified toxic agents.
2. **Medical therapy.** Clomiphene citrate, hCG, tamoxifen citrate, oral kallikrein, pentoxifylline, and folinic acid have been used for the medical treatment of oligoasthenoteratospermia. Double-blind, placebo-controlled studies have been few. Those that have been performed do not indicate efficacy.
3. **Surgical therapy**
   a. **Varicocele.** A varicocele is found in approximately 15% of fertile men and 40% of infertile men. Surgical correction (varicocelectomy) results in improvement of semen analysis in 40% to 70% of patients. Pregnancy occurs in approximately 40% of couples within 1 year of treatment. Open surgical techniques in which subinguinal, inguinal, or retroperitoneal incisions are employed show roughly similar rates of success. It is important to preserve the testicular artery and lymphatics. Laparoscopy confers no benefit in comparison with the subinguinal approach. Angiographic techniques have been described for selective catheterization of the internal spermatic veins and for treatment of occlusion by injection of sclerosing agents or use of intravenous balloons or stainless steel coils. The pregnancy rate with these techniques appears to be comparable with that for surgical ligation of the varicocele, although contrast reactions and venous injury may occur.
   b. **Partial obstruction** of the ductal system may occur at the level of the ejaculatory ducts or epididymis. Surgical correction via transurethral resection of the ejaculatory duct or microsurgical reconstruction may lead to a normalization of semen parameters. The clues to the diagnosis of partial ejaculatory duct obstruction are reduced semen volume and seminal deficiency out of proportion to what would be expected from the history, physical examination, and hormonal evaluation. TRUS is ideal to confirm a suspected diagnosis.
4. **Adjunctive reproductive technologies**
   a. **Intrauterine insemination** is often the first therapeutic step after all maneuvers to manage each partner have not led to pregnancy. At the time of ovulation, a semen specimen is processed to remove the seminal fluid and concentrate the sperm fraction, which is then placed into the uterine cavity via a transcervical catheter. This delivers sperm to the upper reproductive tract, closer to the fallopian tubes, where fertilization occurs. It is performed in an office setting without the need for anesthesia. The female partner may be regulated with oral medications to time ovulation more precisely. Parenteral medications may also be added to stimulate multiple follicular development and increase the chances of conception by increasing the number of oocytes

released. Appropriately selected couples will have success in 15% to 20% of cases.

b. ***In vitro* fertilization** involves the incubation of harvested oocytes with processed spermatozoa in *in vitro* culture. Fertilized oocytes (embryos) are then either transferred to the uterine cavity with a transcervical catheter or cryopreserved if of adequate quality. The success of *in vitro* fertilization depends on both oocyte and sperm quality. Fertilization rates are generally in the range of 60% to 70%, with term delivery achieved in 15% of couples. *In vitro* fertilization is recommended if sperm quality is adequate and the couple has failed a protocol of intrauterine insemination. If the sperm have been shown to lack fertilizing ability, or if they are expected to lack such capacity (sperm harvested from the epididymis), or if there are too few sperm in the ejaculate to initiate *in vitro* fertilization, then ICSI is employed.
c. In **intracytoplasmic sperm injection (ICSI)**, delicate micromanipulation equipment is used to place an individual spermatozoon into the cytoplasm of a harvested oocyte. This procedure bypasses all mechanical fertilization barriers. It is particularly useful in situations of severe oligospermia and when the spermatozoa are functionally deficient. Embryos develop in 60% to 80% of manipulated oocytes, with pregnancy occurring in roughly 25% of cases.

Suggested Reading

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Chapter 14 Neoplasms of the Genitourinary Tract

Liam Hurley

The most common genitourinary neoplasms arise in the prostate, bladder, and kidney. Testicular cancer is not common but is nevertheless an important disease because it is a highly malignant tumor that affects younger men. Neoplasms of the renal pelvis, ureter, urethra, and penis are rare.

I. Carcinoma of the Kidney

See also Chapter 8.

A. **Incidence.** Adenocarcinoma of the kidney accounts for almost 90% of all renal neoplasms. Renal cell carcinoma is the third most common genitourinary neoplasm. Each year, renal cell carcinoma afflicts 30,600 people in the United States, and at least 12,000 deaths occur. There is a twofold to threefold male predominance; no obvious racial predilection has been noted. The peak incidence is in the sixth and seventh decades of life, but the disease is seen occasionally even in adolescents. Thirty percent of patients with renal cell carcinoma have metastatic disease at diagnosis, and in 40% who undergo nephrectomy, disease ultimately recurs (25% distant metastasis, 10% regional nodes, 5% local recurrence). The most common site of metastases are the lung and bones, followed in decreasing order by regional nodes, liver, adrenal glands, brain, and other adjuvant organs. Patients with pathologic stage T4 and metastatic disease have a median survival of 6 to 10 months and a 2-year survival of 10% to 20%.

B. **Etiology.** Although the etiology of renal cell carcinoma is unknown, several interesting associations have been noted.
   1. **Estrogens.** Administration of exogenous estrogens produced renal carcinoma in hamsters.
   2. **Diet.** There is a positive correlation between the incidence of renal carcinoma and high consumption of fats, oils, milk, and sugar. Obesity is also a risk factor.
   3. **Renal failure.** About 20 years ago, it was recognized that patients with renal failure who are undergoing hemodialysis are at risk for development of multiple renal cysts—acquired cystic kidney disease and occasionally renal carcinoma. Patients undergoing peritoneal dialysis are also at increased risk. The risk is increased in proportion to the number of years of dialysis. Acquired cystic kidney disease develops eventually in 40% to 80% of patients maintained on long-term dialysis, and approximately 20% of patients with acquired cystic kidney disease have renal neoplasms. The risk in all patients undergoing dialysis may be as high as 8%, and it is 50-fold higher than in the general population.
   4. **Von Hippel-Lindau disease** is strongly associated with renal cell carcinoma, which develops in about two-thirds of patients with von Hippel-Lindau disease. The autopsy incidence is 40% to 60%; multiple and/or bilateral tumors are usually found.
   5. **Toxic agents.** A fourfold to fivefold increased risk for renal cell carcinoma exists in cigarette smokers in comparison with nonsmokers, although the mechanism of this association is unclear. Exposure to heavy metals such as lead and cadmium has also been associated with clinical renal cell carcinoma.

C. **Tumor classification.** Renal adenocarcinoma is also called renal cell carcinoma, clear cell carcinoma of the kidney, hypernephroma, and Grawitz's tumor. The tumor arises from the proximal convoluted tubular cell and has a characteristic yellowish appearance on cut section because of its high lipid content. The term **renal adenoma** is used for tumors less than 3 cm in diameter; however, there is no way to differentiate renal adenomas histologically from adenocarcinomas, and adenomas most likely represent early carcinomas. Several histologic subtypes exist, although these are rarely seen in pure form.
   1. **Clear cell tumors** are composed mostly of round or polygonal cells with abundant cytoplasm containing glycogen. Approximately 25% of renal adenocarcinomas consist principally of clear cells.
   2. **Granular cell tumors** are similar to clear cell tumors except that the cells contain less glycogen and more mitochondria, which impart a granular appearance. Approximately 12% of renal tumors consist of granular cells; their prognosis is slightly worse than that of clear cell tumors.
   3. **Sarcomatoid cells** are spindle-shaped, pleomorphic cells that account for 14% of renal cell carcinomas. This tumor has the worst prognosis of all the histologic types.
   4. **Oncocytoma** is a special form of granular cell tumor characterized histologically by a very large number of intracellular mitochondria. Oncocytic tumors are uncommon, accounting for a very small proportion of renal adenocarcinomas. The tumors have a very good prognosis, which has generated controversy regarding their malignant potential.

D. **Diagnosis.** A discussion of symptoms, signs, and differential diagnosis can be found in Chapter 8. Paraneoplastic syndromes occur in 10% to 40% of patients as a result of specific hormone production by the tumor cells or an immune response to the tumor (Table 14-1). Hepatic dysfunction (Stauffer's syndrome) in the presence of renal cell carcinoma does not imply metastatic disease to the liver and is reversible on removal of the primary tumor.

Finding	Incidence (%)
Hypertension	38
Anemia	36
Fever	17
Abnormal LFT findings	14
Hypercalcemia	5
Polycythemia	3

LFT, liver function test.

Table 14-1. Paraneoplastic syndromes in renal cell carcinoma

E. **Staging.** Currently, the staging system of the American Joint Committee on Cancer (AJCC) (Fig. 14-1) is gradually replacing the older Robson staging system. Table 14-2 compares the AJCC system with the older Robson-Flocks system.

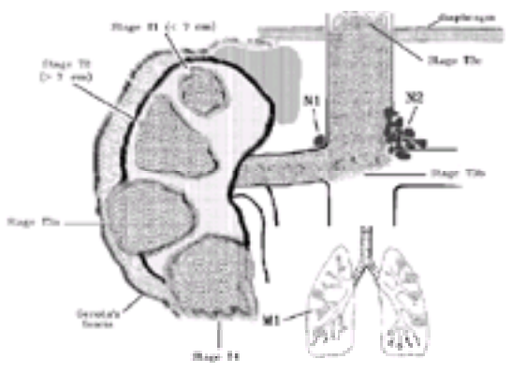

FIG. 14-1. AJCC staging system for renal carcinoma.

AJCC stage		Robson-Flocks stage
Primary tumor		
T1	Tumor 7 cm or less, limited to kidney	I
T2	Tumor 7 cm or greater, limited to kidney	II
T3a	Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia	II
T3b	Tumor grossly extends into renal vein or inferior vena cava	III
T3c	Tumor extends into vena cava above the diaphragm	III
T4	Tumor invades Gerota's fascia	III
Lymph nodes		
N1	Single regional node involved	III
N2	More than one node involved	III
Metastases		
M1	Distant metastasis	IV

AJCC, American Joint Committee on Cancer.

Table 14-2. Comparison of AJCC and Robson-Flocks staging systems in renal cancer

F. **Treatment.** Renal neoplasms are highly resistant to nonsurgical forms of treatment, such as chemotherapy, radiation therapy, hormonal manipulation, and immunotherapy.
   1. **Radical nephrectomy** is distinguished from simple nephrectomy by early control of the renal pedicle and *en bloc* removal of the kidney, ipsilateral adrenal gland, and Gerota's fascia. Radical nephrectomy is the treatment of choice for localized disease. An anterior, thoracoabdominal, or modified flank incision may be used according to the surgeon's preference. Adrenalectomy is required only in patients with preoperative evidence of adrenal involvement or with large tumors of the upper pole.
      a. **Renal artery embolization** can be used to shrink large hypervascular tumors before surgery and to control bleeding and pain in symptomatic patients with inoperable renal cell carcinoma.
      b. Most authorities feel that **regional lymphadenectomy** adds little if anything to survival.
      c. **Vena caval involvement.** Almost 20% of patients with renal cell carcinoma have renal vein involvement, and 5% have extension into the vena cava (Fig. 14-2). Because of the shorter renal vein, vena caval involvement is more common in right-sided tumors. Tumors extending into the vena cava but without invasion of the wall of the vena cava and without extension outside the kidney capsule may have a favorable prognosis following surgical excision. Even tumors extending into the atrium of the heart can be removed with reasonable expectation of long-term survival; these patients require cardiopulmonary bypass, profound hypothermia, and temporary cardiac arrest.

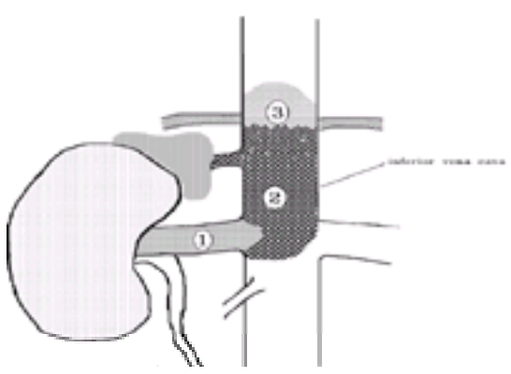

FIG. 14-2. Extension of renal carcinoma into the renal vein and vena cava. *1*, Renal vein only. *2*, Infradiaphragmatic extension. *3*, Supradiaphragmatic extension.

      d. **Metastatic disease.** About 2% of patients with renal cell carcinoma present with a solitary—usually pulmonary—metastasis. Because survival may occasionally be prolonged, removal of the solitary metastases at the time of nephrectomy is a reasonable course in such patients. Nephrectomy in the face of metastatic disease may also be considered to control severe symptoms, including unrelenting flank pain, intractable hemorrhage, fever, and hypercalcemia secondary to tumor hormone production. Finally, nephrectomy in the face of metastatic disease may be reasonable in patients who are to undergo experimental therapy that requires removal of the primary tumor.
      e. **Immunotherapy**. Because of the very poor prognosis in metastatic disease, interest has recently arisen in various immunotherapy protocols. Interferon-a appears to be associated with an objective response rate of 15% to 20%. Interleukin-2 with or without lymphokine-activated killer cells has resulted in 15% to 30% response rates in treated patients. Other therapeutic approaches include gene therapy, tumor vaccines, and monoclonal antibodies (see Chapter 15).
      f. **Treatment results** obtained with radical nephrectomy are given in Table 14-3. Stage T1 disease has an excellent prognosis following radical nephrectomy. In contrast, there are virtually no long-term survivors with metastatic disease, which has a 1-year mortality rate of more than 50%.

Stage	Survival at 5 years (%)	Survival at 10 years (%)
T1	79	73
T2 or N+	40	24
M+	8	0

Table 14-3. Treatment survival according to stage in renal adenocarcinoma

   2. **Partial nephrectomy** is reserved for selected instances of malignant tumor in a solitary kidney or bilateral renal carcinoma. In addition, it may be considered as a nephron-sparing procedure in patients with renal insufficiency who are not yet on dialysis.

II. Carcinoma of the Renal Pelvis and Ureter

A. **Incidence.** Tumors of the upper urinary tract account for about 5% of urothelial neoplasms. A male-to-female preponderance of 2:1 is noted, with an average age at diagnosis of 65. There is no predilection for side, but tumors occur bilaterally in 2% to 4% of patients.
B. **Tumor classification**
   1. **Transitional cell carcinoma** accounts for 85% of renal pelvic tumors and 93% of ureteral tumors. The etiology is similar to that of transitional cell carcinoma of the bladder and is thought to involve chemical carcinogens and cigarette smoking. More than 20% of patients have multiple, rather than single, lesions at diagnosis. Bladder cancer develops in approximately 50% of patients with ureteral or pelvic cancer. Tumors develop in the contralateral kidney in only 3% of patients with unilateral tumors. Two specific groups of patients are at increased risk for the development of renal pelvic tumors.
      a. Persons who for years consume large quantities of **analgesics containing phenacetin or aspirin** have a ninefold greater risk for the development of papillary necrosis and transitional cell carcinoma of the renal pelvis. Tumors in these patients tend to be of a higher histologic grade and stage than are tumors not associated with phenacetin.
      b. **Balkan nephropathy** is an environmental tubulointerstitial renal disease of unknown cause endemic to certain areas of the Balkan Peninsula (Yugoslavia, Romania, Bulgaria, and Greece). Affected patients are at high risk for the development of renal pelvic cancer. The tumors are frequently bilateral (10% of patients) and of low malignant potential.

c. **Other risk factors** are similar to those described for bladder cancer.

2. **Squamous cell carcinoma** is seen in association with chronic inflammation or irritation (e.g., calculous disease) and accounts for 14% of renal pelvic tumors and 5% of ureteral carcinomas. These tumors tend to invade and metastasize early; the 5-year survival rate approaches zero.
3. **Adenocarcinoma** accounts for fewer than l% of renal pelvic tumors, occurs predominantly in women, is associated with renal calculus and pyelonephritis, and has a very poor prognosis. Primary adenocarcinoma of the ureter is extremely rare.

C. **Diagnosis.** Hematuria is the presenting sign in 80% of patients. Pain with or without obstruction may be seen in 40% of patients, and a palpable mass is rare. Intravenous urography (IVU) displays a radiolucent filling defect that can be confirmed by retrograde pyelography. Tumors are at an early stage in 85% and at an advanced stage in 15% of cases without obstruction. Voided urinary cytology is not particularly sensitive, but selective cytology and brush biopsy specimens are usually positive for carcinoma. The initial evaluation of filling defects is performed by ultrasonography (US), computed axial tomography (CT), or magnetic resonance imaging (MRI). CT or MRI is essential for staging and evaluating regional lymph nodes. The recent advent of ureteroscopy has allowed direct visualization and biopsy of suspected lesions. This modality is particularly useful for cases with unexplained filling defects, hematuria, or positive cytology when the diagnosis remains uncertain after conventional diagnostic modalities have been utilized. Angiography is of little usefulness, as the lesions are typically avascular. However, it may demonstrate other causes for renal pelvic filling defects, such as renal artery aneurysms and crossing vessels.

D. **Staging and prognosis**. The AJCC staging system is used in renal pelvic and ureteral tumors and correlates with 5-year survival (Table 14-4).

AJCC stage	Description	Survival at 5 years (%)
Primary tumor		
T0	No evidence of primary tumor	
Ta	Neoplasm confined to mucosa	90
Tis	Carcinoma *in situ*	
T1	Submucosal infiltration only	80-80
T2	Muscular invasion only	17-75
T3	Invasion of periureteral/peripelvic fat or renal parenchyma	
T4	Extension outside kidney into adjacent organs	5
Lymph nodes		
N1	Single regional lymph node, <2 cm in diameter	
N2	One or more lymph nodes, none >5 cm in diameter	
N3	One or more lymph nodes, >5 cm in diameter	
Metastases		
M1	Distant metastasis	

AJCC, American Joint Committee on Cancer.

Table 14-4. AJCC staging system for ureteral-pelvic tumors and 5-year survival

E. **Treatment.** Successful treatment depends on the stage and grade of the tumor, irrespective of the surgical procedure employed. In general, low-grade tumors tend to have a good prognosis, whereas high-grade tumors tend to be deeply invasive and have a poor prognosis.

1. **Nephroureterectomy.** Renal pelvic tumors and tumors of the upper two-thirds of the ureter are best treated by radical nephroureterectomy (kidney, adrenal, ureter, and cuff of bladder). When the ureter is left behind, disease may recur in one-third of patients. The overall 5-year survival rate following radical nephroureterectomy is 84%.
2. **Distal ureterectomy** and reimplantation into the bladder may be used to treat low-grade lesions of the distal one-third of the ureter.
3. **Special situations.** In patients with disease in a solitary kidney or synchronous bilateral superficial lesions, a number of alternative approaches are available. These include open pyelotomy with excision and fulguration, partial nephrectomy, bench surgery with autotransplantation, ureteroscopic resection and fulguration, and intrapelvic treatment with bacille Calmette-Guérin (BCG) or chemotherapy. Currently, there may be a role for endoscopic resection through the ureteroscope, especially for distal ureteral tumors, but only if they are of a low stage and grade. High-grade lesions of the distal ureter should be treated with radical nephroureterectomy.
4. **Metastatic disease.** The management of metastatic or unresected disease involves platinum-based multiagent chemotherapy, similar to that used in bladder cancer. Postoperative radiotherapy to the ureteral bed is controversial and is not employed routinely.

F. **Follow-up care.** There is a 50% to 80% bladder recurrence rate within 18 months. Following surgical removal of tumors of the upper urinary tract, patients should be followed by cystoscopy every 3 months for 3 years, every 6 months for 2 more years, and annually thereafter provided no recurrences are noted.

III. Carcinoma of the Bladder

A. **Incidence.** Bladder cancer is the second most common genitourinary neoplasm, with more than 54,000 estimated new cases diagnosed in the United States in 1998. It is estimated that bladder cancer accounted for more than 12,500 deaths in 1998. The peak incidence is in persons from 50 to 70 years old, with a male-to-female predominance of 3:1.

B. **Tumor classification**

1. **Transitional cell carcinoma** accounts for more than 90% of all cases of bladder cancer.
   a. **Papillary transitional cell carcinoma** appears as an exophytic frondular lesion. The size and number of lesions vary. This is the most common form of transitional cell carcinoma in the bladder. Most of these tumors are small and noninvasive.
   b. **Sessile transitional cell carcinoma** appears as a less frondular, more solid lesion with a broad base. These tumors have a greater tendency to be invasive.
   c. **Carcinoma** *in situ* appears as flat, nonpapillary, somewhat erythematous epithelium; it may occur in association with an exophytic lesion or separately from it. The presence of carcinoma *in situ* is an indicator of increased biologic aggressiveness. Papillary or sessile tumors are more likely to recur or invade when associated with carcinoma *in situ*.
2. **Squamous cell carcinoma** accounts for 7% to 8% of cases of bladder cancer and is usually associated with chronic irritation of the urothelium (e.g., schistosomiasis, bladder calculi, foreign bodies).
3. **Adenocarcinoma** accounts for 1% to 2% of cases and is associated with chronic infection, bladder exstrophy, or urachal remnants in the dome of the bladder. Adenocarcinomas tend to be mucus-secreting tumors.
4. **Other types** include various types of small-cell carcinoma, sarcoma, melanoma, and carcinoid tumors.

C. **Etiology**

1. **Industrial toxins (orthoaminophenols).** Continuous contact with aniline dyes, a-naphthylamine, 4-aminobiphenyl, and benzidine used in the rubber, leather, textile, and dye industries may account for up to 25% of instances of bladder cancer.
2. **Cigarette smoking** may account for up to 25% to 60% of instances of bladder cancer in developed countries. Smoking leads to deficiency of vitamin B_6 (pyridoxine), which is needed to metabolize orthoaminophenols and endogenous products of tryptophan metabolism. Also, 4-aminobiphenyl may be the carcinogen involved.
3. **Other risk factors** include cyclophosphamide, alkylating agents such as thiotepa, and phenacetin-containing analgesics. Radiotherapy of the pelvis is also a risk factor for bladder cancer.

D. **Diagnosis**

1. **Signs and symptoms.** Approximately 80% of patients present with gross, painless hematuria. Dysuria and irritative symptoms are present in 20% of patients—especially those with carcinoma *in situ*. Secondary urinary infection may be present in about 30% of patients with bladder tumors and should not preclude the search for bladder carcinoma. Upper urinary tract obstruction is rare on initial presentation and is a sign of advanced disease in 50% of cases. Approximately 20% of patients with bladder cancer present solely with microscopic hematuria. Ten percent of patients present with symptoms secondary to metastases.
2. **Cystoscopy.** Because transitional cell carcinoma is a field-change process, the entire bladder mucosa must be carefully inspected. Biopsy of the primary lesion should be accompanied by biopsies of adjacent, normal-appearing areas to rule out multicentric involvement.
3. **Urinary cytology.** Cells for microscopic examination are collected from voided urine or bladder washings. Urinary cytologic study is not sensitive (30%) in diagnosing low-grade bladder cancer but is excellent for detecting carcinoma *in situ* and high-grade lesions (90%).
4. **Flow cytometry** is the computerized analysis of DNA content in exfoliated cells. The main advantage over routine cytologic study is the ability of flow cytometry to detect low-grade tumors accurately.
5. **Other urine tests.** Bladder tumor antigen (BTA, Bard) is a latex aggregation assay that detects high-molecular-weight basement membrane complexes, which are present when the tumor cells become invasive and undergo proteolytic degradation. Studies have shown the test to be more sensitive than cytology but less specific. NMP22 (Matritech) is an immunoassay that measures nuclear matrix protein 22. The reported sensitivity has been found to be 70%, but again with a higher incidence of false-positive results. The AuraTech FDP (PerImmune) is a rapid immunoassay that detects the urinary fibrin and fibrinogen degradation products associated with bladder cancer. Its 68% sensitivity is higher than that of cytology.
6. **Radiologic examinations.** The IVU demonstrates a filling defect in the bladder only 60% of the time. Spiral CT with contrast has a similar sensitivity.

E. **Stage and grade of tumors**

1. **Staging.** The AJCC staging system (Fig. 14-3) is gradually replacing the older Jewett classification of urinary bladder cancer (Table 14-5).

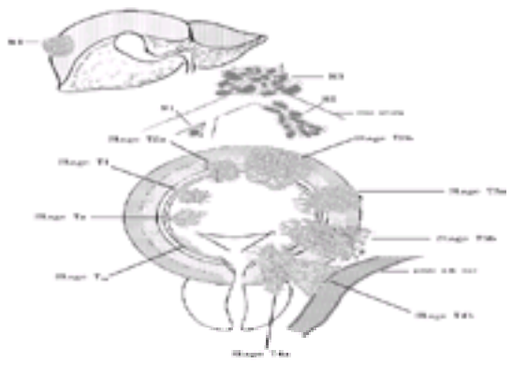

FIG. 14-3. AJCC staging of bladder cancer.

AJCC stage	Description	Jewett stage
Primary tumor		
Tx	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Ta	Noninvasive papillary carcinoma	0
Tis	Carcinoma in situ	0
T1	Tumor invades subepithelial connective tissue	A
T2a	Tumor invades superficial muscle	B1
T2b	Tumor invades deep muscle	B2
T3a	Tumor invades perivesical tissue—microscopic only	C
T3b	Tumor invades perivesical tissue—macroscopic	C
T4a	Tumor invades the prostate, uterus, vagina	C
T4b	Tumor invades pelvic wall, abdominal wall	C
Lymph nodes		
N1	Single regional lymph node, <2 cm in diameter	D1
N2	One or more lymph nodes, none >5 cm in diameter	D1
N3	One or more lymph nodes, >5 cm in diameter	D1
Metastases		
M1	Distant metastasis	D2

AJCC, American Joint Committee on Cancer.

Table 14-5. AJCC and Jewett staging of bladder cancer

2. **Grading.** Currently, most pathologists use a three-grade system proposed by Mostofi:

   Grade 1, mild anaplasia
   Grade 2, moderate anaplasia
   Grade 3, marked anaplasia
3. **Staging procedures**
   a. **Cystoscopy** remains the initial endoscopic procedure used to diagnose bladder cancer and documents the location, size, and appearance of any bladder tumor.
   b. **Biopsy.** In most cases, random bladder biopsies should be performed to rule out carcinoma *in situ*. Prostatic strip biopsies should be performed if a high-grade bladder tumor is present (especially near the bladder neck) or if cytology is positive without evident bladder tumor. Prostatic strip biopsies should also be performed to assess the urethra when a neobladder is being considered.
   c. **Transurethral resection of bladder tumor (TURBT)**, endoscopic resection of tumor performed under anesthesia, is used to remove as much tumor as possible and assess the degree of muscle invasion.
   d. **Bimanual examination** is performed under anesthesia before and after TURBT; it allows assessment of tumor size and any fixation to surrounding pelvic organs or the pelvic side wall.
   e. **Pelvic US** may help determine the extent of local invasion. The advent of newer transurethral and transrectal probes may provide better detail and clarity. US cannot differentiate between tumor extension and inflammatory response.
   f. **CT** of the pelvis may detect nodal metastases greater than 2 cm in size and provide gross assessment of the extent of local disease. CT cannot differentiate local extension of tumor from perivesical inflammation following TURBT.
   g. **MRI** may be able to differentiate tumor from inflammatory response better than CT, and it is a better staging procedure for muscle-invasive disease.
   h. **Other studies**. Chest roentgenography, bone scan, determination of alkaline phosphatase, and liver function tests may be used to rule out metastatic disease.

F. **Treatment by stage of disease**
   1. **Stage Ta/T1.** In 80% of cases, transitional cell carcinoma presents as superficial (Ta/T1) disease. TURBT is followed by cystoscopic surveillance every 3 months for 2 years, every 6 months for 3 years, and annually thereafter. At any recurrence, the surveillance cycle is repeated from the beginning. A urinary cytologic study should be obtained at each follow-up visit. Superficial transitional cell carcinoma has a documented recurrence rate of 50% to 70%, and most recurrences appear within the first 12 months. The prognosis depends on various factors (Table 14-6). Recurrences are most often of the same grade and stage as the original tumor, but up to one-third are of a higher grade.

Cystoscopic finding		
Tumor size	>5 cm	35% muscle invasion
	<5 cm	9% muscle invasion
Tumor number	solitary tumors	15–60% recurrence
	multiple tumors	40–90% recurrence
Pathologic findings		
Stage	Ta	4% progression
	T1	30% progression
	T1,G3	50% progression
	Tis	>50% progression (without adjuvant therapy)
Grade	1	50% recurrence, 2% progression
	2	60% recurrence, 11% progression
	3	80% recurrence, 45% progression
Findings at first cystoscopy		
Negative		80% no further recurrence
Positive		10% no further recurrence

Table 14-6. Prognostic factors in superficial bladder cancer

   a. **Intravesical chemotherapy.** Clinical trials have shown no clear advantage with respect to progression, time to appearance of distant metastasis, or duration of survival. A significant advantage was found, however, in terms of disease-free survival. Thus, intravesical chemotherapy following TURBT may help reduce future recurrences (see Table 15-4).
   b. **Immunotherapy** with intravesical BCG has been used as prophylaxis against tumor recurrence (60% response rate), for carcinoma *in situ* (70% response rate), and for residual carcinoma after TURBT (30% to 60% response rate). In general, the therapy appears to be safe and effective. BCG is an attenuated strain of *Mycobacterium bovis* that is capable of eliciting a local granulomatous response and occasionally causes disseminated disease. BCG preparations from different manufacturers may vary considerably in therapeutic effectiveness. The mechanism of action of BCG in bladder carcinoma is unknown, but it appears to be immunologically based because interleukin-2 has been found in the urine of patients who have responded to BCG treatment.
      1. **Method of administration of BCG.** There is no standard protocol for BCG administration, and there is no consensus regarding the optimal length of treatment. A recent study confirmed the efficacy of maintenance therapy for carcinoma *in situ* in which BCG is instilled once a week three times at 3 months, 6 months, and every 6 months to 3 years. This study of maintenance therapy confirmed a reduction in recurrence rate and somewhat improved survival. A description of our current treatment program follows:
         a. Catheterize the patient's bladder with a 16F (French) Foley catheter.
         b. Mix one ampule Tice strain BCG (1×10^8 to $8 \times 10_8$ organisms) with 60 mL of saline solution and instill via Foley catheter.
         c. Retain in bladder approximately 2 hours (remove Foley catheter after instillation).
         d. Treat weekly for 6 weeks.

e. For the second course of treatment, include maintenance therapy (three weekly instillations every 3 months for 1 year).

Wait 2 weeks following TURBT before starting BCG therapy. Perform surveillance cystoscopy and a urinary cytologic study every 3 months during treatment.

2. **Complications of BCG therapy.** Bladder irritability occurs in nearly all patients for 1 to 2 days. Mild bladder symptoms may be treated with antihistaminic, anticholinergic, antispasmodic, or nonsteroidal antiinflammatory agents. Other adverse reactions include malaise, fever, and nausea. Systemic disease is called “BCG-osis” and requires antituberculosis therapy. Such patients have prolonged fever, abnormal liver function test results, and pulmonary infiltrates. BCG should not be instilled in patients with an active urinary tract infection.
3. **Follow-up.** If recurrent tumor is noted at cystoscopy, reinstitute BCG therapy weekly for 6 weeks and then proceed with maintenance therapy (three weekly instillations every 3 months for 1 year). It has been found that multiple courses of therapy can increase the response rate. If the patient has recurrent or residual disease after two courses of BCG therapy, however, the likelihood of success with additional courses of treatment is minimal. Such patients are at high risk for development of invasive or metastatic cancer and should be considered candidates for intravesical chemotherapy, radiotherapy, or cystectomy. Cystectomy should also be considered if the disease involves extensive areas of bladder mucosa or the prostatic urethra. The same is true of patients with multiple superficial bladder tumors involving extensive areas of bladder mucosa that cannot be treated by endoscopic means and in whom intracavitary therapy has failed.

c. **Management of BCG-refractory disease**. About 30% of patients may fail several courses of BCG therapy. **Intravesical interferon-**a**-2b** may produce responses in up to 40% of patients, including those who have failed intravesical BCG therapy. After catheterization of the bladder, 100 million units of interferon-a-2b are mixed with 30 to 50 mL of normal saline solution and instilled into the bladder. The catheter is withdrawn and the fluid is retained for about 2 hours. The course is given weekly for 12 weeks and then monthly for 1 year. Mild-to-moderate flulike symptoms are the most common adverse response to intravesical interferon-a-2b. Under certain circumstances, patients with superficial bladder cancer may be candidates for cystoprostatectomy (Table 14-7).

Failure after two courses of intravesical chemotherapy-immunotherapy
Prostatic involvement
Persistent grade 3 lesions
Uncontrollable recurrence of Ta disease not amenable to transurethral resection
Persistence of tumor in nonfunctioning bladder

Table 14-7. Indications for cystectomy in Ta/T1 disease

2. **Stage T2a.** Radical cystoprostatectomy with pelvic lymph node dissection and ileal loop diversion, continent diversion, or neobladder remains the treatment of choice for bladder cancer invading the muscle layer. The efficacy of preoperative radiotherapy continues to be unclear. Prospective randomized studies indicate no statistically significant difference in 5-year survival (40% to 70%) between patients receiving external-beam radiation therapy with cystectomy and patients receiving cystectomy alone. Those favoring preoperative radiotherapy use one of two approaches: 45 to 50 Gy to the whole pelvis followed by cystectomy 1 to 2 weeks later or 20 Gy over 5 days followed immediately by cystectomy. In Europe, many still favor the use of external-beam radiation therapy in an attempt to cure the disease. Cystectomy is then reserved for the local recurrence that may develop in 20% of cases following such radiotherapy. When this approach is used, the 5-year survival rate is comparable with but not quite as good as that with cystectomy. **Partial cystectomy**, sometimes in combination with radiation and chemotherapy, may be considered if the tumor is solitary with well-defined margins and is located away from the trigone and bladder neck. Fewer than 8% of patients with bladder cancer fulfill these criteria.
3. **Stages T2b, T3a, N+.** Initial management is the same as for stage B1 disease (e.g., radical cystoprostatectomy and urinary diversion or neobladder). However, because a large percentage of these patients will have evidence of microscopic disease in their pelvic lymph nodes, some thought should be given to adjunctive chemotherapy. If a preoperative decision is made to use chemotherapy, cystectomy and diversion are justified in node-positive disease. Current chemotherapeutic regiments include methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC), and cisplatin, methotrexate, and vinblastine (CMV). Most studies have suggested a longer recurrence-free interval for those given adjuvant therapy, although most studies have shown no effect on disease progression rates and no survival benefit. The median survival for patients receiving M-VAC is about 12 months, with only 3.7% of patients continuously relapse-free at 6 years. With surgery alone or surgery with preoperative external-beam radiation, the 5-year survival rate is 15% to 40% in stages T2b and T3 and less than 30% in node-positive bladder cancer. With radiotherapy alone for node-positive disease, the 5-year survival rate is 17%.
4. **Stage M+.** Involvement of organs outside the pelvis carries a grave prognostic significance, and fewer than 5% of patients survive more than 5 years. More than 50% of patients with stage M+ bladder cancer die within 1 year. Palliative measures should be undertaken for relief of symptoms. Chemotherapeutic agents as mentioned above can also be administered.

IV. Prostate Cancer

A. **Incidence and etiology.** Prostate cancer is the second most common malignancy in male adults as well as the second most common cause of cancer-related deaths in the United States. The American Cancer Society estimates that prostate cancer was newly diagnosed in 317,000 patients in 1996, and 41,000 deaths resulted. In 1998, the incidence of new patients decreased to just above 200,000, with an estimated 40,000 deaths. The chance of a man acquiring prostate cancer during his lifetime is about 15%. The incidence of prostate cancer is 50% greater in blacks than in whites and relatively uncommon in Asians. The cause of prostate cancer is unknown, but several associations have been noted.
   1. **Genetic Influences**. The risk for development of prostate cancer is increased two to three times if a father or brother has had the disease.
   2. **Hormonal factors.** Virtually all prostate cancer cells exhibit some degree of androgen dependence. This is supported by the observation that prostate cancer does not occur in eunuchs.
   3. **Chemical factors.** Workers in the rubber, fertilizer, and textile industries have increased rates of prostate cancer, as do men continuously exposed to cadmium, a known antagonist of zinc. A diet high in saturated fat and cigarette smoking have also been suggested to have an association with prostate cancer.
   4. **Other factors.** In comparison with controls, patients with prostate cancer have been noted to be more sexually active, more promiscuous, and more likely to have been exposed to venereal disease, although no cause-and-effect relationships have been demonstrated.

B. **Tumor histology and grading.** More than 95% of prostatic neoplasms are adenocarcinomas arising from prostatic acinar cells at the periphery of the gland. This contrasts with benign prostatic hyperplasia (BPH), which develops from inner periurethral tissues. Squamous cell carcinoma and transitional cell carcinoma of the prostate occur only rarely. Prostate cancer exhibits a wide variety of histologic appearances, even within the same specimen. There is no universally accepted system of grading the degree of malignancy; however, all systems take into account in varying degree the cytologic characteristics and the glandular morphologic characteristics.
   1. **The Mostofi system** takes these two factors into account equally in a three-grade system.
   2. **The M. D. Anderson Hospital system** ignores cytologic findings and assesses the percentage of gland formation in a four-grade system.
   3. **The Gleason system.** Also ignoring cytologic features, Gleason established five grades of glandular morphology. The two most prominent glandular patterns are graded from 1 to 5. The sum of these two grades will range from 2 to 10, with 2 representing the most differentiated and 10 representing the most anaplastic tumors. There is a rough correlation between the Gleason grade and the biologic behavior of the tumor, but this is also true of other grading systems. The Gleason system is the one most widely used today because it has the best clinical correlation.

C. **Diagnosis and staging.** Until the advent of measurement of prostate specific antigen (PSA), prostate cancer was usually clinically silent until metastatic disease produced symptoms. Diagnosis depended entirely on routine digital rectal examination. The digital prostate examination is still very important, but at present many other studies also contribute to diagnosis and staging.
   1. **Prostate biopsy or aspiration cytology.** Prostate biopsy is most commonly performed through the transperineal approach with various types of instruments (Fig. 14-4). The transrectal approach may also be used. A discrete area of induration in a man older than 50 has a 50% chance of being carcinomatous on transperineal or transrectal needle biopsy. Transrectal US improves diagnostic sensitivity and increases the accuracy of fine-needle aspiration.

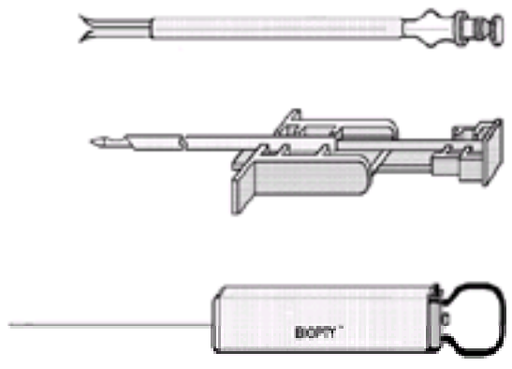

FIG. 14-4. Prostate biopsy instruments. Vim-Silverman needle **(top)**, Tru-cut biopsy needle **(middle)**, Biopty spring-actuated biopsy gun **(bottom)**.

2. **Route of spread.** Prostate cancer spreads by lymphatic and hematogenous routes. The primary sites of lymphatic metastases are the external iliac (obturator group), internal iliac, and presacral nodes. In general, the larger and less differentiated the primary tumor, the higher the incidence of lymphatic metastases. Occasionally, the supraclavicular nodes are involved via the thoracic duct. Hematogenous spread to bone, lung, liver, and kidneys occurs late in the disease.
3. **Tumor markers**
   a. **Prostate-specific antigen (PSA)** is a glycoprotein produced only by prostate cells. Thus, it is specific to the prostate but not to prostate cancer. PSA levels have been measured in various ways, including PSA density, PSA velocity, age-specific PSA, and free PSA. The advantages of these approaches remain to be established. Nevertheless, PSA measurement is very useful (a) for screening asymptomatic men (in conjunction with digital rectal examination); (b) as an aid in staging prostate cancer, especially with respect to seminal vesicle and lymph node involvement; and (c) as a way to follow response to radical prostatectomy and radiotherapy.
   b. **Prostatic acid phosphatase** was the most widely used tumor marker in the past but is rarely used today. It is elevated in 75% to 80% of patients with metastatic prostate cancer and in 10% to 30% of patients with local disease. It lacks the specificity and sensitivity needed to be a reliable screening test for prostate cancer. It remains occasionally useful in detecting metastatic disease and in monitoring therapy.
4. **Bone scanning** is very useful in detecting metastatic disease. Bony metastases occur in about 80% of patients with advanced disease. Of these, about 80% are osteoblastic lesions and 5% osteolytic; the rest are mixed osteoblastic and osteolytic lesions. Phosphate labeled with technetium 99m is rapidly taken up by bone, which is metabolically active. Bone scans are more sensitive than skeletal radiography and are able to detect lesions up to 6 months before they are apparent on x-ray films. However, bone scans are less specific than radiography, and increased uptake occurs in arthritis, fractures, Paget's disease, and hyperparathyroidism and after recent trauma. Recent reports have suggested that a bone scan may be omitted if the PSA level is below 10 ng/mL in a patient with prostate cancer.
5. **CT** can assess gross local extension and nodal metastases larger than 2 cm. The sensitivity is unacceptably low, ranging from 27% to 75%. Specificity is between 66% to 100%.
6. **Transrectal ultrasonography (TRUS)** has been shown to be valuable in assessing the presence and extent of prostate cancer. Its role in diagnosis stems primarily from its ability to detect small lesions and guide biopsy procedures. It is very accurate in the assessment of capsular invasion, especially into the seminal vesicles. As an isolated examination, however, TRUS is not a useful staging modality at the current time.
7. **Pelvic lymphadenectomy** remains the most accurate staging method available. The external iliac, obturator, and internal iliac lymphatic chains are dissected bilaterally for pathologic examination. The surgical morbidity is minimal and includes wound complications, lymphocele, and lymphedema of the penis and lower extremities. Pelvic lymph-adenectomy is generally performed in conjunction with radical retro-pubic prostatectomy. It is generally omitted in patients selected for radical perineal prostatectomy, brachytherapy, or external-beam radiotherapy. The PSA level may be used to predict the incidence of pelvic lymph node involvement (Table 14-8).

PSA	Pathologic evidence of capsular penetration (%)	seminal vesicle involvement (%)	positive lymph nodes (%)
≤4	25	1	1
4.1–10	30	5	10
10.1–20	40	20	20
>20.1	30	20	35

PSA, prostate-specific antigen.
Modified from Partin AW, et al. *J Urol* 1993; 150:110.

Table 14-8. Serum PSA and incidence of capsular penetration, seminal vesicle and lymph node involvement

8. **Molecular staging.** Polymerase chain reaction amplification can detect circulating PSA messenger ribonucleic acid (mRNA) in the blood or bone marrow of patients with known metastatic disease. However, the clinical applicability of this test is not yet known as the percentage of false-positive and false-negative results is high.
9. **Other newer techniques**, such as endorectal coil MRI and monoclonal antibodies, may provide a more precise localization of prostate cancer. Preliminary studies of monoclonal antibodies report positive predictive values ranging from 50% to 80%, with accuracy rates of 65% to 80%.

D. **Staging nomenclature.** The AJCC staging system (Fig. 14-5) is gradually replacing the Whitmore-Jewett system that was widely used in the past (Table 14-9).

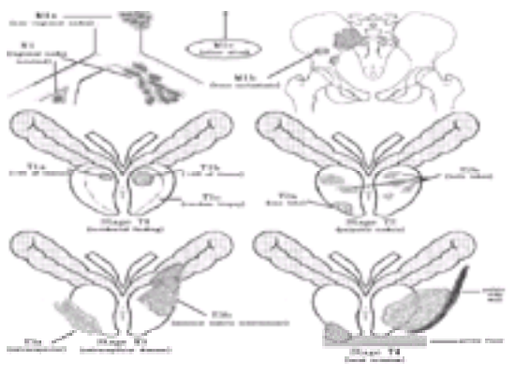

FIG. 14-5. AJCC staging of prostate cancer.

AJCC stage	Description	Whitmore-Jewett stage
Primary tumor		
Tx	Tumor cannot be assessed	
T0	No evidence of tumor	
T1a	Tumor found incidentally at TURP ≤5% of resected tissue	A1
T1b	Tumor found incidentally at TURP >5% of resected tissue	A2
T1c	Nonpalpable tumor identified because of an elevated PSA value	B0
T2a	Tumor involves one lobe	B1
T2b	Tumor involves both lobes	B2
T3a	Extracapsular extension (unilateral or bilateral)	C1
T3b	Seminal vesicle involvement	C2
T4	Tumor invades the bladder neck, external sphincter, levator muscle, or pelvic side wall Elevated PAP	B0
Lymph nodes		
Nx	Regional nodes not assessed	
N0	No regional lymph node metastasis	
N1	Metastasis to regional (pelvic) lymph nodes	
Metastases		
M1a	Metastasis to nonregional lymph nodes	D2
M1b	Metastasis to bone	D2
M1c	Metastasis to other sites	D2
	Hormone-refractory metastatic disease	D2

PAP, prostatic acid phosphatase; TURP, transurethral resection of prostate; AJCC, American Joint Committee on Cancer.

Table 14-9. AJCC and Whitmore-Jewett staging systems in prostate cancer

E. **Approach to treatment by stage of disease.** Treatment methods for localized disease include surgical, radiotherapeutic, and hormonal approaches. These are summarized in Table 14-10. See Chapter 15 for specific information on hormonal and chemotherapeutic agents and Chapter 16 for a discussion of radiation therapy.

I. Radical prostatectomy
   a. Perineal approach
   b. Retropubic approach
   c. Transcoccygeal approach
II. Radiation therapy
   a. External beam alone
   b. Interstitial radiation
      1. ^{125}I alone with external-beam radiation
      2. ^{103}Pd alone or with external-beam radiation
      3. High-dose ^{192}Ir alone or with external-beam radiation
III. Hormone manipulation
   a. Bilateral orchiectomy
   b. Estrogen therapy (diethylstilbestrol)
   c. Progestational agents (megestrol acetate)
   d. Luteinizing hormone-releasing hormone (LHRH) analogs (leuprolide, goserelin)
   e. Antiandrogens (cyproterone acetate, flutamide, bicalutamide, nilutamide)
IV. Cryosurgery

Table 14-10. Treatment modalities in localized prostate cancer

1. **Prostate cancer screening.** Although the impact of prostate cancer screening and early detection programs is debatable, some recent reports show a 30% drop in the incidence of age-adjusted prostate cancer from 1992 to 1994, a decline in metastatic disease by 60% since it peaked in 1986, and most importantly a decline (6%) in prostate cancer mortality between 1991 and 1995 in the United States. However, the mortality from other forms of cancer also declined during this time interval. Thus, it remains to be shown whether the decline of prostate cancer mortality can be explained by the increased frequency of PSA-driven therapy during the past decade.
2. **Stage T1a**. No definitive treatment is recommended currently, although careful follow-up is appropriate. It is critical to ascertain that the patient is truly at stage T1a and not T1b. This distinction is especially important in patients who are younger than 70 years of age and might be candidates for curative surgery or radiation therapy. Within 3 months of the initial diagnosis of stage T1a prostate cancer, residual cancer within the prostate should be ruled out by needle biopsy, fine-needle aspiration, or transurethral resection. If no residual tumor is found, long-term, age-adjusted survival equal to that of the population without cancer can be expected. However, some have advocated more aggressive therapy for patients less than 55 years of age.
3. **Stage T1b.** Patients with stage T1b disease should be treated aggressively. At pelvic lymph node dissection, between 30% and 40% of patients will be upstaged to stage N+/D1. Either external-beam radiation therapy or radical prostatectomy may be used in treating stage T1b prostate cancer. Previous TURP has not been an impediment to successful radical surgery, in terms of either technical ease or achievement of cure. Patients with stage T1b disease are not usually candidates for interstitial irradiation; there is usually insufficient prostatic tissue remaining after TURP for placement of the radioactive seeds. Deferred conservative treatment has generally been a valid option in patients older than 70 years of age with a low Gleason score, clinically localized prostate cancer (stage T1a), and life expectancies of 10 years or less.
4. **Stage T2.**
   a. **Radical prostatectomy.** Patients with stage T2 disease are ideal candidates for radical prostatectomy if **pelvic lymph node dissection** rules out lymph node involvement. The PSA and Gleason score may be used together to predict the incidence of organ-confined disease (Table 14-11). The incidence of node-positive disease is very low in patients with low-grade tumors (Gleason score <4) and/or a PSA level below 10 ng/mL; pelvic lymphadenectomy may be omitted in such patients. Radical prostatectomy may be performed via either a retropubic, perineal, or transcoccygeal approach. The prostate is removed *en bloc* along with the seminal vesicles. The bladder neck is reconstructed and anastomosed to the distal membranous urethra. In localized prostate cancer, radical prostatectomy offers the best chance of long-term disease-free survival. **Neoadjuvant hormone therapy** has been advocated before radical prostatectomy to induce a lower stage, decrease positive surgical margins, and effect a reduction in long-term cancer recurrence rates. However, pathologic downstaging and a significant difference with respect to PSA progression have not been noted. Incontinence following radical prostatectomy is the principal complication and has a reported incidence varying from 5% to 25%. Impotence from disruption of the nerve supply to the penis during classic radical prostatectomy is common (>80%); however, newer surgical techniques that spare the pelvic nerves have resulted in preservation of potency in 20% to 60% of patients.

	Gleason score			
PSA	≤4	5	6	≥7
≤4	80	75	60	45
4.1–10	75	65	50	35
10.1–20	55	50	35	25
>20.1	20	15	10	5

Modified from data in Partin AW, et al. J Urol 1993; 150:110.

Table 14-11. Stage T2 prostate cancer: incidence of organ-confined disease

   b. **External-beam radiation therapy** achieves survival rates equivalent to those of radical prostatectomy at 5 and 10 years following diagnosis; however, statistics show a definite advantage to radical surgery at 10 to 15 years. Prostate cancers with a higher Gleason grade (³7) have fared poorly with radiation, and radical surgery has been recommended. The treatment schedule can be tedious—with 6 to 8 weeks usually required for delivery. Radiation therapy offers an alternative treatment in patients who are poor surgical risks or who refuse surgery. Complications of radiation therapy include proctitis, cystitis, urethral stricture, and erectile impotence, especially in patients with preexisting vascular disease.
   c. **Interstitial irradiation**, also referred to as **Brachytherapy**, has become increasingly popular to treat stage T2 disease. Iodine 125 and palladium 103 give good local control of low-volume disease. A recent study from Seattle demonstrated biochemical outcomes comparable with those of radical prostatectomy and external-beam irradiation after 7 years (disease-free survival, 79%). Minimal morbidity was reported, with no prostate cancer deaths. All patients treated with radiation therapy, whether external-beam or interstitial, should be followed carefully. Periodic PSA measurement and rectal examinations are essential for follow-up. If residual cancer is demonstrated by biopsy, there is a high likelihood of future metastases.
5. **Stage T3.**
   a. **External-beam radiotherapy.** Traditionally, stage T3 disease has been treated with external-beam radiotherapy because of the high incidence (35% to 60%) of understaging by clinical methods. Pelvic lymphadenectomy is especially important in this group to determine the best mode of therapy. However, numerous studies have found poor local control as judged by PSA measurement or biopsy after treatment. New three-dimensional conformal radiation that allows higher doses of radiation to be used with reduced complications may improve these results. Also, the use of **neoadjuvant hormonal therapy** with radiation has been shown to reduce local progression and increase metastasis-free survival with a possible survival advantage. Because radiation and hormonally mediated apoptosis appear to be induced by different mechanisms, their interaction may well be synergistic. In addition, there is a potential reduction in radiation-associated morbidity.
   b. **Brachytherapy** with external-beam radiation and neoadjuvant hormones has also been explored with good results.
   c. **Adjuvant radiotherapy** has been advocated for **positive-margin disease** or a late rising PSA. Possible complications of irradiation of the prostatic bed include proctitis, cystitis, fistula formation, urinary and/or fecal incontinence, and edema of the scrotum and lower extremities.
   d. **Hormonal therapy** will reduce PSA by 95% and improve symptom-free survival, but overall survival has not been affected.
6. **Stage N+, M+, or D (Jewett).** Metastatic prostate cancer remains a therapeutic dilemma for the urologist. Hormonal manipulation will achieve a response in up to 90% of patients; however, the timing and method of hormonal therapy remain controversial. Hormonal treatment in general does not appear to improve

survival but may increase the disease-free interval in patients without symptomatic metastases.

a. **Immediate versus delayed hormonal therapy** remains controversial. The rationale for deferring hormonal management until progression of disease is based on several considerations. Localized prostate cancer is primarily asymptomatic; hormonal therapy is usually efficacious only for up to 3 years; and studies indicate that 10-year disease-free survival in patients with grades 1 and 2 tumors is more than 85%, although it is only 34% for grade 3 tumors. Approximately 40% of patients die of other causes because of their age at diagnosis (>70 years). On the other hand, recent data, including those from a large randomized trial, suggest that more patients progressed from M0 to M1 disease (p <.001) and that metastatic pain occurred more rapidly in deferred patients. More than twice as many patients required TURP because of local progression. In addition, pathologic fracture, spinal cord compression, ureteral obstruction, and development of extraskeletal metastasis were twice as common in deferred patients. A covariant analytic review of data from the Veterans Administration Cooperative Urological Research Group studies suggests that initiating therapy when patients have minimal metastatic disease may be beneficial. Delayed hormonal therapy may be appropriate for older patients with a life expectancy of 10 years or less and localized prostate cancer (stage T1 or T2) or for patients who value potency over other factors. Early hormonal therapy may be appropriate for younger patients, those with more advanced disease, and patients who do not want the “no treatment” option.
b. **Bilateral orchiectomy** appears to be the most consistent means of endocrine manipulation. Results are immediate, there is virtually no operative morbidity, and patient compliance is not a problem.
c. **Medical castration** may be achieved by a variety of agents. See Chapter 15 for discussion of their use in prostate cancer.
d. **Combined androgen blockade** is the combination of surgical or medical castration with peripheral antiandrogen blockade in the treatment of advanced prostate cancer. Although not all trials have shown a benefit of combined androgen blockade over conventional therapy, two of the largest controlled trials, the National Cancer Institute (NCI) Intergroup 0036 Study and the Urological Group of the European Organization on Research and Treatment (EORTC) 30853 Study, demonstrated statistically significant prolonged survival for patients treated by combined androgen blockade compared with those treated by surgical or medical castration alone (particularly for minimal metastatic burden). Combined androgen blockade should be considered in all patients in whom flare-ups must be blocked and in patients who have not responded to monotherapy.
e. **Antiandrogens** may also be considered as monotherapy (see Chapter 15). **Intermittent androgen ablation** is a new technique that might improve overall survival by delaying the emergence of androgen-independent clones while improving the overall quality of life. Antiandrogen withdrawal has also been shown to decrease PSA levels. This **antiandrogen withdrawal syndrome** has been demonstrated with nonsteroidal as well as steroidal (e.g., megestrol) antiandrogen agents. A point mutation in androgen-binding receptors that may sensitize tumor cells to the antiandrogen agent is theorized. Aminoglutethimide and ketoconazole can be used to lower serum testosterone quickly in cases involving spinal cord compression secondary to metastases.
f. **Hormone-resistant disease.** There is little effective therapy for patients in whom hormonal manipulation has failed. Palliation may be achieved with focal irradiation to metastatic sites in bone. Strontium 89 has been approved for the management of pain arising from skeletal metastases. Strontium is a radiopharmaceutical that emits a b-particle and localizes in bone after intravenous injection. Approximately 70% to 80% of patients experience pain relief. Chemotherapy has produced little response, either objective or subjective.

V. Testicular and Extragonadal Germ Cell Cancer

A. **Incidence.** Testis cancer is the most common tumor in boys and men ages 15 to 35 years. Approximately 7,200 new instances of testis cancer were reported in the United States in 1997, and about 350 deaths. Testicular tumors make up 1% to 2% of all male malignancies but 12% of all cancer deaths in patients between the ages of 20 and 35. The incidence is relatively higher in people of Scandinavian descent and extremely low in blacks. A person with testis cancer has a 500-fold greater chance for development of a contralateral tumor than does the general male population; however, simultaneous bilateral tumors are seen in only 1% to 2% of patients. Patients with a history of cryptorchidism have a 40- to 70-fold increase in incidence of testis cancer regardless of whether orchidopexy was carried out. Approximately 5% of germ cell cancers arise in extragonadal sites, particularly in the mediastinum and retroperitoneum.
B. **Pathology and classification** are summarized in Table 14-12.

I. Germ cell tumors	90%
a. Seminoma	50%
1. Classic	(85% of all seminomas)
2. Anaplastic	(5–10% of all seminomas)
3. Spermatocytic	(5–10% of all seminomas)
b. Embryonal	20%
1. Adult	
2. Juvenile (yolk-sac tumor)	
c. Teratocarcinoma (teratoma and embryoma)	10%
d. Teratoma	5%
1. Mature	
2. Immature	
e. Choriocarcinoma	1%
II. Gonadostromal tumors	5%
a. Leydig's (interstitial) cell	
b. Sertoli's cell	
c. Granulosa cell	
III. Secondary (metastatic) tumors	
a. Lymphoma/leukemia	
b. Prostate	
c. Melanoma	
d. Lung	

Table 14-12. Classification of testis tumors

C. **Diagnosis.** Testicular tumors usually present as an asymptomatic swelling or mass in the scrotum. All masses arising from the testis should be considered carcinoma until proved otherwise. Testicular pain is a presenting complaint in only 20% of patients. Systemic symptoms from metastatic disease and hormone production (gynecomastia) are seen in 10% and 5% of cases, respectively. The average delay in diagnosis is 4 to 6 months. On physical examination, a palpable testicular mass is usually present. In 10% of instances, the presence of a hydrocele may hinder palpation of the testis. Scrotal US can be very useful in differentiating a testicular mass from epididymitis, hydrocele, spermatocele, testicular torsion, and inguinal hernia. Other physical examination findings include lymphadenopathy, abdominal mass, and chest abnormalities. Patients with extragonadal tumors often present with pulmonary complaints (mediastinal tumors) or back pain or abdominal mass (retroperitoneal tumors).
D. **Route of spread.** Testis tumors metastasize in predictable, orderly fashion via the retroperitoneal lymphatics to the paravascular nodes at the level of the renal hilum. Tumors arising in the right testis metastasize primarily to the lymph nodes between the aorta and vena cava below the right renal vein. Tumors on the left side metastasize to the preaortic and paraaortic lymph nodes on the left. Right-sided tumors, unlike left-sided tumors, can cross the midline, making the surgical template for each retroperitoneal procedure different. Iliac and suprahilar nodes are rarely involved without direct extension from the primary nodes. Hematogenous spread to the lungs may be seen with choriocarcinoma or bulky nodal disease.
E. **Staging.** The AJCC staging system (Fig. 14-6) is becoming more widely accepted, but the Memorial Sloan-Kettering system is still frequently used (Table 14-13).

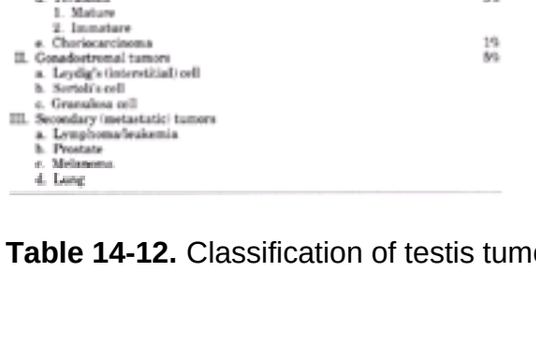

FIG. 14-6. AJCC staging of testis cancer.

AJCC stage	Description	Memorial Sloan-Kettering stage
Primary tumor		
Tx	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Intratubular tumor (carcinoma in situ)	A
T1	Tumor limited to testis, including rete testis	A
T2	Tumor extends beyond tunica albuginea or shows vascular-lymphatic invasion	
T3	Tumor in radius spermatic cord (with or without vascular-lymphatic invasion)	
T4	Tumor invades scrotum (with or without vascular-lymphatic invasion)	
Lymph nodes		
N1	Regional lymph node involvement, < 2cm in diameter and/or 5 or fewer nodes involved	B1
N2	Regional lymph node involvement, more > 5 cm in diameter and/or more than 5 nodes involved	B2
N3	One or more regional lymph nodes involved, > 5 cm in diameter	B3
Metastases		
M1a	Nonregional lymph nodes involved or pulmonary metastases	C
M1b	Other distant metastases	C

AJCC, American Joint Committee on Cancer.

Table 14-13. AJCC and Memorial Sloan-Kettering staging systems for testis cancer

1. **Tumor markers** in the serum are a-fetoprotein (AFP) and the b-subunit of human chorionic gonadotropin (b-hCG) (Table 14-14). Almost 75% of mixed germ cell testis tumors will produce an elevation of one or both markers. However, the absence of tumor marker elevation does not rule out primary or metastatic malignancy because as many as 50% of patients with low-volume retroperitoneal disease may have no elevation of tumor markers. The primary role of serum tumor markers is not in staging but in monitoring disease progression or response to therapy.

Histology	Incidence (%)	HCG elevated (%)	AFP elevated (%)
Pure seminoma	35	5	0
Embryonal	20	60	70
Teratocarcinoma	10	60	60
Teratoma	5	25	40
Choriocarcinoma	1	100	0

HCG, human chorionic gonadotropin; AFP, a-fetoprotein.

Table 14-14. Frequency of elevated tumor markers in testis cancer

   a. **AFP** is a glycoprotein produced by fetal yolk sac, liver, and the gastrointestinal tract. AFP is not elevated in pure seminoma or choriocarcinoma. Because the metabolic half-life of AFP is 5 days, persistence of high levels of AFP 4 weeks after orchiectomy indicates metastatic disease. False-positive results can occur with hepatoma, hepatitis, and bronchogenic, stomach, or pancreatic cancer.
   b. **hCG**, a glycoprotein produced by syncytiotrophoblastic cells, is composed of an a-subunit identical with that of luteinizing hormone (LH) and a b-subunit unique to hCG. Normal males do not produce significant amounts of b-hCG except from testicular tumors. Serum levels of b-hCG are elevated in 100% of patients with choriocarcinoma (Table 14-14). However, pure seminomas produce only low-grade elevations of b-hCG; marked elevation signifies the presence of associated teratocarcinoma or choriocarcinoma. The half-life of hCG is 24 to 36 hours; persistence of high levels of hCG 7 days after orchiectomy indicates metastatic disease.
   c. **Lactic dehydrogenase**, particularly isoenzyme 1, is elevated in advanced seminomas and nonseminomatous disease. This test is useful for monitoring treatment when levels of AFP and hCG are normal or have normalized.
   d. **Placental alkaline phosphatase** is detected in 65% of seminomas. It may be the most sensitive marker for metastatic seminomatous disease and for relapse.
2. **Abdominal CT** is the recommended radiologic examination for preoperative staging and metastatic workup. Although it is not very accurate with low-volume (stage B1) disease, it is excellent for nodal involvement measuring more than 2 cm. False-positive scans are rare.
3. **Chest CT** will identify a small subset of patients with normal findings on chest x-ray films but low-level pulmonary metastases. Currently, chest roentgenography is sufficient to exclude metastatic lung disease if the abdominal CT findings are negative.

F. **Primary treatment**

1. **Testicular tumors.** Radical inguinal orchiectomy is indicated in most cases as the first therapeutic maneuver, even with extensive metastatic disease. The testicle is approached through an inguinal incision. The spermatic cord is temporarily clamped before the scrotal contents are examined. If the diagnosis of testicular tumor is confirmed, high inguinal orchiectomy is performed, with the spermatic cord ligated and transected at the level of the internal inguinal ring. Transscrotal exploration or needle biopsy of the testis should be avoided for fear of contaminating the lymphatic channels of the scrotal skin.
2. **Extragonadal tumors.** For primary extragonadal seminoma, radiotherapy is the primary treatment. For nonseminomatous tumors, primary chemotherapy is given, with surgical excision of residual masses.

G. **Treatment after orchiectomy**

1. **Seminoma** is exquisitely radiosensitive, and external-beam radiotherapy is the mainstay of treatment after orchiectomy in low-volume disease (see Chapter 16).
   a. **Stage A.** Prophylactic external-beam radiation to the ipsilateral retroperitoneum (iliac and paraaortic nodes up to the diaphragm) in a dose of 25 to 30 Gy produces cure rates of better than 90%. Relapse after retroperitoneal radiotherapy is about 4% and usually beyond the irradiated field. These failures are salvageable by chemotherapy or by further radiotherapy to the site of relapse. Although the morbidity of radiation is considered minimal by most urologists, some radiation concerns include infertility, secondary long-term malignancy (stomach, colon), nausea, immunosuppression, and overtreatment in 75% of patients, as the incidence of occult metastasis in clinical stage A seminoma is only 25%. As a result, treatment options after radical orchiectomy other than radiation have included **surveillance** (although this must be carried out carefully and only in properly selected patients who are committed to appropriate follow-up) and adjuvant single-agent chemotherapy, with good efficiency. The available data suggest that almost 100% of patients with stage A testicular seminoma are cured, whichever approach is chosen. In addition, one European trial indicates that omission of the pelvic field produces relapse-free survival equivalent to that achieved with pelvic plus paraaortic radiation treatment.
   b. **Stages B1 and B2.** Treatment is the same as in stage A, with the addition of 10 to 15 Gy to the site of nodal involvement. If the lower aortic or common iliac areas appear involved on CT, the contralateral pelvic nodes are included in the field. Prophylactic supradiaphragmatic radiation is not needed if no radiographic or clinical evidence suggests disease. Prior chest radiation will compromise the patient's capacity to receive full-dose chemotherapy because of marrow suppression and will also increase the risk for pulmonary toxicity (e.g., bleomycin). The 10% to 20% of patients with stage B1 seminoma in whom relapse occurs above the diaphragm respond extremely well to chemotherapy, as seminomas are more chemosensitive than nonseminomas.
   c. **Stages B3 and C.** Radiation therapy has not been very successful, and combination chemotherapy has now become the primary therapy for high-volume disease. Because of the success of chemotherapy in testis cancer, even with seminoma the trend is to avoid external-beam radiation and proceed with chemotherapy in high-volume disease. During the past 20 years, with new chemotherapeutic agents, the survival of patients with all stages of seminoma has been 95% to 98%. Management of the residual masses in seminomas that are found in 30% to 70% of cases after chemotherapy is controversial. In advanced-stage seminoma following chemotherapy, most resected masses have shown fibrosis and necrosis. Currently, resection is not recommended in cases in which the mass is smaller than 3 cm. For larger masses, some centers recommend either radiation, surveillance, or resection and biopsy.
2. **Nonseminomatous germ cell tumors**, unlike seminomas, demonstrate little radiosensitivity. Treatment consists of retroperitoneal lymphadenectomy with or without combination chemotherapy.
   a. **Stage A**

      Please see Fig. 14-7.

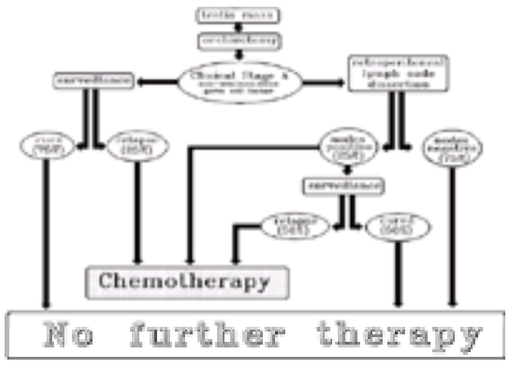

FIG. 14-7. Algorithm for the management of clinical stage A testis cancer.

1. **Retroperitoneal lymph node dissection** is presently the recommended therapy for Stage A nonseminomatous germ cell tumors. Approximately 25% of patients thought to have clinical stage A disease will be understaged. Cure rates average 90% in pathologic stage A disease after retroperitoneal lymph node dissection. Of those who relapse, 90% do so within the first 2 years (usually within the chest) and respond well to chemotherapy. Salvage rates of 100% can be achieved.
2. **Surveillance.** Many centers are recommending close surveillance after orchiectomy without retroperitoneal lymph node dissection as safe and effective treatment in clinical stage A nonseminomatous germ cell tumors. Certain high-risk pathologic features within the orchiectomy specimen, such as the presence of embryonal elements, vascular and lymphatic invasion, tunica invasion, and epididymal involvement, and the absence of yolk sac element, argue against surveillance. Approximately 25% of patients will have evidence of retroperitoneal disease during surveillance. If surveillance is chosen, close follow-up monitoring is required, as some relapses (2% to 3%) occur more than 2 years after orchiectomy. This can be economically costly as well as labor-intensive, although 75% of patients avoid surgery. Proponents of retroperitoneal lymph node dissection cite the therapeutic advantages of surgery in addition to more accurate staging and a better relapse model (chest vs. abdominal relapse), which makes follow-up studies easier (external-beam radiation vs. CT). Furthermore, the morbidity associated with retroperitoneal lymph node dissection, including ejaculatory disorders, has decreased with the use of modified and nerve-sparing template protocols.
3. **Follow-up.** Patients should be followed monthly during the first year after retroperitoneal lymph node dissection and every other month during the second year. Because the incidence of bilateral disease is 12%, the opposite testis must be palpated at each visit. Chest x-ray films and serum markers are checked every 3 months for year 1, every 4 months for year 2, every 6 months for years 3 to 5, and annually thereafter until year 10. CT is performed every 3 months for year 1, every 6 months for year 2, and annually for years 3 to 10.

b. **Stages B1 and B2.** Retroperitoneal lymph node dissection is routinely performed for accurate staging of patients with stages B1 and B2 disease. More importantly, up to 90% of patients can be cured with retroperitoneal lymph node dissection alone. Relapsing disease responds well to chemotherapy when discovered early (95%). Nevertheless, the trend is toward two cycles of combination chemotherapy following retroperitoneal lymph node dissection for pathologic stage B2 and even stage B1 disease. Relapse with stage B disease after retroperitoneal lymph node dissection but no chemotherapy is 50%, versus 2% after two cycles of postoperative chemotherapy. Stage B3 is treated like stage C disease.

c. **Stages B3 and C.** Advanced disease (Fig. 14-8) is best treated with primary chemotherapy. Platinum-based regimens achieve an 80% cure rate in stage C disease. Retroperitoneal lymph node dissection plays a secondary role and is used to confirm the effectiveness of chemotherapy. If CT reveals evidence of persistent nodal disease after chemotherapy, surgical exploration is used to establish the histologic picture. Studies have shown these persistent nodal masses to consist of fibrous tissue in 40% of cases, mature teratoma in 40%, and persistent viable tumor in 20%. With viable malignancy, salvage chemotherapy is necessary (see Chapter 15). Timing of the excision of residual tumor is crucial. Markers must have normalized before surgical excision is undertaken. If not, further chemotherapy is indicated.

FIG. 14-8. Algorithm for the management of testis cancer at clinical stage B3 and beyond. *RPLND*, retroperitoneal lymph node dissection.

VI. Cancer of the Penis

A. **Incidence.** Carcinoma of the penis is extremely rare in the United States, accounting for fewer than 0.5% of adult male malignancies or one to two cases for every 100,000. There is a 10- to 20-fold higher incidence in less developed countries. Patients tend to be 50 to 70 years of age.

B. **Etiology.** Penile carcinoma is almost never seen in circumcised men, leading to speculation that chronic irritation may be a causative factor. A viral origin (human papillomavirus) also has been suggested because the incidence of penile carcinoma is higher in men whose sexual partners have cancer of the uterine cervix.

C. **Classification of penile neoplasms**

1. **Epithelial dysplasia**
   a. **Leukoplakia** is associated with chronic irritation and often found adjacent to carcinoma.
   b. **Balanitis xerotica obliterans** is a severe, chronic inflammatory lesion of the glans (meatus) and foreskin.
2. **Carcinoma** *in situ* consists of malignant changes without invasion through the basement membrane.
   a. **Erythroplasia of Queyrat** consists of erythematous velvety plaques on the glans; the condition is often painful and clearly premalignant.
   b. **Bowen's disease** is intraepithelial carcinoma of the penile shaft. It is a harbinger of visceral malignancy in 25% of patients.
3. **Squamous cell carcinoma** accounts for 98% of cases of penile cancer, with approximately 40% of patients presenting with superficial disease at diagnosis. It is also called epidermoid carcinoma. Verrucous carcinoma (giant condyloma of Buschke-Lowenstein) constitutes approximately 5% of penile cancers. This variant of squamous cell carcinoma spreads locally with a characteristically sharply defined deep margin and has a low metastatic potential. It is usually well controlled with local excision.
4. **Basal cell carcinoma** is extremely rare.
5. **Metastatic tumors** to the penis are rare, but 75% of them are of genitourinary origin—most commonly bladder and prostate cancers followed by colorectal cancers. Cancer of the penis is essentially squamous cell cancer of the penile skin. The primary lesion usually occurs on the glans penis or inner surface of the foreskin. Invasion of the corporal bodies and urethra is more common than metastatic disease. Death from penile cancer usually results when local growth leads to sepsis or bleeding and inanition.

D. **Route of spread** is via the regional lymphatics to the superficial and deep inguinal nodes and then to the iliac nodes. Lymphatics from the prepuce drain to the superficial and deep inguinal lymphatics. Lymphatics of the glans, corpora, and urethra drain to the deep inguinal and external iliac nodes. Distant metastases occur in fewer than 10% of patients and involve lungs, liver, and bone. Patients with local penile recurrence have a mean survival of 7 years, whereas inguinal nodal recurrence is associated with a mean survival of less than 2 years.

E. **Diagnosis.** Carcinoma of the penis usually begins as a small lesion, most commonly on the glans penis or prepuce. Lesions may be papillary or ulcerative. Most penile carcinomas are not painful, which may account for the long delay in seeking medical attention. It has been reported that up to 50% of patients delay medical treatment for at least 1 year from the time of initial awareness of the lesion. Other symptoms may include penile discharge and dysuria. Approximately 50% of patients have palpable inguinal nodes at the time of presentation, but these are usually inflammatory rather than neoplastic (see below). Diagnosis is established by punch biopsy or excisional biopsy in the operating room. The differential diagnosis includes syphilitic chancre, chancroid, and condylomata

acuminata.

F. **Staging.** The **Jackson staging system**, based on degree of local invasion and metastases to lymph nodes and other organs, correlates well with 5-year survival. Table 14-15 compares the Jackson and AJCC staging systems.

AJCC stage	Description	Jackson stage
Primary Tumor		
T_{is}	Carcinoma in-situ	
Ta	Noninvasive verrucous carcinoma	I
T1	Invasion of subepithelial connective tissue	I
T2	Invasion of corpus spongiosum or cavernosum	II
T3	Invasion of urethra or prostate	IV
T4	Invasion of other adjacent structures	IV
Lymph nodes		
N1	Metastasis in a single superficial inguinal lymph node	III
N2	Metastases in multiple or bilateral superficial inguinal lymph nodes	III
N3	Metastases in deep inguinal or pelvic lymph nodes, unilateral or bilateral	III
Metastases		
M1	Distant metastases	IV
Definition of Jackson staging system		
Stage I, tumor confined to penile skin without invasion of corporal bodies		
Stage II, invasion of corpora but no nodal or distant metastases		
Stage III, tumor confined to shaft; regional lymph node metastases		
Stage IV, tumor beyond shaft; or distant metastases		

AJCC, American Joint Committee on Cancer.

Table 14-15. AJCC and Jackson staging systems in penile cancer

G. **Treatment**

1. **Surgery.** Because most penile carcinomas are initially superficial and located at or near the glans, early diagnosis often makes it possible to avoid radical surgery. Lesions located entirely on the prepuce may be cured by circumcision alone. Small lesions on the glans may be treated effectively by laser therapy or Mohs' technique. Most instances of penile carcinoma, however, will require at least partial penectomy to ensure disease-free margins of 2 cm. In cases involving the entire shaft or base of the penis, total penectomy and perineal urethrostomy are required.
   a. **Role of regional lymphadenectomy.** The status of the inguinal lymph nodes and how they are managed are most important determinants of patient survival in penile cancer. About 50% of patients have palpable adenopathy at presentation. Of these patients, only 30% to 60% will have histologic evidence of tumor in lymph nodes. In the remainder, adenopathy is caused by infection or inflammation of the penis. Of the patients without palpable adenopathy at presentation, up to 20% will have histologic evidence of nodal disease. Overall, 35% of patients, regardless of their physical examination, will have inguinal lymph nodes with tumor. Consequently, bilateral ilioinguinal node dissection has been advocated on both therapeutic and prognostic grounds. Arguments for early lymph-adenectomy are based on the higher 5-year survival rate of these patients in comparison with that of patients in whom lymph-adenectomy is delayed. Lymph node biopsies are of limited staging value.
   b. **Technique of lymphadenectomy.** Bilateral node dissection is associated with considerable morbidity, including lymphedema and wound necrosis. Changes in technique have limited the complications that were once seen after lymph node dissection; these include sparing the greater saphenous vein and covering the wound with sartorius muscle.
2. **Radiation.** External-beam radiation (50 Gy over 5 weeks) has been used as an alternative to partial penectomy. It may be especially useful in younger patients with minimally invasive lesions to avoid the psychologic trauma of penectomy; however, radiation is minimally effective in larger, invasive lesions, and morbidity from radiotherapy in such cases can be quite high. Another technique to maximize local dose employs **iridium 192** wire brachytherapy. Circumcision must be performed before radiation treatment to avoid local morbidity. However, the recurrence rate at 2 years is 63%, and 80% by 5 years.
3. **Stage T1 penile cancer.** For the patient with a stage T1 primary tumor and palpable adenopathy, a 2- to 3-week course of antibiotics is prescribed. If the adenopathy resolves, the patient is followed closely. If adenopathy does not resolve or develops later, an ipsilateral inguinal lymph node dissection is performed. If the nodes are positive for tumor, the patient is upstaged to N+ disease.
4. **Stage T2 or T3 penile cancer.** For patients with stage T2 or T3 penile cancer and no palpable adenopathy, an ipsilateral lymph node dissection should be performed. If the nodes are positive for disease, contralateral lymph node dissection is performed because of the 25% chance of contralateral disease developing via lymphatic crossover. Recently, superficial node dissection has been performed as a staging procedure. Total lymphadenectomy of nodes deep to the fascia is performed later only if the superficial nodes are positive. This reduces the incidence of surgical morbidity.
5. For **Stage N3** patients, pelvic lymph node biopsy is performed first. Bilateral lymph node dissection is performed only if the result of this pelvic lymph node biopsy is negative. This course is dictated by the fact that cure is rare if pelvic nodal disease is present. Iliac nodes positive for tumor metastases have been found in 15% to 30% of patients with positive inguinal nodes.
6. **Metastatic disease** has not been treated very successfully. Radiation therapy for node-positive disease has resulted in less than a 12% cure rate for stages T1, T2, and T3 disease. Most treatment protocols rely on chemotherapeutic agents such as bleomycin, cisplatin, and methotrexate, with methotrexate demonstrating up to a 60% response rate, although this is usually not long-lasting. Combined modalities have included postoperative adjuvant chemotherapy and radiation to positive nodal disease.

H. **Prognosis.** For localized disease without metastasis, the 5-year survival rate is 60% to 90%. With inguinal but not iliac nodal involvement, this drops to 30% to 50%. When iliac nodes are involved, the 5-year survival rate is 20%. There are no known 5-year survivors among patients with distant metastases.

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Chapter 15 Medical Management of Genitourinary Malignancy

Sanjay Razdan and Dolly Razdan

Malignancies of the genitourinary organs demonstrate widely varying sensitivities to currently available anticancer agents. At one end of the spectrum are germ cell tumors of the testis. As a direct consequence of their high degree of chemosensitivity, such tumors are curable in the vast majority of instances. On the other hand, conventional chemotherapy has had essentially no impact on survival in patients with adenocarcinoma of the kidney. Between these two extremes are carcinomas of the bladder and prostate, wherein some success with chemotherapy has been achieved. Impressive rates of response have been achieved with the use of combination chemotherapeutic regimens in bladder cancer. In prostate cancer, however, only modest success with cytotoxic chemotherapy has been achieved, although hormonal management can delay the appearance of metastases.

I. General Principles

A. **Selective toxicity.** For an anticancer drug to be clinically useful, it must exhibit greater toxicity against malignant cells than against normal cells. The principle of selective toxicity was first applied successfully in the area of antimicrobial chemotherapy. Unlike the major qualitative differences between microorganisms and normal host cells, however, the differences between malignant and normal cells are much more subtle. As a result, the gap between antitumor effect and intolerable host toxicity (“therapeutic index”) is often narrow, limiting the clinical usefulness of many chemotherapeutic agents.

B. **Mechanisms of drug activity**

1. **Cell growth cycle.** Both normal and neoplastic cells pass through a qualitatively similar process of cell replication. This cell cycle consists of several phases, which are characterized by specific kinetic or synthetic activities (Fig. 15-1). After the completion of mitosis (M), cells spend a variable period of time synthesizing RNA and proteins (G1); a phase of DNA synthesis (S) follows, then a second phase of RNA and protein synthesis (G2). During mitosis, cells divide and two daughter cells are formed. Within any tissue, whether normal or neoplastic, a fraction of cells is not actively replicating; the term G0 denotes this “resting” phase. Cells in G0 may be recruited back into the replication cycle via the G1 phase. Most chemotherapeutic drugs exert their antineoplastic effect by interfering with the synthesis or function of crucial macromolecules. These drugs are often classified according to their activity with respect to the cell cycle. Some agents (cytarabine, methotrexate) are most active against cells in a particular phase and are termed **cycle-specific phase-specific drugs**. Others (cyclophosphamide, doxorubicin) are most active against cycling cells but are not most active during any particular phase of the cycle; they are termed **cycle-specific phase-nonspecific drugs**. A third category [carmustine (BCNU), lomustine (CCNU)] appears to be active irrespective of whether the cells are replicating; these are termed **cycle-nonspecific drugs**.

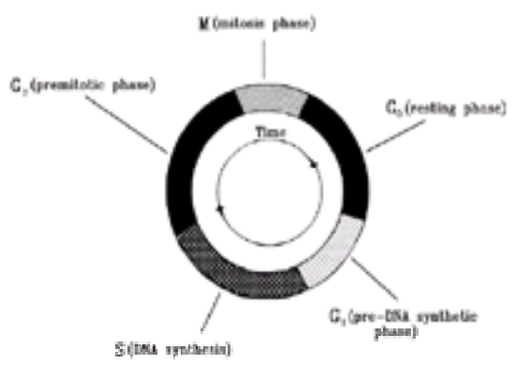

FIG. 15-1. The cell cycle. *M*, mitosis; *G1*, pre-DNA synthetic phase; *S*, DNA synthetic phase; *G2*, premitotic phase; *G0*, resting phase.

2. **The log cell kill hypothesis** states that a constant fraction of neoplastic cells will die with any drug treatment, irrespective of the size of the tumor. For convenience, the fractional cell kill is often expressed as a logarithm. The exponential growth of a tumor treated by surgery and then chemotherapy is depicted in Fig. 15-2. Note that unless 100% of tumor cells are ablated by treatment—an unlikely result with any currently available chemotherapy regimen—regrowth is likely. However, multiple treatment cycles delivered at sufficiently frequent intervals can theoretically eradicate all tumor cells completely.

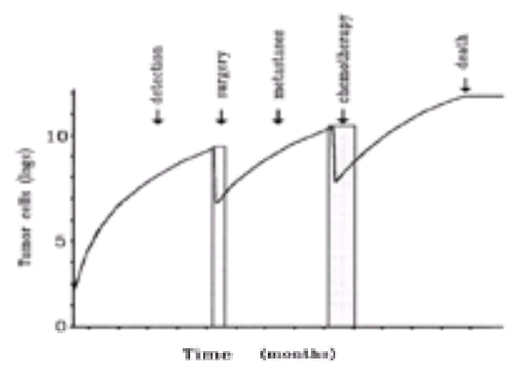

FIG. 15-2. The log cell kill hypothesis. Each treatment induces a 2 log tumor cell reduction, which, coupled with an intercycle tumor regrowth of 0.5 log, results in a net tumor cell kill of 1.5 log per treatment.

3. **Drug resistance.** In the preceding example (Fig. 15-2), complete tumor eradication depended on a number of factors, including uniform cancer cell sensitivity to the cytotoxic agent employed. Unfortunately, in the real world, cancer chemotherapy is often unsuccessful—not only because some cancer cells within a given tumor are not sensitive to a given drug but also because initially sensitive cells can acquire resistance to multiple chemotherapeutic agents during the course of treatment.
   a. **Acquired resistance.** Tumor cells may develop drug resistance for a number of reasons. Generally, if tumor cells are resistant to a particular agent, they will also be resistant to other agents in the same class or with a similar mechanism of cytotoxic action. Conversely, they will remain sensitive to agents with a different mechanism of action.
      1. **Kinetic resistance** is presumed to be a common mechanism accounting for the failure of cycle- and phase-specific agents to kill neoplastic cells. For example, in many human tumors, the bulk of the neoplastic cells are in the resting (G0) phase.
      2. **Inadequate delivery.** An antineoplastic agent may fail to reach the tumor cells in adequate concentration because of poor perfusion of necrotic tumor, poor absorption from the gastrointestinal tract, or, in the case of tumors of the central nervous system, the blood-brain barrier.
      3. **Biochemical resistance.** A number of biochemical mechanisms can foil effective drug action, including accelerated drug breakdown, decreased

activation, cell-bypass mechanisms, impermeability of cell membranes, and increased repair of cytotoxic lesions. **Multiple drug resistance** may be conferred by a glycoprotein that enhances drug efflux from cells.

b. **Natural resistance.** Cancer cells may have an inherent resistance to a drug without previous exposure to the agent, so-called natural resistance. The theory of natural resistance holds that with increasing tumor size, a steady state is reached in which most cells are no longer rapidly proliferating. Furthermore, the larger the tumor mass, the more likely it is that drug-resistant cells will develop. This theory, although unproven, explains the inverse relationship between tumor size and chemoresponsiveness as well as the superiority of combination chemotherapy over single-drug therapy in many situations.

C. **Toxicity.** Cancer chemotherapeutic agents are often associated with frequent and severe adverse effects. Such toxicity may severely limit patient tolerance and the ultimate clinical usefulness of a regimen. It is the responsibility of any physician administering these agents to be familiar with the toxic profile of each drug and to monitor the patient properly so that appropriate action can be taken to limit toxicity. With the exception of nausea and vomiting, the most common toxicities of chemotherapeutic agents derive from their effects on the rapidly growing cells of the bone marrow and epithelium. Adverse effects are discussed in more detail in the section on chemotherapeutic agents.

D. **Guidelines for chemotherapy**

1. Establish a **pathologic diagnosis**. Antineoplastic drug therapy should never, except in rare circumstances, be instituted without a firm cytologic or histologic diagnosis.
2. Establish the **stage of disease**. In this chapter, tumor-node-metastasis (TNM) staging refers to the most recent American Joint Committee on Cancer (AJCC) system. Proper planning of treatment and follow-up both depend on accurate assessment of tumor stage at the time of diagnosis.
3. Establish the patient's **performance status**. Table 15-1 summarizes the commonly used Karnofsky performance scale. In many forms of cancer, the patient's performance status has proved to be one of the most important prognostic factors with respect to tolerance and response to chemotherapy.

Rating (%)	Characteristics
100	Normal, no evidence of disease
90	Minor symptoms or signs
80	More pronounced symptoms or signs
70	Cannot work but able to care for self
60	Requires some assistance
50	Requires considerable assistance
40	Requires special care and assistance
30	Severely disabled
20	Hospitalization necessary
10	Death imminent
0	Dead

Table 15-1. Karnofsky performance scale

4. Establish **treatment goals**. Realistic goals should be established based on the histologic diagnosis, tumor stage, and patient performance status (Table 15-1). In some diseases, a complete response (CR) is a realistic goal (testis cancer), but in others, palliation or a partial response (PR) is all that can be achieved (bone metastases in prostate cancer).
5. Consider the **risks and benefits** of chemotherapy.
6. Establish the appropriate **dose, schedule, and route** of administration.
7. Establish **response criteria**. It is crucial to define objective response criteria at the initiation of treatment (Table 15-2). The most rigorous response criteria are based on patient survival or reduction in tumor size. When the extent of disease is poorly defined, subjective patient response criteria may be employed (e.g., bone pain in prostate cancer).

Type of response	Definition
Complete	complete disappearance of all measurable lesions
Partial	>50% reduction of all measurable lesions no increase in any lesion no new lesions
Stable	<50% reduction of measurable lesions or <25% increase of measurable lesions
Progression	>25% increase of measurable lesions or appearance of new lesions

Table 15-2. Clinical criteria for treatment response

8. Establish a system to monitor **toxicity**. For most agents, this includes determination of white blood cell and platelet counts and performance of liver function tests at regular intervals during and after chemotherapy. For some agents, additional monitors are needed, such as tests of renal function, pulmonary function, and nerve conduction.

E. **Combination therapy**, in which chemotherapy is combined with surgery and/or radiotherapy, is sometimes indicated. For certain patients who have undergone cancer surgery and manifest known risk factors for relapse or development of metastatic disease, chemotherapy may be indicated even though no evidence of relapse or recurrence is present. This is called **adjuvant therapy**. Examples of known risk factors include a high tumor grade, presence of tumor at resection margins, or intravascular invasion. In contrast, therapy administered before surgery (**neoadjuvant therapy**) is intended to treat undetectable micrometastases and reduce tumor size (**tumor debulking**).

II. Chemotherapeutic Agents

Please see Fig. 15-3.

FIG. 15-3. Mechanisms by which chemotherapeutic agents interfere with DNA replication and protein synthesis.

A. **Alkylating agents** are exemplified by cyclophosphamide and *cis*-platinum.

1. **Mechanism of action.** As the name implies, this group of agents impairs cell function by substituting alkyl groups for hydrogen atoms on a variety of biologically important molecules. The action of these drugs on DNA interrupts the accurate or complete replication of the DNA molecule and results in mutagenesis or cell death. The alkylating agents are cell cycle-specific but not phase-specific and thus can kill cells at all points in the growth cycle. In

addition, at least some drugs in this class appear also to act on noncycling cells (cycle-nonspecific).

2. **Toxicity** is summarized in Table 15-3.

	Alkylating agents		Antimetabolites		Vinca alkaloids		Antibiotics	
Reaction	CY	CS	MT	FU	VB	VC	DR	BL
Myelosuppression	–	+	+++	++	+++	++	+++	+
Nausea, vomiting	+++	+++	+	++	++	+	++	+
Diarrhea	+	+	++	++	+	–	+	–
Alopecia	++	+	++	+	++	++	+++	++
Nephrotoxicity	–	+++	++	–	–	–	–	–
Neurotoxicity	–	+	–	+	++	+++	–	–
Cardiac toxicity	–	–	–	–	–	–	+++	–
Pulmonary toxicity	–	–	+	–	–	–	–	+++

CY, cyclophosphamide; CS, cisplatin; MT, methotrexate; FU, 5-fluorouracil; VB, vinblastine; VC, vincristine; DR, daunorubicin; BL, bleomycin.

Table 15-3. Toxicity of selected chemotherapeutic agents

   a. **Hemorrhagic cystitis** can develop in up to 10% of patients during or after cyclophosphamide therapy. Its incidence may be reduced by keeping the patient well hydrated and encouraging frequent emptying of the bladder. See Chapter 7 for the treatment of hemorrhagic cystitis.
   b. **Renal tubular damage.** Acute renal tubular necrosis is associated with administration of *cis*-platinum and is often the dose-limiting factor. Renal dysfunction related to platinum develops in approximately 25% of patients. It may be prevented for the most part by vigorous hydration and mannitol- or furosemide-induced diuresis.
   c. **Ototoxicity**, manifested as high-frequency hearing loss, is quite common with *cis*-platinum. Periodic hearing tests are recommended.
   d. **Peripheral neuropathy** is not uncommon with increasing cumulative doses of *cis*-platinum and can mandate a halt to therapy.
   e. **Secondary neoplasia.** An increased risk for secondary malignancy is associated with virtually all alkylating agents.
   f. **Amenorrhea or azoospermia** is common with all alkylating agents. Azoospermia following chemotherapy lasts for approximately 18 months in most patients but can be permanent.
   g. **Pulmonary fibrosis** is uncommon but well described with several alkylating agents, particularly the nitrosoureas and mitomycin C. Periodic pulmonary function testing may be required in patients receiving these agents.

B. **Antimetabolites** are exemplified by methotrexate and 5-fluorouracil (5-FU).
   1. **Mechanism of action**. The antimetabolites are a group of low-molecular-weight compounds that structurally resemble normal cell metabolites involved in nucleic acid synthesis. They exert their antineoplastic action by interfering with enzyme systems or by being incorporated into nucleic acids. For example, methotrexate inhibits dihydrofolate reductase, thus interfering with DNA synthesis. The antimetabolites are for the most part cycle-specific phase-specific, and the number of cancer cells that can be killed by a single exposure is limited. As a result, increased efficacy requires either more prolonged drug exposure, repeated drug doses, or recruitment of cells into active DNA synthesis. The antimetabolites tend to be the most schedule-dependent of all classes of antineoplastic agents.
   2. **Toxicity** (see Table 15-3). Doses of methotrexate in excess of 80 mg/m^2 require increased hydration, urinary alkalinization, and monitoring of serum levels. Administration of citrovorum factor (folinic acid) may alleviate the toxicity of methotrexate if given within the first few hours after methotrexate administration. By providing a form of folate, it is hoped that normal cells may be "rescued" without a reduction in the antitumor activity of methotrexate. Additional miscellaneous toxicities include the following:
      a. **Neurologic toxicity** is not uncommon with very high doses of cytarabine and occasionally with 5-FU.
      b. **Skin hyperpigmentation** is occasionally seen with 5-FU.
      c. **Renal tubular damage.** Renal insufficiency requires substantial dose reduction or discontinuance of methotrexate.

C. **Vinca alkaloids** are natural products derived from the periwinkle plant. Although vincristine and vinblastine are closely related, their spectrum of activity and toxicity profiles are considerably different.
   1. **Mechanism of action.** The primary antitumor effect appears to result from binding to microtubular cell proteins, which disrupts the process of mitosis. Classically, these are considered cell cycle-specific phase-specific agents. However, they also appear to be capable of killing nonproliferating cells by interfering with RNA and protein synthesis.
   2. **Toxicity.** See Table 15-3.
      a. **Neurotoxicity.** Both vinca alkaloids, particularly vincristine, can produce a dose-related mixed motor-sensory or autonomic neuropathy, or both. This toxic effect typically begins with paresthesias of the fingers and toes and often is dose-limiting. It can lead to progressive neurologic impairment if treatment is continued.
      b. **Extravasation necrosis**. Both vinca alkaloids can produce a severe local tissue necrosis if extravasation occurs during intravenous (IV) administration.
      c. **Dose-modification factors.** Substantial dose reduction or withdrawal is required for both drugs in the presence of liver dysfunction.

D. **Antibiotics** such as doxorubicin and bleomycin are produced by the soil fungus *Streptomyces*.
   1. **Mechanism of action.** All the agents in this class are capable of binding with DNA to inhibit its synthesis and that of DNA-dependent RNA. The antibiotics are capable of acting at several phases of the cell cycle and are thus cycle-specific phase-nonspecific agents.
   2. **Toxicity**
      a. **Cardiotoxicity.** Doxorubicin (Adriamycin) can produce a cumulative dose-related cardiomyopathy that is irreversible and often fatal. The incidence of this delayed toxic effect is quite low (1% to 2%) below a cumulative dose of 550 mg/m^2. Above this dose, the incidence rises progressively. Patients receiving doxorubicin should be followed with serial echocardiograms and electrocardiograms.
      b. **Extravasation necrosis.** Doxorubicin can produce severe local tissue necrosis on venous extravasation.
      c. **Pulmonary toxicity.** Bleomycin can produce a severe, dose-related pulmonary fibrotic process. The cumulative lifetime dose should not exceed 400 U, and pulmonary function should be monitored during treatment. Pulmonary toxicity is characterized by the insidious onset of cough, pleuritic pain, and dyspnea. There is no treatment other than discontinuation of bleomycin, and lung function still may not improve.
      d. **Dose modification.** The dose of doxorubicin must be severely reduced in the face of liver dysfunction. Substantial dose reductions of bleomycin are required in the presence of renal impairment.

III. Hormonally Active Agents

A. **Testosterone**, the principal male androgen, is secreted by the testes in response to luteinizing hormone (LH) (Fig. 15-4A). Orchiectomy remains an effective means of reducing serum testosterone levels (Fig. 15-4B). Of the circulating hormone, 98% is bound to sex hormone-binding globulin and albumin and 2% is free. On entry into cells, testosterone is converted by 5a-reductase to its active form, **dihydrotestosterone**. Dihydrotestosterone is then translocated to the cell nucleus. More than 90% of the nuclear dihydrotestosterone is derived from testosterone, the remainder being converted from the weak adrenal androgens androstenedione and dehydroepiandrosterone (Fig. 15-4A). Testosterone provides negative feedback to the hypothalamus and controls the secretion of LH.

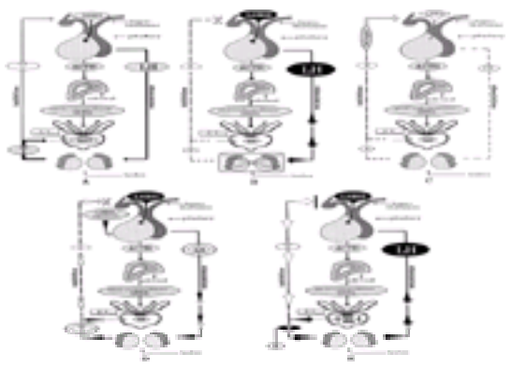

FIG. 15-4. A: Normal hypothalamic-pituitary-gonadal axis. **B:** Effect of orchiectomy. **C:** Effect of exogenous estrogenic compounds. **D:** Effect of LHRH agonists. **E:** Effect of nonsteroidal antiandrogens (flutamide). *LHRH*, luteinizing hormone-releasing hormone; *LH*, luteinizing hormone; *ACTH*, adrenocorticotropic hormone; *DHEA*, dehydroepiandrosterone; *DHT*, dihydrotestosterone; *T*, testosterone.

B. **Luteinizing hormone-releasing hormone (LHRH) agonists** include leuprolide and goserelin. Following their administration, LH and testosterone secretion initially increase (the **flare reaction** that occurs in 5% to 10% of patients) and then fall drastically (Fig. 15-4D). Common side effects are impotence, loss of libido, and hot flashes.

C. **Nonsteroidal antiandrogens** include flutamide, nilutamide, and bicalutamide. The compounds block the peripheral actions of testosterone, both in the prostate and the hypothalamus (Fig 15-4E). Loss of negative feedback to the hypothalamus results in a gradual increase in serum testosterone, which returns to normal after 1 year of treatment. Potency is preserved in 75% of patients. Gynecomastia, diarrhea, and liver dysfunction are common side effects. Nilutamide causes visual disturbances and alcohol intolerance.
D. **Estrogenic compounds** such as diethylstilbestrol, conjugated estrogens, and estradiol substitute for the negative feedback effect of testosterone and suppress the secretion of LH. This results in lowering of serum testosterone to castrate levels. Side effects include loss of potency, gynecomastia and breast tenderness, peripheral edema, thrombophlebitis, and pulmonary embolus. Diethylstilbestrol at a daily oral dose of 1 to 3 mg is a cost-effective mode of androgen-withdrawal therapy, but it has been largely replaced by gonadotropin-releasing hormone (GnRH) agonists because of their lower incidence of cardiovascular toxicity and side effects.
E. **Steroidal antiandrogens** include cyproterone acetate (not currently available) and megestrol acetate. These compounds produce an estrogen-like effect at the hypothalamus (Fig. 15-4C) as well as a peripheral androgen blockade similar to that of flutamide (Fig 15-4E). In contrast to estrogenic compounds, steroidal antiandrogens are not associated with significant cardiovascular morbidity. The most frequent side effects are impotence, loss of libido, and breast swelling.

IV. Biologic and Immunologic Agents

A. **Bacille Calmette-Guérin (BCG)** is an attenuated strain of *Mycobacterium bovis* that has been used as an antituberculosis vaccine for many years. It has found major application as intravesical therapy for superficial bladder cancer. BCG appears to have the ability to bind to tumor cells and disrupted epithelium. Following intravesical administration of BCG, increased urine levels of interleukin-1, interleukin-2, and tumor necrosis factor have been detected. Major complications are dysuria, urgency, and hematuria. About 5% of patients manifest systemic illness with fever of 103°F or higher.
B. **Interferons** are a family of molecules subdivided into a, b, g, and w subtypes. Interferons appear to augment the effectiveness of cytotoxic T cells and monocytes. Interferon-a-2 administered parenterally appears to have some activity in metastatic renal carcinoma. Intravesical administration of interferon-a-2 in patients with superficial bladder cancer has produced objective response rates of 40%. The agent has also been used in combination with intravesical BCG. Side effects include fever, malaise, myalgia, headache, anorexia, diarrhea, and mild neutropenia.
C. **Interleukins** are protein products of leukocytes that modulate activity of other leukocytes. Interleukin-2 induces proliferation of T cells and monocytes. Interleukin-2 has been used in metastatic renal cancer, producing a PR in 15% and a CR in 5% of patients.

V. Renal Cell Carcinoma

A. **Overview.** Renal cell carcinoma extending beyond the limits of surgical resection has proved notoriously refractory to cytotoxic chemotherapy. For this reason, a number of investigations are under way to explore other treatment modes, such as interferon, active specific immunotherapy, and adoptive immunotherapy. The treatment option most commonly employed in patients who are not included in a study protocol is hormonal therapy with progestational agents.
B. **Hormonal therapy in renal cancer.** Progestational agents were originally reported to produce objective response rates of 15% to 20%. The antiestrogen tamoxifen also has been noted to have modest activity in this disease. Recent studies using more rigid response criteria have failed to substantiate the initial reports, however. These studies have consistently shown that fewer than 5% of patients benefit from hormonal therapy. Because of the modest toxicities of these agents, however, they continue to be employed.

   The most common regimens are the following:

   1. **Megestrol acetate** (Megace), 40 to 80 mg orally four times daily
   2. **Medroxyprogesterone acetate** (Depo-Provera), 500 mg intramuscularly weekly for 4 weeks, monthly thereafter
   3. **Tamoxifen**, 10 mg orally twice daily

C. **Chemotherapy.** Unfortunately, currently available cytotoxic chemotherapy has had very little impact on this disease. No single agent or combination regimen has produced an objective response rate higher than 10%. Vinblastine was once considered conventional therapy, but despite changes in the mode of administration (1.4 mg/m^2 every 24 hours IV for 4 days vs. a bolus of 5 mg/m^2 weekly) or when combined with other drugs, objective response rates remain low, at about 7%.
D. **Immunologic therapy**
   1. **Interferon** (recombinant leukocyte or human lymphoblastoid interferon) has produced partial regressions in 15% to 20% of treated patients. Median response durations range from 6 to 10 months. The mechanisms of actions are not understood but may include direct tumor antiproliferative effects and immunostimulatory effects. Intramuscular or subcutaneous doses of 5 to 10 × 10^6 IU/m^2 have been most often used.
   2. **Interleukin-2** with or without lymphokine-activated killer (LAK) cells has resulted in 15% response rates in treated patients. Some of these responses have been complete and durable. The mechanism of action seems to be the activation of host immune mechanisms.
   3. **Other immunologic approaches**
      a. **Autolymphocyte therapy** involves administration of autologous peripheral blood lymphocytes activated *in vitro* by supernatants of anti-CD3-activated autologous peripheral blood lymphocytes. Preliminary results have been promising in improving median survival, and confirmatory trials are currently being carried out.
      b. **Future immunotherapy** will attempt to introduce more therapeutic specificity. The transfer of cytokine genes to autologous renal carcinoma cells may permit new vaccination strategies to induce specific antitumor immunity.

VI. Urothelial Cancer

A. **Overview**. Chemotherapy has been used in urothelial cancer in several clinical settings; (a) superficial bladder cancer amenable to intravesical chemotherapy; (b) low-grade, low-stage urothelial cancer of the upper tract; (c) advanced local or metastatic bladder cancer; and (d) advanced or metastatic urothelial cancer of the upper tract. Results from numerous trials suggest that intravesical chemotherapy can favorably alter the natural history of superficial bladder cancer by decreasing recurrence rates. In contrast, chemotherapy has had a much more modest impact in patients with advanced local or metastatic disease. Recent studies suggest, however, that bladder cancer may be more chemoresponsive than previously thought and that perioperative chemotherapy may be useful.
B. **Intravesical therapy** in superficial bladder disease (Tis, Ta, and T1) is used to eradicate residual disease and decrease recurrences by up to 50%. The most commonly used agent is BCG. Other intravesical agents are thiotepa (CR 29%, PR 26%), mitomycin C (CR 48%, PR 26%), and doxorubicin (CR 38%, PR 35%) (Table 15-4). See also Chapter 14.

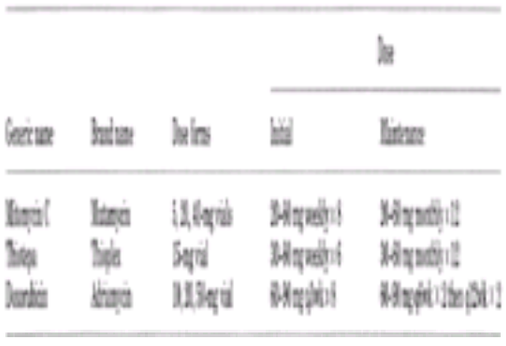

Table 15-4. Intravesical chemotherapeutic agents in bladder cancer

C. **Chemotherapy in locally advanced (stages T2 through T4) disease.** The use of chemotherapy has been disappointing. Neoadjuvant chemotherapy is

thought to result in downstaging of local tumor, reduce the incidence of micrometastases, and prevent distant metastasis. However, most trials thus far have failed to show a survival benefit with single-agent or multiagent regimens based on *cis*-platinum. At present, chemotherapy cannot be recommended for routine use.

D. **Chemotherapy in metastatic (stages N2 and M1) disease.** At the present time, candidates for systemic chemotherapy include patients who relapse after surgery or radiotherapy and the 10% of patients who present with metastatic disease.
   1. **Single agents.** A number of drugs have demonstrated activity against bladder cancer when used as single agents (CR 0%, PR 15% to 35%). Doxorubicin, *cis*-platinum, and methotrexate appear to be the most active in this disease. Single-agent schedules that have been used include the following:
      a. ***Cis*-platinum**, 40 to 100 mg/m^2 IV every 3 to 4 weeks
      b. **Doxorubicin**, 40 to 60 mg/m^2 IV every 3 weeks
      c. **Cyclophosphamide**, 650 to 100 mg/m^2 IV every 3 weeks
      d. **Methotrexate**, 40 mg/m^2 IV weekly (low dose) or 100 to 250 mg/m^2 (moderate dose) with folinic rescue every 3 weeks
   2. **Combination regimens.** Current results indicate that several combination regimens based on *cis*-platinum are superior to any single agent. The most promising regimens include *cis*-platinum and methotrexate in three- or four-drug combinations. The M-VAC protocol from Memorial Sloan-Kettering Hospital [methotrexate, vinblastine, doxorubicin (Adriamycin), *cis*-platinum] has yielded an overall response rate of approximately 70%, with a CR in up to 35% of patients. The toxicity of this regimen is severe, however, and experience in managing chemotherapy-induced cytopenia is essential before this or other regimens can be considered. Two of the most active combination regimens are the following:
      a. **CMV**, *cis*-platinum 100 mg/m^2 IV day 2; methotrexate 30 mg/m^2 day 1; vinblastine 4 mg/m^2 IV days 1 and 8. Cycles are repeated every 21 days.
      b. **M-VAC**, methotrexate 30 mg/m^2 IV days 1, 14, and 21; vinblastine 3 mg/m^2 IV days 2, 14, and 21; doxorubicin (Adriamycin) 30 mg/m^2 IV day 2; *cis*-platinum 70 mg/m^2 IV day 2. Cycles are repeated monthly.
   3. **Assessment of response.** Clear therapeutic goals and parameters of response should be delineated before chemotherapy is instituted. Response to chemotherapy, particularly with combination regimens, appears to occur promptly within 4 to 6 weeks of inception of therapy. Patients who have not demonstrated a response after two cycles should not be subjected to unnecessary morbidity from continued treatment.
   4. **Complications.** The major toxicities of the agents employed in bladder cancer have been outlined previously. Of particular concern are the nephrotoxicity of *cis*-platinum, cardiotoxicity of doxorubicin, and severe myelosuppression caused by all these agents with the exception of *cis*-platinum.

VII. Prostate Cancer

Despite increased efforts at screening for prostate cancer, about 15% of patients with prostate cancer present with advanced-stage disease that is not amenable to either surgical or radiation therapy. Although significant palliation may be achieved with hormonal therapy, radiotherapy, or chemotherapy, survival has been prolonged only minimally.

A. **Hormonal therapy.** The androgen dependency of the human prostate gland has been appreciated for at least 60 years. In many ways, prostate cancer is the male equivalent of breast cancer in women, especially with respect to the role of hormonal manipulation in advanced disease. The neoplastic prostate cell retains a dependency on androgenic hormones for optimal growth, although this dependence is seldom complete. Thus, any agent or procedure that interferes with the production, release, binding, or actions of androgens may potentially inhibit the growth of the prostate cancer cell.
   1. **Androgen deprivation** continues to be the most frequently used initial treatment for symptomatic metastatic prostate cancer (Table 15-5). Androgen deprivation may be achieved by bilateral orchiectomy, administration of estrogens, steroidal antiandrogens, or synthetic analogs of GnRH. Bilateral orchiectomy continues to be used—although rarely—in cases of poor compliance with medication schedules. Administration of estrogens may be considered when financial barriers preclude obtaining injectable synthetic pituitary inhibitors. Any of these treatment approaches will produce subjective responses in 75% to 80% of patients with symptomatic metastatic prostate cancer; the response can be expected to last approximately 1 year. Estrogens are relatively contraindicated in patients with a history of thromboembolic disease or congestive heart failure. Estrogen is usually administered as diethylstilbestrol at a daily dose of 1 to 3 mg orally. With measurement of serum testosterone levels to monitor effectiveness, the lowest effective dose should be used. Low-dose radiation (900 to 1,200 cGy in three doses) to the breasts should be administered before diethylstilbestrol is initiated to prevent painful gynecomastia. Hormones can be started 2 to 3 days later.

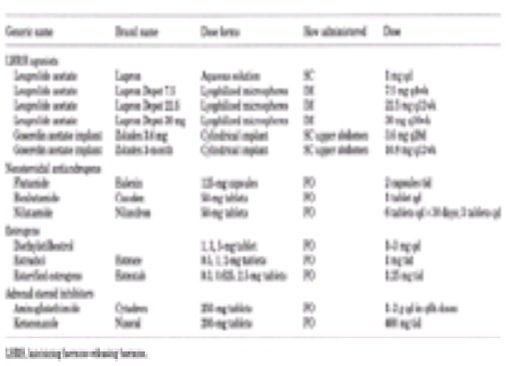

Table 15-5. Antiandrogen therapy

   2. **LHRH agonists.** Leuprolide (Lupron) and goserelin (Zoladex) are synthetic analogs of GnRH; both are available in depot forms that allow convenient monthly, 3-monthly or 4-monthly injections. They appear to be therapeutically equivalent to estrogens, without the cardiovascular complications. LHRH agonists are often administered in conjunction with flutamide. The advantage of this combination is blockade of the LHRH agonist flare reaction by flutamide and blockade of flutamide gynecomastia by the LHRH agonist.
   3. **Other regimens.** Patients who do not respond initially to hormonal therapy or who relapse after an initial response seldom respond to alternative hormonal treatment. Therapeutic strategies that have been employed include blockade of adrenal androgen production (amino-glutethimide and megestrol acetate) and peripheral androgen blockade (flutamide and megestrol acetate). The antifungal imidazoles, typified by ketoconazole, have been found to inhibit both adrenal and testicular testosterone production. Ketoconazole has produced objective responses in patients with prostate cancer, most often when used as the initial hormone therapy. Another drug that has aroused some interest is suramin, which inhibits cytokine platelet-derived growth factor. It has shown a response rate of better than 40%; the rate of serious side effects has been less then 20% with careful monitoring of plasma drug levels. The results of all these alternative strategies, when employed as salvage therapy, have been disappointing.

B. **Cytotoxic chemotherapy**
   1. **Factors hindering the use of chemotherapy in prostate cancer.** The role of chemotherapy in prostate cancer remains to be defined. A number of factors, some unique to prostate cancer, hinder attempts at improved definition of this role.
      a. **Difficulties in quantifying response.** Most patients with prostate cancer have disease that is not amenable to measurement by standard response criteria.
      b. **Poor performance status** is typical of patients with prostate cancer because of their advanced age and debilitation.
      c. **Bone marrow reserve is often limited** because of marrow replacement by tumor and previous irradiation. This factor limits patient tolerance of drugs with significant myelosuppressive activities.
   2. **Active agents.** A number of active agents have been identified, including doxorubicin, cyclophosphamide, 5-FU, methotrexate, and *cis*-platinum. In addition, a number of combination chemotherapy regimens and chemotherapy-hormonal agent combinations have been evaluated. CRs are rare, and objective PRs are uncommon. No single agent has demonstrated clearly superior efficacy against this tumor. Combination chemotherapy has not been shown to be superior to single agents. Chemotherapy has not provided any demonstrable survival benefit in prostate cancer, and median survival is 30 to 40 weeks in most studies; however, considerable pain relief and palliation can be achieved in patients who demonstrate some response.
   3. **Specific regimens.** Given its modest efficacy in this disease, chemotherapy should be offered only if specific and attainable treatment goals such as pain relief can be identified. In view of the lack of demonstrable superiority for combination regimens, single agents should be given preference. Overall responses for these agents range from 15% to 30%. Specific single agents include the following:
      a. **Doxorubicin**, 20 mg/m^2 IV weekly or 60 mg/m^2 IV every 3 weeks
      b. **Methotrexate**, 40 mg/m^2 IV weekly every 3 weeks
      c. ***Cis*-platinum**, 40 to 60 mg/m^2 IV every 3 weeks
      d. **Cyclophosphamide**, 600 to 1,000 mg/m^2 IV every 3 weeks
      e. **5-FU,** 500 mg/m^2 IV weekly

4. **Toxicity** of these agents has been discussed previously. Appropriate dose reductions should be made in patients with limited bone marrow reserve. Doxorubicin is contraindicated in patients with a history of heart disease. In addition, many patients with prostate cancer have considerable renal impairment, precluding the use of *cis*-platinum and methotrexate.

VIII. Testicular and Extragonadal Germ Cell Cancer

A. **Overview.** The introduction of highly effective chemotherapeutic regimens for germ cell tumors of the testis has been one of the most important advances in oncology during the past 15 years. The most dramatic impact has been in patients with advanced disease. In these patients, combination chemotherapy now forms the cornerstone of treatment. The initial evaluation and staging of testis cancer are discussed in Chapter 14. For the purposes of this discussion, stage B1 or B2 disease will be termed stage II **nonbulky disease**, and stage B3 disease will be called **bulky disease**. The importance of tumor markers in this disease cannot be overemphasized. Germ cell tumors, whether testicular or extragonadal, produce two glycoproteins, the b-subunit of human chorionic gonadotropin (b-hCG) and a-fetoprotein (AFP). The relative frequency of elevated markers according to histologic type is given in Table 14-5. In addition to contributing to the initial staging process, serial marker determinations during treatment provide a useful index of response. Their greatest usefulness, however, may be during posttreatment follow-up, when a rising serum marker level may herald a relapse months before any macroscopic evidence of disease is noted.

B. **Chemotherapy in early disease**

1. **Pure seminoma.** Because of the exquisite sensitivity of seminomas to radiation therapy (see Chapter 16), chemotherapy plays no role in the initial management of patients with stage I and nonbulky stage II seminomatous disease. Observation after orchiectomy has been suggested because retroperitoneal lymphadenopathy will never develop in 15% of patients. However, the standard of care is still infradiaphragmatic radiation. The small minority of patients who relapse after radiation therapy should nearly all be curable with the use of an appropriate combination chemotherapy regimen based on *cis*-platinum.
2. **Nonseminomatous tumors.** Patients with early nonseminomatous tumors traditionally have undergone retroperitoneal lymph node dissection following inguinal orchiectomy, regardless of the presence of clinical evidence of metastatic disease in the retroperitoneum. Recently, a number of investigators have described a policy of close clinical follow-up alone following orchiectomy in patients without clinical evidence of metastatic disease (clinical stage A). This policy is based on the high probability of cure with appropriate chemotherapy in the 20% to 30% of such patients who ultimately relapse after orchiectomy alone. A policy of “watchful waiting” in clinical stage A disease places the responsibility for a rigorous surveillance program on both patient and physician. This policy should still be viewed as investigational. Patients found to have no retroperitoneal disease after undergoing retroperitoneal lymph node dissection (pathologic stage A) can expect cure rates in excess of 90% with no further therapy. In contrast, patients with pathologic stage B disease have a 40% to 50% relapse rate following retroperitoneal lymph node dissection. Postoperative adjuvant chemotherapy has been used in this situation to lower the relapse rate. Results from a large national study of adjuvant chemotherapy for stage B disease suggest that relapses can be eliminated by giving two cycles of platinum-based chemotherapy after retroperitoneal lymph node dissection; however, patients who relapse can virtually all be cured with four cycles of the same regimen given at the time of relapse. Thus, two equally reasonable therapeutic options exist in this situation, and the final choice rests with the patient and physician. In many European centers, retroperitoneal lymph node dissection has been abandoned because of the 50% relapse rate, and primary chemotherapy is used instead.

C. **Chemotherapy in advanced disease**

1. **Initial treatment regimens**. Regardless of histologic type, chemotherapy is the optimal initial therapy in metastatic testis cancer (bulky stage B and stage C) and in primary extragonadal tumors. The best results have been obtained with intensive, platinum-based, three- to five-drug combinations. Such regimens produce CRs in approximately 80% of patients with advanced disease, with an overall cure rate of 70% to 75%. The two most commonly used combinations, which appear to have equal efficacy, are the following:
   a. **Bleomycin-etoposide-platinum (BEP).** The following dosages are repeated every 3 weeks for three to four cycles:
      1. **Bleomycin**, 30 U IV days 2, 9, and 16
      2. **Etoposide (VP-16)**, 100 mg/m^2 IV daily for 5 days
      3. ***Cis*-platinum**, 20 mg/m^2 IV daily for 5 days
   b. **Vinblastine-actinomycin-bleomycin (VAB-6).** The following dosages are repeated every 3 to 4 weeks for three cycles, with bleomycin omitted during cycle 3:
      1. **Vinblastine**, 4 mg/m^2 IV day 1
      2. **Actinomycin D**, 1 mg/m^2 IV day 1
      3. **Bleomycin**, 30 U IV push day 1; then 20 U/m^2 per day continuously over days 1 through 3
      4. ***Cis*-platinum**, 120 mg/m^2 IV day 4
      5. **Cyclophosphamide**, 600 mg/m^2 IV day 1
2. **Aggressive combination chemotherapy**. Patients with bulky stage B or C, lung nodules larger than 5 cm, or bone or brain metastases do not do well on standard chemotherapy and should be considered for more aggressive therapy.
   a. ***Cis*-platinum**, 20 mg/m^2 IV over 30 minutes on days 1 through 5
   b. **Etoposide**, 75 mg/m^2 IV over 45 minutes on days 1 through 5
   c. **Ifosfamide**, 1,200 mg/m^2 IV over 30 minutes on days 1 through 5, and bladder protection with mesna 120 mg/m^2 just before ifosfamide and 1,200 mg/m^2 continuous infusion each day until 16 hours after the last dose of ifosfamide
3. **Assessment following induction chemotherapy** involves a careful restaging of the patient by assessing all areas known to have disease previously and repeating tumor marker determinations (see Figure 14-8). Patients in whom markers and all radiographic findings have normalized require close follow-up with no additional treatment.
   a. Patients with **pure seminomatous disease** in whom markers normalize but radiographic abnormalities persist also require no further therapy in most cases. In such patients, surgical resection of these areas of suspected residual disease has almost uniformly yielded fibrosis and necrotic tissue without viable tumor. An exception may occur in patients with bulky stage B disease with teratomatous elements in their original tumor; at surgery, teratomatous elements are not infrequently found in the retroperitoneum.
   b. In **nonseminomatous disease** with persistent radiographic abnormalities but normalization of markers, persistent tumor is found in 30% to 40% of patients at surgical exploration. Thus, whenever it is technically feasible, patients with persistent radiographic abnormalities after induction therapy of nonseminomatous disease should undergo surgical resection. If residual cancer is found, such patients should receive two additional cycles of platinum-based combination therapy with appropriate dose reduction or elimination of bleomycin. Patients with pure nonseminomatous disease who manifest persistently elevated markers after induction chemotherapy should be considered for salvage chemotherapy (see below).
4. **Complications of treatment**. Platinum-based regimens can produce formidable toxicity. Nausea and vomiting during drug administration can be a severe problem; all patients should receive an antiemetic regimen (dexamethasone plus metoclopramide). To minimize potential nephrotoxicity, all patients need to be aggressively hydrated and have their urine output monitored carefully. All these chemotherapy regimens are associated with severe and potentially life-threatening myelosuppression. White cells and platelets must be monitored carefully, and prompt intervention is required at the first sign of infection. Miscellaneous toxicity includes mucositis, vinblastine-induced ileus, peripheral neuropathy, alopecia, Raynaud's phenomenon, and bleomycin-induced pulmonary fibrosis.
5. **Follow-up after treatment** is essential in achieving optimal cure rates in these patients. Most recurrences are within the first year after treatment and nearly all by 2 years. The response rate to subsequent treatment is inversely proportional to the volume of disease, hence the necessity for early detection of recurrent disease. Following achievement of a CR to chemotherapy or surgery, patients should undergo clinical examination, chest roentgenography, and serum marker determination every month during the first year, every 2 months during the second year, and at progressively longer intervals thereafter.
6. **Salvage chemotherapy**. One of the most promising regimens for use after failure of primary chemotherapy involves the addition of ifosfamide to etoposide (VP-16) and *cis*-platinum. Ifosfamide is an analog of cyclophosphamide. This regimen, called VIP, results in a CR rate of approximately 33% as a salvage protocol.
   a. **Vinblastine**, 0.2 mg/kg IV push
   b. **Ifosfamide**, 1,200 mg/m^2 IV over 30 minutes days 1 through 5 with mesna
   c. ***Cis*-platinum**, 20 mg/m^2 IV over 30 minutes days 1 through 5 with hydration
7. **Autologous bone marrow transplant.** Patients with progression during platinum-based chemotherapy or failure of prior *cis*-platinum, vinblastine, and bleomycin (PVB), etoposide (VP-16), and ifosfamide should be evaluated for autologous bone marrow transplant. In the past, results have been disappointing, with virtually no remissions lasting longer than 1 year. However, more recent studies have shown 15% to 20% long-term disease-free survival when high-dose carboplatin and etoposide are used with autologous bone marrow transplant. Unfortunately, this approach is associated with significant treatment-related toxicity.

IX. Carcinoma of the Penis

Methotrexate, bleomycin, *cis*-platinum, and 5-FU all appear to have some activity against penile cancer. Topical 5-FU has been used with some success in

premalignant lesions. Experience with systemic chemotherapy is quite limited in the United States because of the rarity of the disease. Combined therapy with bleomycin and radiotherapy has been reported to be surprisingly effective. The protocol involves 5,800 cGy of radiation over 38 days combined with 225 mg of bleomycin. More than 90% of patients demonstrated a CR, and 5-year disease-free survival was 70%.

Suggested Reading

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Chapter 16 Radiation Therapy of Genitourinary Malignancy

Anthony Zietman

Although radiation therapy is used widely in the treatment of urologic malignancy, its principles are poorly understood. In some situations, it is the mainstay of treatment (radical radiotherapy). In others, it is used to eradicate microscopically persistent local disease after surgery (adjuvant radiotherapy). In still others, its role is purely palliative. The role of radiation in this setting should not be minimized, as it often contributes to an improved quality of life for the cancer patient. This chapter outlines the basic principles of radiation therapy as they apply to urologic problems.

I. Physics of Radiation

A. **Types of radiation.** Radiation energy consists of high-energy x-rays, g-rays, or particles (charged or uncharged). These forms of radiation differ mainly in their method of production, degree of penetration into tissue, and biologic effect. Because they are electromagnetic waves that travel at the speed of light, x-rays and g-rays are characterized by very high frequencies and short wavelengths. Because of their similarity to light, x-rays and g-rays are sometimes referred to as photons. When high-energy electrons (produced within a linear accelerator) collide with the atomic nuclei of heavy metals such as tungsten, x-rays are emitted. A tungsten target is found in the head of every linear accelerator. In contrast, g-rays are produced naturally from the decay of isotopes such as iodine 125 (^{125}I) or cobalt 60 (^{60}Co). In other respects, however, g-rays are identical to x-rays. Particle beams consist of subatomic particles that are either charged (electrons, protons, a-particles) or uncharged (neutrons).

B. **Penetrating ability.** In general, the greater the energy of the electromagnetic radiation, the greater is its ability to penetrate tissue. High-energy x-rays tend to spare the surface (“skin-sparing effect”) and produce their greatest effects in deeper tissues. Modern megavoltage therapy units can produce beams with energy from 2 to 23 million electron volts. Such high-energy beams have eliminated the radiation skin reactions or “burns” characteristic of the lower-energy therapy used a generation ago. In contrast to x-rays, electron particles have very low penetration and are useful for treating surface lesions while deeper tissues are spared.

C. **Measurement of radiation energy.** This is based on the amount of ionization (expressed in terms of the quantity of free electrons released) that results when a standardized quantity of air is exposed to radiation. The standard unit of radiation is the roentgen. Specifying the amount of radiation in terms of roentgens, however, does not describe the ability of the x-ray beam to penetrate tissue, nor does it describe how much energy is absorbed by the tissue. This is because the penetrating ability of the x-ray beam depends on the energy of the beam and certain characteristics of the irradiated tissue, especially its density. The need to describe the biologic dose of delivered radiation led to the development of other units, such as the rad and, more recently, the gray. The relationship between the roentgen and the gray may be thought of as similar to that between the administered dose of a drug and the absorbed dose.

II. Radiobiology

A. **Radiation-tissue interaction.** The major effect of radiation in tissues is the ionization of oxygen and water (radiation hydrolysis) to form free radicals (Fig. 16-1). These free radicals are able to react with nuclear and mitochondrial DNA, resulting in breaks in the double strand. Although the cell and the nucleus contain DNA repair molecules, these mechanisms are overwhelmed after a given radiation dose that varies according to radiation type and cell type. Radiation may also affect membrane-bound macromolecules (signaling systems) and initiate programmed cell death (apoptosis). The effects of radiation on cellular DNA are instantaneous, but cell death does not usually occur immediately. It is deferred until the cell next attempts to divide. Lethality may not be expressed for several cell growth cycles. When apoptosis is the dominant mechanism, however, a much more rapid form of cell death can occur. This explains the rapid shrinkage of lymphomas treated by radiation.

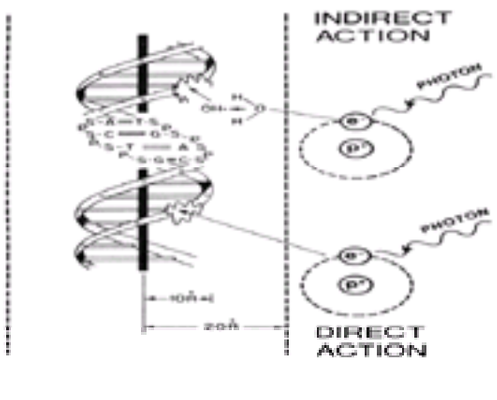

FIG. 16-1. Radiation either directly fractures double-stranded DNA or acts through the production of free radicals.

B. **Factors in the radiation sensitivity of malignant tissues**
   1. **Intrinsic radiosensitivity.** A wide variation in radiation sensitivity exists between tumor types. Generally speaking, lymphomas are the most sensitive and melanomas the least. In between, transitional and squamous cell carcinomas are more sensitive than adenocarcinomas or sarcomas.
   2. **Tumor mass.** The larger the tumor mass, the greater the number of tumor cells that must be inactivated by radiation. Smaller tumors therefore require lower doses than larger tumors. Some tumors can be so large that the dose of radiation required would be intolerable to the surrounding normal tissue.
   3. **Repopulation.** Some tumors when depleted in number of cells can respond by increasing their proliferative rate to overcome the loss. This may become a limiting factor if the radiation is delivered in too protracted a fashion. Accelerated repopulation may play a role in the rapid recurrence of some transitional cell carcinomas of the bladder after radiation.
   4. **Reoxygenation.** Hypoxic tissues are less sensitive to radiation, which works in part through the generation of oxygen radicals. Large necrotic tumors may contain a hypoxic core, which limits their curability.

C. **Factors affecting the radiation sensitivity of normal tissues.** Normal tissues may be grouped into two types: early- and late-responding. Early-responding tissues, such as mucous membranes, are quickly depleted because of their rapid turnover time. However, they are easily regenerated after therapy by surviving

stem cells and by ingrowth from adjacent, untreated mucosa. This explains the rapid development of cystitis and urethritis during radiation treatment for a urologic tumor. These symptoms usually begin to abate within a month after completion of therapy. Late-responding tissues, on the other hand, have slow turnover times and do not express any damage until months or years later. In these tissues, loss of parenchymal cells leads to atrophy, and microvascular obliteration leads to fibrosis. This can result in contraction of the bladder, a chronic rectal ulcer, or erectile impotence. These tissues may be preferentially spared by using multiple small doses of radiation to a high total dose (fractionation). The rationale is that late-responding tissues differ from early-responding tissues and most tumors in that they are capable of repairing small amounts of DNA damage after small doses of radiation.

D. **Measurement of biologic effect**
   1. **External-beam therapy (teletherapy).** This refers to the delivery of radiation from a source some distance from the target. When x-rays are delivered to living tissue, some pass through, and some are absorbed. It is the absorbed dose that interacts with tissues to produce the biologic effects. The unit of absorbed dose was the rad, which was an acronym for radiation absorbed dose. The rad now has been replaced by the gray (Gy), which equals 100 rads or centigrays (cGy).
   2. **Interstitial therapy (brachytherapy).** This is short-distance therapy in which a radioisotope is placed directly within a tumor or body cavity. The description of dose is somewhat different for brachytherapy than for teletherapy. The unit most commonly used is the millicurie (mCi), defined as 3.7×10^{7} disintegrations per second. To convert these measurements into Gy is a complex process that takes into account the distance from the source and the density of the tissue being irradiated. Different radioisotopes have different energies that determine how they can be used. Iodine 125 produces very low-energy g-rays. It can thus be left inside a prostate gland indefinitely and the radiation will not reach any of the surrounding tissues, let alone other people. Other sources, such as iridium, may be used for prostate implants, but they have a higher energy and would thus represent a radiation hazard if left inside a patient.

III. Clinical Radiotherapy

When a patient is referred for radiation therapy, the initial consultation is used to establish the goals and feasibility of such treatment. Curative treatments involve high total doses of radiation to maximize the likelihood of eradicating tumor. Multiple fractions, usually exceeding 30, have to be given to maximize the likelihood of destroying the tumor and minimize normal tissue damage. Adjuvant treatments are also curative, although because only microscopic tumor burdens are faced, lower total doses of radiation can be used. Multiple fractions are again preferred. In palliation, the aim of radiation is to shrink the tumor quickly and end a distressing symptom. Low doses of radiation are sufficient, and they can be given in just a few fractions to minimize inconvenience. Once accepted for therapy, a tumor is carefully localized by clinical examination and all available radiology. This is the process of **simulation**, in which precise **treatment portals** are established. In modern radiotherapy departments, computers are used to calculate the number and angle of the beams and the doses to be delivered through each beam. **Conformal three-dimensional radiation therapy** is a term used to describe highly accurate multiple-beam radiation that excludes as much normal tissue from treatment as possible.

A. **Renal cell carcinoma**
   1. **Primary radiotherapy.** Renal cell carcinoma is generally considered radioresistant. Preoperative radiation has been shown to have no impact on survival. Postoperative radiotherapy to the renal bed in doses of 40 to 50 Gy may be given in cases of local extension or nodal metastases. Randomized trials have shown improvements in local control, but there has been no evidence of improved survival. The radiation dose that can be administered to this site is limited by the proximity of the liver and small bowel. Intraoperative radiation and brachytherapy may play a role in the future.
   2. **Palliative therapy.** This is indicated in metastatic renal cell carcinoma for the management of painful bony lesions or spinal cord compression. High doses of 45 to 60 Gy are usually required during a period of 3 to 6 weeks. Treatment needs to be more fractionated than in metastatic hormone-refractory prostate or metastatic bladder cancer because of the remarkable longevity of some patients with renal cell carcinoma.

B. **Wilms' tumor.** Radiotherapy may be indicated as adjuvant treatment in some cases of Wilms' tumor in childhood. This tumor is very radiation-sensitive, and improved survival has resulted from combining radiation with surgical removal of tumor. Radiotherapy in young children has a tendency to slow or even halt vertebral growth. It has been shown that when postoperative chemotherapy is given to children with early-stage disease and favorable histology, adjuvant radiation does not further improve survival. Thus, the current trend is to give radiation only to selected patients, such as those with unfavorable histology, stage III or stage IV disease, positive margins, or gross tumor spillage during surgery. In such cases, 10 Gy is given to the flank. Metastatic sites may also be treated with low-dose radiation in conjunction with systemic chemotherapy.

C. **Bladder cancer**
   1. **Primary external-beam therapy.** This may be effective in the treatment of invasive bladder cancer and is widely used as a primary modality in some European countries. The 5-year local control is only in the order of 30% to 40%, considerably less than that obtained with cystectomy. For this reason, in the United States radiation alone is reserved for patients who are poor surgical candidates. The efficacy of radiation, however, may be considerably improved by prior transurethral debulking of the tumor and the synchronous administration of cisplatin, a radiation sensitizer. Much higher rates of local control are possible, and some centers now use this bladder-sparing approach as primary therapy. Patients who are not controlled undergo prompt salvage cystectomy.
   2. **Postcystectomy radiation.** When a surgically removed tumor is massive and adherent to the pelvic side wall, the risk for local recurrence is extremely high. Postoperative irradiation can be given to a total dose of 45 to 50 Gy, but because the bladder is no longer present to displace the small bowel, small-bowel complications (adhesions, stricture) are common. If postoperative irradiation is anticipated, a pelvic sling should be inserted at the time of surgery. Radiation may also be reserved for salvage of local pelvic failure following cystectomy. As it is unsafe to administer the high doses necessary for tumor eradication, cisplatin is usually given concomitantly as a tumor sensitizer.
   3. **Palliative radiotherapy.** In patients with unresectable disease, severe bleeding may develop. Administration of 30 to 50 Gy over 3 to 4 weeks is usually sufficient to stop the hematuria. Bone metastases are treated as for prostate cancer.

D. **Prostate cancer**
   1. **Stages T1 through T2b.** A dose of 60 to 72 Gy is commonly given in divided fractions of 1.8 to 2.0 Gy/d 5 days a week for a total of 7 to 8 weeks. The likelihood of cure depends on the Gleason score and pretreatment levels of prostate-specific antigen (PSA). The chance of cure is better than 70% for a tumor with a Gleason score of 6 or less and a PSA level below 10 ng/mL. When the PSA exceeds 20 ng/mL or the tumor Gleason score is 8 to 10, cure is very unlikely because of occult micrometastatic disease. Irradiation of the regional lymph nodes may prevent local progression within the pelvis, but it does not improve survival. Because of potential morbidity, it is now usually omitted.

      Brachytherapy is an alternative to external-beam therapy for early-stage disease. Iodine 125 or palladium 103 seeds are inserted through the perineum under transrectal ultrasound (TRUS) guidance (Fig. 16-2). This type of therapy allows a high dose of radiation to be given (150 to 200 Gy), but because of the slow decay of the sources, it is given over many months or even years. It is difficult to compare a radiation dose given this way with that delivered by external beam in terms of biologic effect. Recently reported early results of brachytherapy are encouraging.

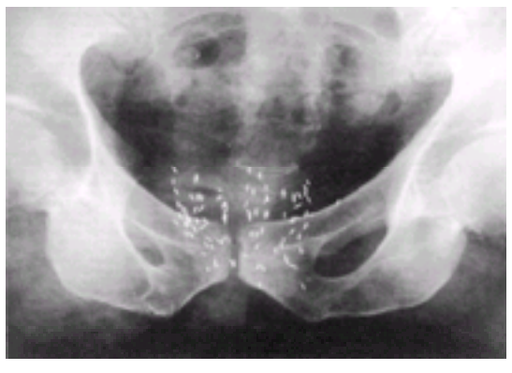

FIG. 16-2. Radiograph showing the distribution of iodine 125 seeds used in the treatment of localized adenocarcinoma of the prostate.

   2. **Stages T2c through T4.** These tumors are too bulky to be eradicated by safe doses of external radiation. Androgen deprivation is commonly administered 2 to 4 months before radiation to shrink the tumor and, through apoptosis, sensitize it to radiation. Despite the improved progression-free survival rates obtained with combination therapy, cure remains unlikely because of the high incidence of occult micrometastases.
   3. **Postoperative radiation.** A dose of 60 Gy over approximately 6 to 7 weeks may be administered to the tumor bed after radical prostatectomy when the likelihood of locally persistent disease is high (e.g., when the surgical margins are positive). The likelihood of lasting local control is very high and is in the order of 80% to 90%. Irradiation of the tumor bed for salvage may be attempted when the PSA rises after radical prostatectomy and a metastatic workup has

proved negative. This is unlikely to be beneficial when the original tumor pathology is of a high grade or seminal vesicle invasion is present. Under these circumstances, the detectable PSA is more likely to represent occult micrometastatic disease than local persistence. Androgen deprivation would be more appropriate.

4. **Palliation**
   a. **Bone metastases.** These occur frequently in prostate cancer and can be treated with local radiotherapy when androgen ablation has failed. Doses of 8 to 30 Gy given over 1 to 14 days in one to 10 treatments are effective at controlling pain 80% of the time. If multiple sites of skeletal pain exist, it might prove more convenient to give a single intravenous dose of the bone-seeking radioisotope strontium 89. When pathologic fracture has occurred, radiation can be given after orthopedic fixation to promote healing.
   b. **Spinal cord compression.** Extradural metastases may lead rapidly to catastrophic paraplegia (Fig. 16-3). This is an indication for urgent treatment with corticosteroids (4 mg of dexamethasone orally every 6 hours) and radiation (generally 30 to 40 Gy).

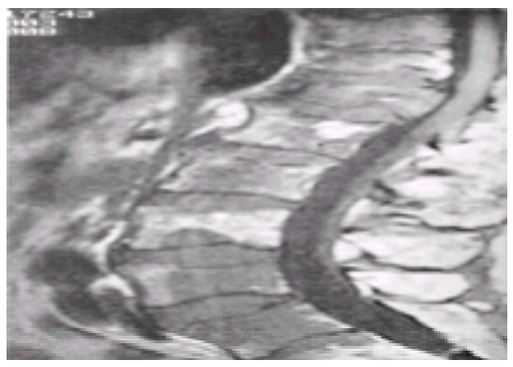

FIG. 16-3. Magnetic resonance image (MRI) showing spinal cord compression from metastatic prostate cancer. This is an emergency that requires prompt treatment with corticosteroids and radiation.

   c. **Local tumor progression.** This may cause outflow obstruction and bleeding. Although transurethral resection is usually performed for obstruction by prostate cancer, radiotherapy may be considered if operative risk is high, the patient refuses surgery, or previous surgery has failed. Again, doses from 30 to 40 Gy over 2 to 3 weeks may result in a decrease in size of the prostate and abatement of symptoms.
   d. **Gynecomastia.** This is a troublesome complication of estrogen and some antiandrogen therapy. It can be prevented by breast irradiation (15 Gy in three doses to each breast).

E. **Testis cancer.** Although chemotherapy is now the major form of treatment for nonseminomatous germ cell tumors and advanced seminoma, radiotherapy is still used regularly in the management of stages A and B seminoma.
   1. **Stage A disease.** Despite orchiectomy, about 25% of patients have occult metastases within the paraaortic and ipsilateral pelvic lymph nodes. Orchiectomy is therefore followed by administration of 25 to 30 Gy over 3 to 4 weeks to these nodal areas. Seminoma is exquisitely radiation-sensitive, and so low doses that rarely produce any lasting damage to normal tissues within the field are sufficient to eradicate microscopic disease. Radical orchiectomy and adjuvant radiation together in stage A disease result in cure rates of 95% to 98%. The few failures are usually salvaged with chemotherapy.
   2. **Stage B disease.** This is subdivided according to the bulk of the retroperitoneal metastases. In retroperitoneal disease measuring less than 2 cm in diameter (stage B1), the same radiation treatment is given as in stage A, with the addition of a further 5 Gy to the mass itself. With this mode of therapy, the 5-year disease-free survival rate is 95%. In patients with 2- to 5-cm diameter disease in the retroperitoneum, radiation still offers an 85% chance of cure and is preferable for men who do not wish to have their fertility compromised by chemotherapy. Those who have bulkier stage B tumors are usually treated by primary chemotherapy, with radiation given to residual masses greater than 3 cm in diameter.

F. **Penile and urethral cancer**
   1. **Squamous cell carcinoma of the penis.** Although the primary treatment mode in the United States is surgical excision, radiotherapy may be used. Small lesions measuring less than 3 cm in diameter may be treated with high-dose superficial electron-beam radiation. Cure rates at 3 years approach 90%, and the penis is preserved (Fig. 16-4). Interstitial radiation with iridium is an alternative method of delivering a high dose quickly to a small area. When the lesions exceed 3 cm in size, local control with radiation is less likely and penectomy may be preferred. If the patient declines or is medically unsuitable, then penile irradiation is combined with elective radiation to the inguinal lymph node areas.

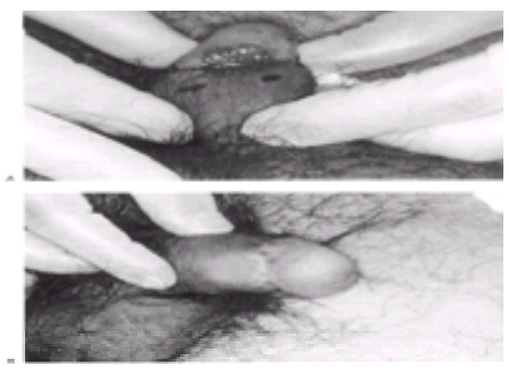

FIG. 16-4. A small, 1.5-cm penile squamous cell carcinoma before **A:** and 1 year after **B:** superficial electron-beam radiation therapy.

   2. **Urethral cancer.** Malignancy in the male anterior urethra can be treated in the same way as penile cancer. Tumors in the posterior urethra are treated in a manner similar to that for prostate cancer, with radiation doses of 60 to 70 Gy to the primary tumor. If the cancers are of the transitional cell type, concomitant *cis*-platinum can also be given, as for bladder cancer. In female patients, carcinoma of the urethra requires interstitial implantation. This is combined with external-beam radiation to the inguinal and deep pelvic lymph nodes.

IV. Complications of Radiotherapy

As previously mentioned, the complications of radiation can be divided into those occurring during or immediately after treatment (early effects) and those occurring months to years later (late effects).

A. **Early effects.** The early effects of radiation are generally short-lived and respond well to symptomatic treatment.
   1. **Local reactions.** These include skin changes and mucositis. High-energy radiotherapy beams, such as those produced by the linear accelerator or cobalt units, tend to spare the skin and produce little erythema. A temporary acute cystitis and proctitis are, however, quite common. Cystitis manifests as urinary frequency and dysuria in the third or fourth week of radiation. It is usually managed by anticholinergic or locally anesthetic medications. Proctitis occurs 3 weeks after the start of radiation and usually presents as tenesmus, increased bowel frequency, and occasional rectal bleeding. Diarrhea occurs only when large fields are used to treat pelvic lymph nodes. Proctitis is managed by a low-residue diet, antispasmodic agents, and steroid suppositories. Doses of 25 to 30 Gy will generally affect hematopoiesis within the marrow of the irradiated bones. This can be an issue in patients with bladder cancer or seminoma who have been previously treated by chemotherapy. In these situations, if the white cell count falls below 2,000/mm ^{3} or the platelet count is less than 50,000/mm ^{3}, radiation should be stopped until recovery has occurred.
   2. **Systemic reactions.** These can occur after wide-field radiation, such as is given for seminoma. Nausea is common after radiation to the upper abdomen but rarely lasts more than a few days. If it is severe, antiemetics may be prescribed as needed. General fatigability is quite common during external-beam radiation. There are no systemic effects from interstitial brachytherapy.

B. **Late effects.** Late effects may occur because of parenchymal cell loss leading to tissue atrophy and because of an obliterative endarteritis that may provoke fibrosis. The clinical manifestations depend on the organ irradiated, the state of its vasculature, the radiation dose given, and the radiation fractionation. The degree of early reaction cannot be used to predict the degree of late effects, if any.

1. **Kidney.** This is a sensitive organ, and radiation nephritis with tubular obliteration has been described in patients who have received 20 to 25 Gy to both kidneys. It manifests as chronic renal failure at least 1 year after radiation. The clinical setting in which it can occur is very uncommon these days, as whole-abdominal irradiation is infrequently used for anything but palliation of lymphoma or ovarian cancer. Unilateral kidney irradiation may lead to hypertension.
2. **Ureter.** The ureters rarely show any long-term effects from radiotherapy. Stricture is a remote possibility.
3. **Bladder.** In the days when low-energy equipment was prevalent and daily radiation doses large, radical radiation for bladder cancer was followed by the development of bladder contracture or hemorrhagic cystitis in up to 20% of cases. This problem has now largely been eliminated by the use of small radiation fractions and sophisticated technology.
4. **Prostate and seminal vesicles.** Ejaculatory volume is reduced following radiation therapy. Urethral stricture occurs in 1% to 5% of patients undergoing prostate or bladder irradiation. The rate is closer to 15% in patients who have had a prior transurethral resection of the prostate (TURP). Although incontinence rarely occurs after external-beam radiation, it may be seen after prostate brachytherapy in patients who have had a prior TURP.
5. **Male and female gonads.** These are relatively radiation-sensitive. Although the Leydig's cells (and therefore testosterone production) of male adults are quite radioresistant, the spermatogonia are exquisitely sensitive to radiation and are rapidly eliminated by doses of 0.8 Gy or more. The spermatogonia will be replaced in 6 to 24 months, and recovery of the sperm count follows. Permanent azoospermia results only from direct doses of 6 Gy or more. In most major centers, young men treated for seminoma will have their remaining testis shielded with lead to reduce the radiation dose to well below 1 Gy. Sperm banking is not usually recommended unless chemotherapy is to be part of the treatment. Ovaries are more radiation-resistant, but permanent sterility can be expected after 12 to 15 Gy of pelvic irradiation.
6. **Erectile function.** Impotence resulting from radiation may start 6 or more months after therapy. Its incidence may be as high as 50% for those receiving external-beam radiation and approximately 30% for those receiving prostatic implants. It results from the effect of radiation on the proximal corpora to cause a venous leak and the effect on the neurovascular bundles around the prostate. The risk for impotence is higher in older men and those who smoke or have diabetes.
7. **Vagina.** Vaginal stenosis occurs very infrequently after bladder irradiation. It is more commonly seen after high-dose radiation for cancer of the cervix and uterus. When it occurs and causes sexual dysfunction, it may be treated with lubricants and vaginal dilators.
8. **Gastrointestinal tract.** This is sensitive to radiation in doses of 50 Gy or more and can lead to fibrosis, stenosis, and even fistula formation. Most of these effects are minimized by limiting the radiation dose to 50 Gy or less and carefully choosing a radiation-beam arrangement that avoids the small bowel when possible. When treating bladder cancer, radiation oncologists minimize the dose to the small bowel, as this may be required in the future for urinary diversion.

Suggested Reading

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Chapter 17 Genitourinary Infection

Colm Bergin

I. General Principles

Urinary tract infection, cystitis, and prostatitis syndromes are common clinical problems in urology. Most patients with these problems do not have underlying anatomic, metabolic, or functional abnormalities. General factors that may affect the clinical approach include patient age, sex, and state of immunocompetence, site of infection, and the infectious agent. Local factors, including blood supply and presence of obstruction, are also important considerations.

II. Classification of Urinary Tract Infections

A. **Bacteriuria** (the presence of bacteria in the urine) should be distinguished from **urinary tract infection**, which implies invasion of genitourinary tissue.
B. **First infection** is the first documented episode of significant bacteriuria.
C. **Unresolved bacteriuria** refers to failure to eradicate the infecting organism. Causes of unresolved bacteriuria include the following:
   1. **Bacterial resistance** to the antibiotic chosen for treatment is noted in approximately 5% of patients on antimicrobial therapy. Tetracyclines, penicillins, sulfonamides, cephalosporins, and trimethoprim are capable of transferring R-factors that make bacteria simultaneously resistant to multiple agents, including ampicillin, cephalosporins, and others. The fluoroquinolones and nitrofurantoin do not cause R-factor resistance and are ideal for therapy in this setting.
   2. **Multiple-organism bacteriuria** may fail to resolve when different bacterial species have mutually exclusive sensitivities.
   3. **Rapid reinfection** with a new resistant species during initial treatment for the original sensitive organism may occur.
   4. **Azotemia** may lead to poor excretion of antibiotic into the urine.
   5. **Papillary necrosis** may prevent adequate concentration of antibiotic in the urine.
   6. **Infected calculi, bladder tumors, or foreign bodies** may act to protect sensitive bacteria from antimicrobial inhibition.
   7. **Patient noncompliance** should be suspected when the urine culture during therapy reveals the same organism and sensitivity that were identified on initial culture.
D. **Recurrent infection** refers to repeated infection interrupted by periods of sterile urine. It is caused by either persistence of bacteria within the urinary tract or reinfection by a new organism from a source outside the urinary tract.
   1. **Bacterial persistence** refers to cases in which urine is sterilized by therapy but a persistent source of infection remains. Examples include infected stones and foreign bodies, chronic bacterial prostatitis, urethral or bladder diverticula, and renal abscess. Although bacterial persistence is relatively uncommon, it is the only surgically curable cause of recurrent urinary tract infection.
   2. **Reinfection** accounts for 80% of recurrent infections. Most cases represent new infections with a new organism after initial therapy has sterilized the urine. Reinfections tend to occur more than 2 weeks after completion of therapy and are more frequent after cases of cystitis. Most recurrent infections in female patients are reinfections of the urinary tract caused by bacteria that ascend from the rectum to the vaginal introitus and then into the bladder. Reinfections in men are usually associated with an anatomic or functional abnormality of urine transport. The possibility of a vesicoenteric or vesicovaginal fistula should be considered when there is a history of pneumaturia, fecaluria, diverticulitis, previous gynecologic surgery, or radiation therapy.

III. Laboratory Diagnosis

Although colony counts below 100,000 do not necessarily rule out infection, counts in excess of this number are always considered significant. Diagnosis depends on proper specimen collection to avoid contamination, prompt culturing, and quantitative bacteriologic techniques. If prompt culturing is not possible, containers should be transported in iced water and stored at 4°C. Cooling stops bacterial growth, but bacteria may still grow on media the following day. The urinary white cell count will be affected.

A. **Specimen collection.** Urine collected in a normal patient by suprapubic aspiration is sterile and represents the gold standard of diagnosis of urinary tract infection (Table 17-1). It is best to examine urine collected under supervision in the clinic or hospital rather than samples taken at home. In men, the specimen should be collected before prostatic examination to prevent contamination by prostatic secretions. Collection of urine from a drainage bag is not a reliable technique for urine culture.

Colony count (CFU/mL)	Method of collection		
	Clean catch	Catheterization	Suprapubic aspiration
<10,000	2%	2%	100%
10,000–100,000	5%[a]	50%	100%
>100,000	80%[b]	95%	100%

CFU, colony-forming units.
[a] Probably higher in male patients.
[b] If obtained from two consecutive specimens, 95%.

Table 17-1. Probability of infection based on single-specimen colony counts

1. **Men.** Urine should be collected with the midstream clean catch method. In uncircumcised men, the foreskin should be retracted and the meatus cleansed with antiseptic. The first 25 mL of urine is passed without collection. The sterile container is then placed into the urinary stream and 50 to 100 mL is collected. The urine should be cultured as soon as possible after collection.
2. **Women.** After the labia are separated with one hand, the urethral meatus is cleansed with an antiseptic. A wiping motion toward the perineum should be used (to avoid contamination). After the first 25 mL is passed, the next 50 to 100 mL is collected in a sterile container. If a satisfactory specimen cannot be obtained, urine should be collected by a single straight catheterization of the bladder. A single catheterization causes urinary tract infection in 1% of ambulatory patients and in 5% to 10% of hospitalized patients.
3. **Children.** In very young children, urine is usually collected by cleansing the meatus and placing a sterile plastic bag over the penis or vulva. Suprapubic needle aspiration of the bladder may be required to obtain a reliable urine specimen and is easily accomplished in young children because the bladder is located in a more intraabdominal position than in adults.
4. **Catheterized patients.** In patients with indwelling catheters attached to closed drainage systems, urine for culture may be obtained from the needle port by

using a sterile needle and a syringe to aspirate the urine. A closed drainage system should never be opened to collect urine for culture.

5. **Upper urinary tract.** Neither history nor physical examination can reliably distinguish infection limited to the lower tract from infection affecting the upper tract. Noninvasive tests, including antibody-coated bacteria (ACB), have not proved sensitive or specific enough to be used in clinical practice. The only reliable methods involve invasive procedures (cystoscopy and collection of urine from both catheterized ureters or the bladder washout of Fairley).
6. **Prostatic secretions.** In men with relapsing urinary infection, the most common source is the prostate gland. To make the diagnosis of bacterial prostatitis, the bacteriologic status of the prostate gland may be assessed either by semen culture or by expressing prostatic secretions with prostatic massage (Table 17-2). Firm massage per rectum from side to midline bilaterally causes the contents of the prostatic ducts to be expressed. Vertical strokes in the midline will then project the secretions into the urethra and permit counting of leukocytes. Segmented cultures of the lower urinary tract are used as follows:

Culture result	Interpretation
VB1 ⩾ VB2 or EPS or VB3	Urethral source
EPS and VB3 ⩾ VB1 or VB2	Prostatic source
VB2 ⩾ VB1 or EPS	UTI without prostatic source
VB1 = VB2 = EPS = VB3	UTI with prostatic source

VB, voided urine; EPS, expressed prostatic secretions; UTI, urinary tract infection.

Table 17-2. Interpretation of segmented urine cultures

   a. The first 10 mL of voided urine (VB1) represents the urethral flora.
   b. The midstream specimen (VB2) represents the bladder flora.
   c. The expressed prostatic secretions (EPS) obtained by massage represent the prostatic flora.
   d. The final specimen is the first 10 mL of urine voided immediately after prostatic massage (VB3) and represents the combined flora of the bladder and prostate.

B. **Microscopic examination of urine**
   1. **Unspun urine.** Examination of fresh unspun urine is useful when one or more bacteria or one or more leukocytes per oil-immersion field are observed.
   2. **Centrifuged urine** should be examined under high power (x400).
      a. **Pyuria** is defined as the presence of at least five leukocytes per high-power field in men and more than 20 leukocytes per high-power field in women. Ten or more leukocytes per high-power field are observed in 60% to 80% of patients with positive urine cultures. However, 25% of patients with negative urine cultures may also have pyuria. The differential diagnosis of sterile pyuria includes antibiotic effect, atypical organisms (*Mycobacterium tuberculosis, Chlamydia, Ureaplasma*), chronic interstitial nephritis, uroepithelial tumor, or nephrolithiasis.
      b. **Bacilluria** correlates well with culture results. Only 10% of patients with negative cultures have bacteria in the centrifuged urine specimen. Gram's stain should be performed on specimens demonstrating bacilli.

C. **Dipstick** detects the presence of leukocyte esterase and nitrite; the former corresponds to significant pyuria and the latter to the presence of Enterobacteriaceae, which convert urinary nitrate to nitrite. Dipstick has a sensitivity of 75% to 95% and a specificity of 65% to 95%. The positive predictive value is relatively low at 30% to 40%, and the negative predictive value is 99%. Thus, these tests may be an alternative means of ruling out urinary tract infection when microscopy is not available.

D. **Interpretation of urine culture.** Results depend on method of collection, type of organisms, the patient's clinical symptoms, and number of colony-forming units per milliliter of urine.
   1. **Organisms.** *Escherichia coli* is cultured from more than 80% of urine specimens in patients with uncomplicated cystitis or pyelonephritis. *E. coli* is cultured in the vast majority of community-acquired infections; *Klebsiella* species and *Enterobacter* species are more likely to be hospital-acquired. Infections with *Pseudomonas* species and *Candida albicans* usually occur in patients with poor resistance who have received multiple courses of antibiotics. *Staphylococcus* species may be true pathogens, especially in the setting of obstruction. *Proteus* infections are often associated with struvite or “infection” calculi. Most urinary pathogens are incapable of producing infection calculi, as they lack the enzyme urease, which alkalinizes the urine by converting urea to ammonia. This leads to supersaturation, a decrease in solubility of magnesium and calcium phosphate, and formation of stones composed of struvite and apatite. *Proteus* species, *Klebsiella* species, occasionally *Pseudomonas* species, and *Staphylococcus* species possess this enzyme. Multiple organisms are isolated in only 5% of true infections.
   2. The **colony count in midstream voided urine** has been compared with that in urine obtained by suprapubic bladder aspiration or bladder catheterization. Based on studies in asymptomatic women, Kass proposed the criterion of 100,000 colonies per milliliter as a positive test result for urinary infection. In an asymptomatic woman, a finding of more than 100,000 colonies per milliliter has an 80% positive predictive value, whereas in a symptomatic woman, such a finding has a 95% positive predictive value. However, the usefulness of this cutoff point depends on the method of collection and the clinical situation.
      a. **False-negative results**
         1. Of acutely symptomatic women demonstrated to have bladder bacteriuria on suprapubic aspiration, fewer than 50% had more than 100,000 colonies per milliliter in the midstream specimen.
         2. With markedly dilute urine or very frequent voiding, the colony count may be artificially reduced.
         3. Antibiotic therapy may suppress counts.
         4. Soaps or detergents used in specimen collection may suppress counts.
      b. **False-positive results** may be caused by contamination during collection or more commonly by delay in specimen culturing.

IV. Indications for Evaluation of Urinary Tract Infection

The need to evaluate a patient in detail will be based on the clinical presentation, history, examination findings, response to antimicrobial therapy, and history of recurrent infections. A presentation or history of urinary tract infection in male patients warrants evaluation. In female patients, recurrent, relapsing, or persistent urinary tract infection warrants investigation. In either sex, sepsis, fever, urinary tract infection lasting more than 7 days, gross hematuria, evidence of obstruction, or a history of stones are all indications for further evaluation. Risk factors such as pregnancy, diabetes, immunosuppression, or other debilitating disease should also be taken into account.

V. Treatment of Asymptomatic Bacteriuria

Treatment is recommended in certain clinical situations.

A. During **pregnancy.** A 3-day regimen of amoxicillin, oral cephalosporin, or trimethoprim/sulfamethoxazole (TMP/SMX) should be given (except in the third trimester).
B. Before **urological instrumentation, endoscopy, or surgery**
C. After **removal of a long-term indwelling catheter**
D. In **renal transplant recipients** or other immunosuppressed patients
E. In **children**

VI. Bacteremia and Septic Shock

Gram-negative bacteremia arises from the urinary tract in 33% of cases. Most commonly, it occurs in a hospitalized patient following instrumentation or develops from a primary focus in the genitourinary tract.

A. **Etiology.** Genitourinary bacteremia is most commonly caused by aerobic gram-negative bacteria such as *E. coli* and *Klebsiella, Enterobacter, Serratia, Pseudomonas*, or *Proteus* species. Following transrectal prostatic biopsy, anaerobic bacteria (*Bacteroides fragilis*) may be causative. Gram-positive bacteria, particularly enterococci, are occasionally the causative organisms. Patients with bacteriuria before instrumentation or with urinary tract obstruction are at particular risk.

B. **Diagnosis**
   1. **Fever**, especially with chills, should be considered evidence of bacteremia in any patient who has recently undergone genitourinary instrumentation. Fever may be absent at the onset of sepsis, as approximately 10% of patients may be hypothermic and another 5% may be unable to mount a fever in response to infection.
   2. **Other symptoms and signs** include tachycardia, tachypnea, hypotension, and oliguria. A change in mental status such as confusion or agitation may also occur. Later, the patient may become lethargic, confused, and stuporous; the skin may become cold and moist.
   3. **Laboratory findings.** Leukocytosis is common. Thrombocytopenia occurs in 50% of patients with early sepsis. Advanced or fulminant sepsis may be accompanied by liver function abnormalities, jaundice, hypoxia, azotemia, and disseminated intravascular coagulation (DIC).

C. **Septic shock** may occur in up to 25% of bacteremic patients. Generally, shock develops rapidly and early (within 12 hours) after the onset of bacteremia. Early or “warm” shock is characterized by intense vasodilatation, increased cardiac output, and little or no hypotension. Late or “cold” shock is characterized by severe systemic hypotension (systolic pressure <90 mm Hg) accompanied by intense peripheral vasoconstriction (clammy skin), decreased cardiac output, and anuria or oliguria.

D. **Treatment**
   1. **Initial measures.** Patients need to be assessed hemodynamically (pulse, blood pressure, respiration rate), and cultures of blood and urine are required. A Gram's stain of the urine is essential in determining whether gram-positive or gram-negative organisms are present. A complete blood cell count, renal function tests, coagulation screen, and liver function tests should be ordered. Determination of arterial blood gases may also be necessary.
   2. **Antibiotics.** If one or more organisms have been cultured previously and sensitivity to antibiotics determined, the appropriate antibiotics should be administered immediately. More often, the causative organism is unknown and empiric antibiotic treatment is indicated until the causative organism has been identified (see below for a discussion of antibiotic therapy). To cover possible gram-positive (especially enterococcal) infection, ampicillin or one of the cephalosporins should be added to the empiric regimen. If anaerobic bacteria are suspected (following trans-rectal biopsy), antimicrobial coverage will need to be broadened accordingly (e.g., clindamycin, metronidazole, or a second-generation cephalosporin, depending on other antimicrobial agents used and patient history of drug allergy).
   3. **Cardiovascular support** requires placement of a central venous pressure line or Swan-Ganz catheter in most instances. If the patient is hypotensive, administer crystalloids and colloids and correct acidosis and hypoxemia if present. Volume expansion is continued as long as the venous pressure remains below 15 cm H_2O or pulmonary wedge pressure remains below 22 mm Hg. If hypotension is not corrected by these measures, a dopamine infusion should be initiated at 2 to 5 mg/kg per minute and then titrated to maintain blood pressure at near-normal levels and urine output at 30 to 50 mL/h.
   4. **Pulmonary support** includes administration of 5 L of oxygen per minute by face mask. If respiration is inadequate as indicated by blood gas determination, intubation is indicated with mechanical ventilation to maintain the oxygen tension above 70 mm Hg and carbon dioxide tension below 40 mm Hg.
   5. **Corticosteroids** have been advocated in septic shock for many years, but the rationale for their use remains controversial. Large-scale multicenter trials have demonstrated an increase in morbidity and mortality among septic patients given large doses of corticosteroids.

VII. Infection of the Upper Urinary Tract

A. **Acute pyelonephritis** is acute bacterial infection of the kidney. Symptoms of lower urinary tract infection may be noted 1 to 2 days before or concurrently with an episode of upper urinary tract infection.
   1. **Etiology and pathogenesis.** The most common cause is aerobic gram-negative bacteria (*E. coli* most often). Gram-positive organisms such as staphylococci and enterococci rarely cause pyelonephritis. Infection with urea-splitting organisms, such as *Proteus mirabilis* and some strains of *Klebsiella*, leads to a highly alkaline urine secondary to liberation of ammonia. This promotes the precipitation of struvite stones in the collecting system of the kidney.
      a. **Ascent from the lower tract** is the most common mechanism of infection.
      b. **Vesicoureteral reflux** is absent in most patients with pyelonephritis and not all patients with reflux have clinical evidence of pyelonephritis, but reflux is associated with an increased risk for infection.
      c. **Obstruction** increases the risk for pyelonephritis through stasis of urine. Obstruction may be congenital or acquired. Pyelonephritis is more common in patients with neurogenic bladder dysfunction, which leads to a high intravesical pressure that is transmitted to the upper urinary tract.
      d. **Hematogenous spread** is often associated with staphylococci from the skin or gram-negative bacteria from the gastrointestinal tract.
      e. **Anatomic factors.** Acute pyelonephritis is more common in female patients (the shorter urethra may predispose to colonization of the lower tract). The prostate secretes antibacterial factors that may provide some protection from infection.
      f. **Diabetes mellitus** may predispose to infection by causing obstruction by sloughed renal papillae, bladder dysfunction, and decreased host resistance. A rare form of pyelonephritis caused by gas-forming organisms—“emphysematous pyelonephritis”—is seen almost exclusively in diabetic patients.
   2. **Clinical findings** include fever, chills, flank pain, and dysuria. Constitutional symptoms are common. Examination reveals tenderness of the costovertebral angle, abdominal tenderness, and systemic signs of infection. Urinalysis shows pyuria, bacteriuria, and sometimes microscopic hematuria. Urine culture reveals growth of the causative organism to more than 100,000 colonies per milliliter.
   3. **Radiologic findings.** Roentgenographic examination of the kidneys, ureter, and bladder (KUB) may show calcifications overlying the kidney or ureter, indicating possible obstruction. Ultrasonography (US) is the preferred examination and may provide information regarding obstruction, stones, or abscess without exposing the patient to radiation. Focal infection of the kidney may be visualized with US; this has been termed lobar nephronia. Intravenous urogram (IVU) usually shows some degree of renal enlargement and a decreased nephrogram. Occasionally, there may be complete nonvisualization of the infected kidney.
   4. **Differential diagnosis** includes acute cholecystitis, acute appendicitis, and acute pancreatitis. In women, gynecologic diagnoses may mimic acute pyelonephritis.
   5. **Treatment.** It is important to diagnose and treat complicating factors, such as obstructive uropathy or stones, in addition to addressing the acute pyelonephritis itself. If these factors are not present, therapy consists of specific antibiotics determined by culture and sensitivity. In most cases, however, empiric therapy is necessary pending culture data (Table 17-3). For mild-to-moderate disease treated in the outpatient setting, therapy with oral TMP/SMX or quinolone is recommended for 14 days. Document success with urine culture obtained 1 to 2 weeks after completion of therapy. For severe illness or possible urosepsis when hospitalization is required, use parenteral quinolone, ceftriaxone, or ampicillin and gentamicin until fever resolves for 2 days, and then complete a 14-day course with oral antibiotics. If the clinical response is poor after 48 to 72 hours despite appropriate antibiotics, the presence of an intrarenal abscess, perinephric abscess, or obstructive pyonephrosis must be ruled out. Nitrofurantoin should not be used for the treatment of pyelonephritis because it does not achieve reliable tissue levels. If obstruction of the upper tract is identified, begin antibiotic therapy and establish drainage either with a ureteric stent placed cystoscopically or via percutaneous nephrostomy. Complete removal of calculi is generally required for bacteriologic cure and to prevent further renal damage.

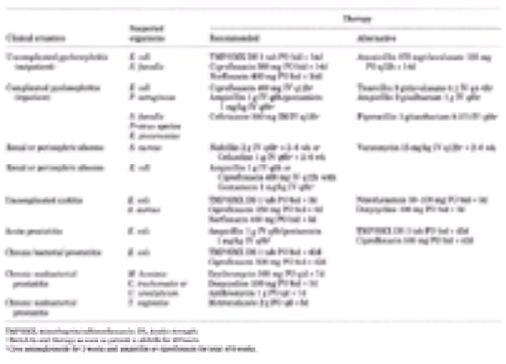

Table 17-3. Empiric antibiotic therapy of genitourinary infection

B. **Chronic pyelonephritis** most commonly refers to radiologic findings of renal scarring, fibrosis, and calyceal deformities presumed to be caused by previous infection. A more appropriate term is **chronic interstitial nephritis**. Differential diagnosis includes analgesic nephropathy, renal tuberculosis, and renovascular disease. Chronic bacterial infection of the kidney in adults is rare. Renal scarring is thought to be the result of infection in childhood, especially when accompanied by vesicoureteral reflux. Renal scarring almost always begins by age 4 and rarely develops in later years. The adult patient with bilateral chronic pyelonephritis usually presents with azotemia and hypertension rather than signs of urinary infection. Radiologic findings include characteristic polar renal scarring with underlying dilated calyces. In bilateral disease both kidneys are small, but in unilateral disease compensatory hypertrophy of the normal kidney occurs.
   1. **Xanthogranulomatous pyelonephritis** is a form of unilateral chronic pyelonephritis characterized by multiple parenchymal abscesses, pyonephrosis, and

poor renal function. The inflammatory response includes the formation of granulomas with lipid-laden macrophages (xanthogranulomas). These cells may be difficult to differentiate from clear cells of renal carcinoma. Although its exact cause is unclear, xanthogranulomatous pyelonephritis seems to be related to a combination of renal obstruction and chronic urinary tract infection. **Predisposing factors** include renal calculi, urinary obstruction, partially treated urosepsis, renal ischemia, altered lipid metabolism, abnormal immune responses, diabetes, and primary hyperparathyroidism. Bacteriuria and pyuria are almost always present. Because of the chronic nature of the disease, two-thirds of patients are anemic and only 50% manifest leukocytosis.

a. **Classification.** Malek divided the disease into three stages based on the amount of renal and perirenal involvement. Each stage is further categorized as focal or diffuse, depending on amount of parenchyma involved.
   1. In stage I (nephric), the characteristic xanthogranulomatous process is confined to the kidney.
   2. Stage II (perinephric) disease affects Gerota's fascia and the renal parenchyma.
   3. Stage III (paranephric) disease involves widespread extension of the process to the retroperitoneum.

b. **Radiologic findings** on IVU typically include a nonvisualized kidney (80%) with calculi in the collecting system (70%). Parenchymal calcifications may also be present.

c. **Treatment.** Patients are generally not cured with antibiotics alone, and surgical intervention is usually required. In many cases, nephrectomy is indicated because the disease cannot be differentiated from renal cell carcinoma.

2. **Papillary necrosis** may result from bacterial infection of the kidney or other causes (chronic abuse of analgesics, diabetes mellitus, sickle cell disease, renal vascular disease, chronic obstruction, hypertension, disseminated intravascular coagulation, lead nephropathy, Balkan nephropathy, hypercalcemia, potassium depletion, radiation nephritis). It is most commonly seen in female diabetics. The pathophysiology is vascular insufficiency leading to necrosis and sloughing of renal papillae. Although the disease is usually bilateral, the symptoms are usually unilateral as the ureter becomes obstructed by one or more necrotic papillae.

   a. **Radiologic findings** are determined by the stage of the disease. The papillae may be calcified with radiolucent centers, or they may be absent. If they are still in the collecting system, they appear as triangular filling defects.

   b. **Treatment** involves control of infection, adequate hydration, and removal of inciting causes. Because the disease is usually bilateral, nephrectomy is recommended only as a lifesaving measure.

3. **Renal and perirenal abscess.** Renal abscess may be secondary to hematogenous spread from a distant site or to direct spread from ascending infection. Perirenal abscesses usually result from rupture of a renal abscess into the perinephric space. Fungi and mycobacterial species have also been implicated. Twenty-five percent of cases may be polymicrobial. Results of urine culture often correlate with abscess cultures, but in some patients the urine culture is positive for bacteria different from those isolated from the abscess. About one-third of patients will have positive blood cultures. Anemia is present in 40% and azotemia in 25%. Pyuria and proteinuria are common, although results of urinalysis may be normal in up to one-third of patients and 40% have sterile urine.

   1. **Pathogenesis.** The organism most commonly involved in hematogenous spread is *Staphylococcus aureus* from a skin lesion, osteomyelitis, or endovascular infection. This form of renal abscess is now rare, as staphylococcal infections are generally treated early in their course. Conditions associated with an increased risk for staphylococcal bacteremia include intravenous drug abuse, hemodialysis, and diabetes mellitus. A solitary renal abscess that involves the cortex of the kidney is termed a **renal carbuncle**. The urine may remain sterile if the abscess does not communicate with the collecting system. Intrarenal abscesses secondary to ascending infection, **medullary abscesses**, account for more than 75% of renal and perinephric abscesses. They are often associated with obstruction by calculi, involve the medulla as well as the cortex, and are multifocal. The cause is almost always gram-negative uropathogens.
   2. **Clinical findings** are determined by the cause of the abscess. A hematogenous abscess will characteristically present with acute onset of fever, chills, and flank pain. There is usually no history of previous urinary tract infection, and the urine may be sterile. In contrast, patients with medullary abscess have a well-defined history of previous urinary tract infection, calculi, obstruction, or surgery. In these patients, the clinical presentation does not differ greatly from that of acute pyelonephritis. Persistence of fever and leukocytosis despite apparent appropriate antimicrobial therapy suggests that simple pyelonephritis is not the diagnosis. Usually, pyuria and bacteriuria are present.
   3. **Radiologic findings.** A renal carbuncle may appear as a space-occupying lesion on IVU. Computed axial tomography (CT) is considered the diagnostic modality of choice, as it will identify the abscess and define its extension beyond the renal capsule and surrounding structures. Medullary abscesses are generally small and multifocal and may manifest only as a poorly functioning kidney. In the presence of a perinephric abscess, the renal outline and the psoas shadow may be obliterated.
   4. **Treatment.** Prompt intervention is required to preserve renal function (Table 17-3).
      a. **Renal carbuncle** caused by *S. aureus* should be treated with 12 g of naficillin per 24 hours (if the strain is methicillin-sensitive). Antibiotic therapy alone may be sufficient if initiated early enough. Parenteral antibiotics should be continued for a minimum of 6 weeks. Typically, fever resolves 5 to 6 days after the initiation of antimicrobial therapy and flank pain improves within 24 hours. A different clinical course suggests an incorrect diagnosis, uncontrolled infection, or resistant bacteria.
      b. **Medullary abscesses** are usually caused by gram-negative organisms. Previously untreated patients should receive a parenteral aminoglycoside with a penicillin or fluoroquinolone. If the abscess develops while the patient is being treated for pyelonephritis, aspiration of the abscess should be carried out to obtain culture material. If the abscess is sterile or grows the same organisms as does the urine, continue the same antibiotic therapy. The aminoglycoside is generally administered for 2 weeks, and the penicillin or fluoroquinolone is continued for more than 2 weeks (duration guided by radiographic resolution; resolution of pain, fever, and malaise; normalization of the erythrocyte sedimentation rate; disappearance of the abscess cavity on CT). Any obstruction of the urinary tract must be relieved. If the abscess is localized, drainage by percutaneous or surgical means may be required. In cases of multiple abscesses involving the entire kidney, nephrectomy may be necessary.

VIII. Infection of the Lower Urinary Tract

A. **Dysuria** is a common complaint and accounts for a significant proportion of clinic visits per year.
   1. In **male patients**, acute dysuria may be caused by sexually transmitted disease, foreign body in the urethra, urethral stricture/periurethral abscess, bacterial cystitis, and carcinoma of the bladder *in situ*.
   2. **Female patients.** Dysuria may or may not be caused by bacterial infection (Table 17-4). Only one-third of women with acute dysuria will have bacterial infection as indicated by the finding of more than 100,00 colonies per milliliter in voided urine. Conversely, of women with acute dysuria and fewer than 100,000 colonies per milliliter in voided urine, 15% will have bacterial infection on suprapubic aspiration. **Urethral syndrome** refers to chronic dysuria of unknown cause in female patients. Urinary infection is usually ruled out by no or low colony counts on culture. However, low bacterial counts in symptomatic patients may be significant and warrant antibacterial therapy. If no clinical response is observed, sexually transmitted disease or vaginitis should be ruled out.

	Bacterial cystitis	STD	Vaginitis
Onset	Acute	Acute	Gradual
Associated symptoms	Suprapubic pain	Nonspecific	Pruritis
Examination	Nonspecific	Vaginal discharge	Vaginal discharge
Urinalysis	Pyuria in >80% Hematuria in 50%	Pyuria No hematuria	No pyuria No hematuria

STD, sexually transmitted disease.

Table 17-4. Differentiation of acute dysuria in women

   a. **Sexually transmitted disease** should be suspected in young, sexually active women, especially those with multiple partners or a new partner in recent months. Among women with acute dysuria, *Chlamydia trachomatis* is found in 7% and *Neisseria gonorrhoeae* in 2%. Rare causes include herpes infection and condyloma acuminata. **Diagnosis** requires a thorough clinical examination to detect pelvic inflammatory disease and obtain material from the cervix and urethra for Gram's stain and culture. The finding of gram-negative intracellular diplococci is diagnostic of gonorrhea, although their absence on Gram's stain obviously does not exclude the diagnosis.
   b. **Vaginitis** is characterized by vaginal discharge, pruritus, and dysuria. The most common organisms are *Trichomonas vaginalis* and *C. albicans*. Nonspecific vaginitis is usually caused by *Haemophilus vaginalis* in combination with anaerobic bacteria. **Diagnosis** is made on the basis of Gram's stain and culture of the discharge. **Treatment:** Trichomonal vaginitis responds to 2 g of oral metronidazole as a single dose (contraindicated in first trimester of

pregnancy). Partners should also be treated. Vaginitis caused by *C. albicans* responds well to topical antifungal therapy (e.g., clotrimazole vaginal cream or miconazole nitrate 2% vaginal cream for 7 to 14 days). Nonspecific vaginitis is treated with 500 mg of oral metronidazole twice daily for 7 days.

c. **Noninfectious conditions** include interstitial cystitis, carcinoma *in situ* or bladder cancer, foreign body, chemical irritation, atrophic changes, neurogenic bladder dysfunction, and perineal muscle spasm or tension.

B. **Acute bacterial cystitis** occurs in the vast majority of women as a result of ascending infection after colonization of the perineum and vaginal introitus. In male patients, bacterial cystitis may be caused by foci of infection in the prostate, outflow obstruction, urinary stone, or bladder cancer. In nonhospitalized, ambulatory patients, bacterial cystitis is caused by *E. coli* in 80% of cases. *Staphylococcus saprophyticus* and *Enterococcus* species may account for another 10%. The remainder are caused by *Klebsiella, Enterobacter, Proteus*, and anaerobic bacteria. *Pseudomonas, Serratia marcescens*, and *C. albicans* account for a large portion of hospital-acquired infections. Patients on broad-spectrum antibiotics and those who are immunocompromised are particularly at risk.

1. **Clinical findings** include abrupt onset of dysuria, frequency, urgency, and suprapubic pain. Fever and costovertebral pain are indicative of involvement of the upper tract. See Table 17-4 for clinical findings that may help differentiate acute bacterial cystitis from vaginitis and sexually transmitted diseases in female patients.
2. **Laboratory findings.** Urinalysis reveals pyuria in almost all cases of bacterial infection. Microscopic hematuria is found in 50% of women with acute cystitis.
3. **Radiologic findings.** Investigations are warranted only in cases of bacterial persistence or unresolved bacteriuria, patients infected with unusual organisms, or patients with symptoms and signs suggestive of disease of the upper tract. Screening should include renal US and a voiding cystourethrogram (VCUG) to detect reflux.
4. **Endoscopy** is indicated in the presence of gross or microscopic hematuria that persists after the infection is treated. Cystoscopy should be delayed until the acute infection has been treated.
5. **Treatment**

   Please see Fig. 17-1.

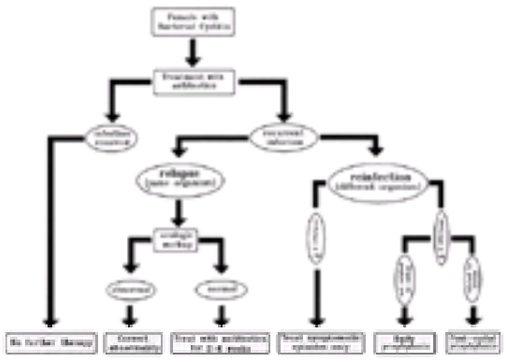

FIG. 17-1. Suggested approach to female patients with recurrent bacterial cystitis. *UTI*, urinary tract infection.

a. **First infection** is very likely caused by *E. coli*. Antibiotic therapy options include TMP/SMX or one of the fluoroquinolones. These agents have little effect on the normal anaerobic and microaerophilic vaginal flora such as *Lactobacillus*. At the same time, they eradicate the infecting *E. coli* strain from the vaginal and fecal reservoir, thus reducing the risk for reinfection. Agents that adversely affect the fecal and vaginal anaerobic flora, such as amoxicillin and first-generation cephalosporins, may enhance the susceptibility to rapid reinfection, particularly if they are not effective in eradicating enteric gram-negative rods from those sites. Resistance to quinolones remains less than 5% in most studies. All regimens are given for 3 to 7 days (consider a 7-day regimen in diabetics, those with more severe symptoms or recent urinary tract infection, patients older than 65 years). Recent controlled trials have demonstrated that single-dose regimens are less effective than 7- to 14-day regimens. Furthermore, single-dose therapy is less likely to be effective in treating infections in which unrecognized complicating factors are present. Single-dose therapy is also unsuitable for treating occult disease of the upper tract. Urine culture should be checked if symptoms persist after more than 72 hours of antimicrobial therapy.

b. **Relapse or bacterial persistence.** The time to relapse is often less than 2 weeks. A detailed evaluation should be carried out for any possible focus of infection. In instances suggestive of vaginitis or sexually transmitted diseases, appropriate cultures should be collected before therapy is initiated. Provided that no focus of infection is found, treat relapsing or persistent infection for 2 to 6 weeks.

c. **Multiple recurrent infections.** Approximately 50% of women will have a second infection within 12 months, almost always with a different organism or a different serotype of the original organism. Such patients are best managed by prophylaxis. Any acute infection should be eradicated by one of the regimens discussed above before any prophylactic regimen is implemented. For women with two or fewer episodes a year, suggest that the patient initiate therapy for symptomatic episodes (3-day regimen). For those women with three or more urinary tract infections per year, determine whether symptoms are temporally related to sexual intercourse. If they are, suggest postcoital prophylaxis with one tablet of TMP/SMX, 250 mg of cephalexin, or 50 mg of nitrofurantoin. If there is no discernible relation to coitus, suggest daily or thrice-weekly prophylaxis with the same agents.

C. ***C. albicans***, a normal inhabitant of the gastrointestinal and female genital tract, may become a pathogen in the urinary tract in immunocompromised patients and in those exposed to broad-spectrum antibiotics. Symptoms are generally mild and consist of bladder irritability or flank pain.

1. **Diagnosis** is suggested by observing yeast on microscopic examination of the urine and is confirmed by culture. Fungus balls may cause filling defects in the upper urinary tract on IVU or CT.
2. **Treatment**
   a. **Bladder.** Alkalinize the urine by giving 650 mg of sodium bicarbonate orally every 6 hours to keep the pH at 7.5 or higher. In patients requiring sodium restriction, potassium bicarbonate or potassium citrate may be used instead. In patients unable to take oral medication, sodium bicarbonate may be given intravenously. If this fails to eradicate the infection, irrigate the bladder three times daily with a solution of amphotericin B (50 mg in 1 L of saline solution).
   b. **Renal involvement** may also be treated with the same amphotericin B solution, administered either through a ureteral catheter or preferably through a nephrostomy catheter.
   c. **Candidemia or candidal sepsis** may be treated with 100 mg of fluconazole orally four times daily for 1 to 3 weeks. For patients unable to take oral medication, the same dose may be given intravenously. Amphotericin B, the previous drug of choice, must be given intravenously and is highly nephrotoxic.

IX. Prostatic Infection

Approximately 50% of men experience prostatic symptoms at some time in life. Of patients presenting with complaints that can be referred to the prostate, 5% have bacterial prostatitis, 65% have nonbacterial prostatitis, and 30% have pelviperineal syndrome. Although the vast majority of cases are not caused by bacterial infection, it nevertheless must be excluded. Prostatitis may be caused by gonococcal, tuberculous, fungal, or parasitic infection.

A. **Pathogenesis.** Routes of acquisition of infection include direct reflux of infected urine into prostate ducts, lymphatic spread from the rectum, and hematogenous spread from distant sites. However, the urine is considered the most likely source of prostatic infections. Infections are generally caused by coliform bacteria; *E. coli* accounts for 80%. In 15% of cases, more than one organism is isolated. Enterococci, *S. aureus*, and *S. saprophyticus* may rarely be identified as the cause of infection. The role of *Mycoplasma, Ureaplasma*, and *Chlamydia* species remains uncertain.

B. **Acute prostatitis** is acute infection of the prostatic glands characterized by sudden onset of fever, chills, low back and perineal pain, dysuria, and obstructive voiding symptoms. Constitutional symptoms may also be present. Early diagnosis and treatment are important for both symptom control and the prevention of secondary problems such as gram-negative sepsis, prostatic abscess, or metastatic infection.

1. **Diagnosis.** The prostate is extremely tender, swollen, and warm to the touch. Vigorous prostatic massage is contraindicated because of concern about resulting bacteremia. Microabscesses occur early in the disease, and they may coalesce into a large abscess as a late complication. Transrectal ultrasound (TRUS) or CT will confirm this diagnosis if it is not apparent on clinical examination. Laboratory parameters include leukocytosis and marked pyuria and bacteriuria.
2. **Antibiotic therapy.** Limited drug entry into the prostate is less of a problem in the setting of acute prostatitis, in which permeability is increased; thus, a variety of antimicrobials can be used to eradicate infection. Gram's stain of the urine (if positive) can be used to guide initial therapy. Until results of urine cultures are known, treatment should consist of an aminoglycoside and penicillin combination for those requiring parenteral therapy or an oral fluoroquinolone or TMP/SMX for less severe cases (Table 17-3). Duration of therapy should be at least 4 to 6 weeks to ensure eradication of the infection. Clinical studies of fluoroquinolones suggest that a negative urine culture at 7 days following initiation of therapy predicts cure at the conclusion of the full 4 to 6 weeks of treatment.

3. **Bladder drainage.** The acutely swollen gland may cause urinary retention, which resolves with urinary drainage and antibiotic therapy. In this scenario, bladder drainage via suprapubic catheter is preferable, as urethral catheterization is contraindicated in patients with acute prostatitis.

C. **Prostatic abscess** is very commonly (70%) caused by coliform bacteria; it more frequently occurs in patients with diabetes mellitus. Examination reveals a tender, fluctuant prostate. Treatment consists of antibiotic therapy as outlined for acute bacterial prostatitis combined with surgical drainage (perineal incision and drainage, transurethral resection, or transrectal drainage).

D. **Chronic prostatitis** includes several syndromes, bacterial as well as nonbacterial in etiology.

1. **Chronic bacterial prostatitis** is a generally asymptomatic, indolent bacterial colonization of the prostatic ducts; these may act as a repository of bacteria for colonization of the urine. It is the most common cause of relapsing urinary tract infection in men. Gram-negative rods are the most common etiologic agent, although enterococci, chlamydiae, fungi, and tuberculosis have all been reported. Patients are symptomatic only when bacteriuria is present and complain of irritative voiding symptoms and perigenital pain. Examination of the prostate reveals a normal or minimally tender gland. Urinalysis shows pyuria and bacteriuria during episodes of acute cystitis. When the urine is sterile, segmented urine cultures as described previously should be used to attempt to localize the infection to the prostate. Chronic prostatitis is suspected when VB3 has more than 12 leukocytes per high-power field; more than 20 is almost diagnostic unless leukocytes are also present in VB2. Negative cultures do not exclude the diagnosis, and there have been reports of patients with negative cultures of expressed prostatic fluid but positive cultures of prostate tissue. Treatment is aimed at eradicating the prostatic focus of infection. Fluoroquinolones have significantly improved medical management, with cure rates of 60% to 90% reported. Advantages of quinolones include a broad spectrum of activity, small molecular size, high degree of lipid solubility, and low level of protein binding, all of which enhance prostatic penetration. Apart from TMP/SMX, most antibiotics, including penicillins, cephalosporins, aminoglycosides, sulfonamides, and most tetracyclines, are ineffective. Duration of therapy should be a minimum of 4 to 6 weeks. Men with recalcitrant prostatitis can be treated with radical transurethral resection of the prostate (TURP) (infection is usually harbored in the periphery of the gland and traditional TURP removes only the central adenoma). This surgery cures approximately 40% but is complicated by an increased risk for incontinence.
2. **Chronic nonbacterial prostatitis.** Many patients with symptoms of dysuria and perineal pain have no evidence of urinary or prostatic infection but have large numbers of inflammatory cells in their prostatic secretions. The presence of large numbers of lipid-laden macrophages is particularly suggestive of prostatic inflammation. A definitive role for *Mycoplasma, Ureaplasma, Chlamydia*, or *Trichomonas* remains to be proved, although empiric antimicrobial therapy is aimed at these organisms. Empiric therapy with tetracycline, erythromycin, or azithromycin may be warranted. Treatment of infections caused by *C. trachomatis* is 1 week of doxycycline (100 mg twice daily), erythromycin (500 mg four times daily), or azithromycin (1 g daily). The failure rate after doxycycline or single-dose azithromycin is 2% to 4%; such failures should receive 250 mg of azithromycin per day for 10 days. Other noninfectious causes, such as autoimmunity and neuromuscular dysfunction, have been suggested. Urinary frequency may be ameliorated with the use of low-dose anticholinergic therapy.
3. **Pelviperineal syndrome.** This was previously known as prostatodynia but was renamed because it may not always be caused by prostatic disease. The urine culture will be negative, and expressed prostatic secretions will reveal no inflammatory cells. The condition may be caused by detrusor hyperreflexia or pelvic floor myalgia. Stress seems to play a significant role, whether by cause or effect. Urodynamic studies are required to identify any major abnormalities in the voiding pattern. Treatment with a-adrenergic blockers or biofeedback may help. Significant obstruction of the bladder neck can be relieved with an incision in the bladder neck.
4. **Granulomatous prostatitis** may be caused by tuberculosis but more often represents a nonspecific inflammation of unknown cause. A specific form may be seen inpatients who received intravesical bacille Calmette-Guérin (BCG) therapy for superficial bladder cancer. Biopsy is required to exclude carcinoma.

X. Scrotal Contents

A. **Orchitis** usually results from hematogenous spread during bacterial or viral illness. **Mumps orchitis** is less of a risk in prepubertal boys, but 20% of adolescent patients with mumps have mumps orchitis, and it may be bilateral in 10%. Testicular pain and swelling develop 3 to 4 days after onset of parotitis. The scrotum is erythematous and very tender. Approximately 30% of involved testes suffer permanent loss of spermatogenesis because of pressure necrosis.

B. **Acute epididymitis** initially involves the tail of the epididymis but may spread to involve the entire epididymis, testis (epididymoorchitis), or spermatic cord (funiculitis). Symptoms are usually unilateral, with dull, aching pain radiating to the spermatic cord, lower abdomen, or flank. Pain may be relieved by elevating the testis (Prehn's sign), which may aid in differentiating the condition from acute torsion. Epididymitis is usually caused by one of two types of infection:

1. **Sexually transmitted disease** is usually secondary to *Chlamydia* (most common) or *N. gonorrhoeae*. Isolation of *Chlamydia* requires specific cell media. Serologic testing is rarely of value. The direct fluorescent antibody (DFA) test and enzyme-linked immunosorbent assay (ELISA) have sensitivities of 70% to 85% and 70% to 80%, respectively. Ligase chain reaction (LCR) is at least as sensitive as culture and has the advantage of being rapid and easy to perform. Empiric therapy for *Chlamydia* is commenced once gonorrhea has been ruled out. Uncomplicated chlamydial infection can be treated with 1 g of oral azithromycin or 100 mg of oral doxycycline twice daily for 7 days. Azithromycin as single-dose therapy is 98% effective and is now the preferred regimen because of improved compliance. Alternative treatments include ofloxacin and erythromycin. All sex partners should be evaluated and treated.
2. **Bacterial genitourinary infection** is more common than sexually transmitted disease as a cause of epididymitis in men more than 40 years of age. Gram-negative pathogens are found in the urine, prostate, or urethra, and antimicrobial therapy is guided by culture data. Nonspecific measures include nonsteroidal antiinflammatory drugs, bed rest, and scrotal support. Injection of the spermatic cord with a local anesthetic may be of symptomatic benefit.

C. **Chronic epididymitis.** Symptoms usually consist of mild pain. The epididymis is tender, indurated, and thickened. Antibiotic therapy is the same as for acute epididymitis, extended for 3 weeks. Epididymectomy may be required in some cases.

XI. Male Venereal Disease

A. **General principles.** Patients with venereal disease usually present complaining of urethral discharge (“drip”), dysuria, lesions or ulcerations of the genital skin, or inguinal adenopathy. Infection with multiple organisms is common (e.g., gonorrhea and nongonococcal urethritis). Whenever possible, cultures should be obtained from sexual partners and they should be treated as needed. The United States Public Health Service recommends testing all patients with sexually transmitted diseases for human immunodeficiency virus (HIV).

B. **Epidemiology.** The treatment of venereal disease frequently changes as sexual practices, contraceptive methods, and antibiotic treatment change. Before 1945, syphilis was the most common venereal disease, with gonorrhea the second most common. Currently, the incidence of gonorrhea is declining, but nongonococcal urethritis, genital herpes, and venereal warts are seen with increasing frequency. Syphilis is rarely seen today.

C. **Gonorrhea** is caused by *N. gonorrhoeae*, an intracellular gram-negative diplococcus. The incubation period is 2 to 8 days after sexual contact. Asymptomatic disease may occur in either sex but is much more common in women than in men. Up to 35% of men will have concomitant chlamydial infection. Among homosexual men, the pharynx is affected in 40% and the rectum in 25%. Urethritis is the presenting complaint in more than 95% of infected men. Acute complications include epididymitis, orchitis, and prostatitis. Urethral stricture is a late complication.

1. **Diagnosis** is by urethral smear and culture. The presence of **intracellular** gram-negative diplococci is diagnostic. If only extracellular organisms are seen, one must depend on results of culture for a definitive diagnosis, although in some cases a clinical decision to treat may be made. *Neisseria* grows best at 35° to 37°C in a 3% to 5% carbon dioxide environment. A selective medium is required (Thayer-Martin) to prevent overgrowth by other organisms. Direct immunofluorescence is a rapid assay and has a sensitivity of 84% and specificity of 100% in men. DNA probes have a sensitivity of 90% to 98% and a specificity of 82% to 98%. LCR has a sensitivity of approximately 100% and a specificity of 99%.
2. **Treatment.** Uncomplicated infection may be treated with 125 mg of intramuscular ceftriaxone, 400 mg of oral cefixime, 500 mg of oral ciprofloxacin, or 400 mg of ofloxacin. Approximately 25% of men with gonorrheal infection have concomitant infection with *C. trachomatis*. Thus, a regimen for *Chlamydia* infection as outlined in Table 17-5 should also be prescribed. If a patient has severe allergies, 2 g of intramuscular spectinomycin may be used. All sex partners should be evaluated and treated. Pregnant women should not receive quinolones or tetracyclines. Cases of gonorrhea resistant to quinolones have been reported sporadically, although they remains extremely rare in the United States.

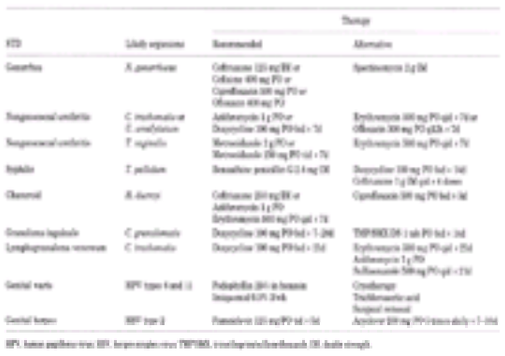

Table 17-5. Antibiotic therapy of sexually transmitted disease in male patients

D. **Nongonococcal urethritis** is most commonly caused by to *C. trachomatis* (40%), *Ureaplasma urealyticum* (30%), *T. vaginalis* (5%), or *C. albicans*. Concomitant gonorrheal infection may be present.
   1. **Clinical features.** The presentation is usually a thin, mucoid urethral discharge associated with dysuria and meatal pruritus. Symptoms associated with Reiter's syndrome may also be present.
   2. **Diagnosis** depends on demonstrating the presence of urethritis in the absence of gonorrheal infection. Presence of more than five leukocytes per oil-immersion field on examination of a urethral smear is indicative of urethritis. To detect *T. vaginalis*, a wet smear can be prepared by mixing a drop of urethral exudate with 1 mL of normal saline solution. *C. albicans* infection can be diagnosed by mixing a drop of exudate with 1 mL of 10% potassium hydroxide on a slide and looking for yeast forms.
   3. **Treatment**
      a. ***Chlamydia*** or ***Ureaplasma*** infection can be treated with 1 g of oral azithromycin or 100 mg of oral doxycycline twice daily for 7 days. Alternative treatments include ofloxacin or erythromycin. All sex partners should be evaluated and treated.
      b. ***T. vaginalis*** should be treated with 2 g of metronidazole orally as a single dose or 250 mg orally three times daily for 7 days. Erythromycin may be used for persistent or recurrent urethritis.

E. **Genital herpes.** The vast majority of cases are caused by herpes simplex virus (HSV) type 2. The incubation period varies from 1 to 30 days, but 3 to 5 days is typical.
   1. **Clinical features.** The first clinical episode is the most severe in patients without prior oral herpes. In men with their first infection, almost all have painful ulcerative lesions on the prepuce, glans, or shaft of the penis; 80% have tender lymphadenopathy, 60% fever, 45% dysuria, and 25% urethritis. The clinical course is less severe for recurrences. Symptoms tend to be more severe in women. Sacral autonomic neuropathy may result in acute urinary retention.
   2. **Diagnosis** is made by cytology or viral culture. A vesicle should be ruptured with a sterile needle and the base rubbed with the swab. Smears can be prepared for Tsank staining and culture.
   3. **Treatment.** Famciclovir has replaced acyclovir. Although its mechanism of action is similar, famciclovir has more favorable pharmacokinetics that enable less frequent dosing. Its bioavailability is approximately 75% (vs. 10% to 20% for acyclovir), and prolonged intracellular levels are achieved. Dosing for acute HSV infection is 125 mg orally three times daily for 5 days (equivalent to 200 mg of acyclovir five times daily for 7 to 10 days). Therapy shortens the duration of pain and reduces viral shedding and duration of systemic symptoms. Recurrent HSV infection can be treated with 125 mg of famciclovir orally twice daily for 5 days. Suppressive dosing is 125 to 250 mg orally twice daily. Suppressive therapy is indicated in patients with more than six recurrences per year.
   4. **Genital warts**, also called condylomata acuminata, are caused by human papillomavirus (HPV types 6 and 11). HPV infection is now one of the most common sexually transmitted diseases in the United States. The incubation period is typically 45 days but may be much longer. Diagnosis is based on the characteristic appearance of the lesion. On the glans and inner prepuce, the lesions are typically exophytic. On skin surfaces, they tend to be small and papular. Treatment choice is determined by wart area, wart count, anatomic site, morphology, cost, and patient preference. Podophyllin (25% in benzoin) is carefully applied weekly to each lesion and washed off after 4 hours. Podofilox 0.5% is available for self-application. Imiquimod 5% cream is applied three times a week at bedtime and left on for 6 to 10 hours. Other treatment options include cryotherapy, trichloroacetic acid, laser, and surgical removal. Sex partners should be evaluated for warts and other sexually transmitted diseases and treated appropriately.
   5. **Genital molluscum contagiosum** appears as raised papules with a central depression on the scrotum or shaft of the penis. The lesions are caused by a poxvirus. Diagnosis is by clinical appearance. Treatment consists of opening each lesion with a pointed applicator dipped in liquid phenol or use of cautery.

F. **Genital ulcerative lesions** are most commonly seen in sexually active men. Only rarely can one make a specific diagnosis clinically, and laboratory tests are needed for confirmation.
   1. **Syphilis** presents a primary genital ulcer, called a chancre, that appears most commonly on the glans penis. The ulcer is typically nontender and rubbery. Diagnosis is confirmed by scraping the base of ulcer and examining the serous material with a dark-field microscope for motile spirochetes. Results of nonspecific serologic tests [e.g., VDRL (Venereal Disease Research Laboratory)] do not become positive until 1 to 3 weeks after the appearance of the ulcer and return to normal in almost all patients treated for primary syphilis. Results of the FTA-ABS (fluorescent *Treponema* antibody absorption) test become positive earlier and usually remain positive for life. Furthermore, in contrast to the VDRL, the FTA-ABS very rarely gives a false-positive result. **Treatment** for primary syphilis is 2.4 million U of benzathine penicillin G given intramuscularly. If the patient is penicillin-allergic, give 100 mg of doxycycline orally twice daily for 2 weeks or 1 g of ceftriaxone intramuscularly every other day up to four doses. Tetracycline or erythromycin may also be used as alternative agents.
   2. **Chancroid**, caused by *Haemophilus ducreyi*, resembles the lesion of primary syphilis. The ulcer may be painful with or without adenopathy. **Diagnosis** is confirmed by Gram's stain of material from the base of the ulcer. The presence of suppurative inguinal adenopathy is nearly diagnostic. **Treatment** options include azithromycin, ceftriaxone, erythromycin, or ciprofloxacin.
   3. **Granuloma inguinale (Donovanosis)** is a chronic infection of genital and perigenital skin caused by *Calymmatobacterium granulomatis*. The genital ulcer is nontender and indurated. Subcutaneous inguinal granulomas develop. Diagnosis is confirmed by demonstrating the organism within monocytes (Donovan bodies) in tissue obtained from the ulcer base. Primary treatment is doxycycline; alternative options include TMP/SMX, ciprofloxacin, and erythromycin. Sex partners need to be examined and treated.
   4. **Lymphogranuloma venereum** is caused by *C. trachomatis*, invasive serotypes L1, L2, and L3. The genital lesion is small and transient. Tender inguinal lymphadenopathy develops. In gay men, proctitis may be a presenting symptom. Diagnosis is best made by culture. Serology is not specific for this infection, as other chlamydial infections may cause elevated antibody titers. The treatment is 100 mg of doxycycline orally twice daily for 21 days. Alternatives include erythromycin, azithromycin, and sulfisoxazole. Ulcers are healed at 7 days in 50% of cases, at 14 days in 80%, and at 28 days in 100%. The relapse rate is 3% to 5%.

XII. Antimicrobial Prophylaxis in Urologic Surgery

To achieve effective antimicrobial prophylaxis, adequate tissue levels must be present at the time of surgical incision. At the same time, there is no benefit to continuing the antibiotic for more than 24 to 48 hours after surgery. Although antimicrobial prophylaxis is not necessary for most patients who have sterile urine at the time of surgery, many continue to advocate short-term antibiotic prophylaxis for endoscopic procedures. If an active urinary infection is present, it should be cleared before the surgery whenever possible. If this cannot be done (e.g, indwelling Foley catheter), perioperative antibiotics are indicated to prevent bacteremia. Patients with valvular cardiac disease or artificial heart valves require prophylaxis for endocarditis before all genitourinary surgery. Prophylactic antibiotics are not needed provided that the urine is sterile before the procedure.

A. **Transrectal prostate needle biopsy.** The patient should receive an enema before the procedure. Prophylactic antibiotics are directed at aerobic and anaerobic bowel flora (Table 17-6).

Clinical situation	Recommendation
Endoscopy	Ciprofloxacin 500 mg PO bid × 2d
Endoscopic surgery	Cefazolin 1 g IM/IV on call to OR and q8h × 24h or Gentamicin 1 mg/kg IM/IV on call to OR and q8h ×24h
Transrectal prostatic needle biopsy	Gentamicin 1 mg/kg IM/IV on call to OR and Clindamycin 300 mg IM/IV on call to OR
Colon and small-bowel surgery	Cefoxitin 2 g IV and Metronidazole 0.5 g IV
Artificial prosthesis	Cefazolin 1 g IM/IV on call to OR and q8h × 24h
Valvular cardiac disease or artificial heart valves	Ampicillin 2 g IM/IV and gentamicin 1.5 mg/kg body weight IM/IV 1 h before surgery Repeat dose 8 h after instrumentation If patient is penicillin-allergic, use vancomycin 1 g IV over 60 min instead of ampicillin

OR, operating room

Table 17-6. Antibiotic prophylaxis in urologic surgery

B. **Colon and small-bowel surgery.** Because the distal ileum has the same bacterial flora as the colon, antibiotic prophylaxis for ureteroileal diversion is the same as that for colonic surgery.
   1. On preoperative day 1, give a clear liquid diet; give 4 L of polyethylene glycol-electrolyte solution (GoLYTELY) at 10 a.m. and 1 g of neomycin-erythromycin base 1 GPO (1 g po) at 1 p.m., 2 p.m., and 11 p.m.; nothing by mouth after midnight.

2. On the day of operation, give 2 g of cefoxitin intramuscularly or intravenously 1/2 hour before surgery and 0.5 g of metronidazole intravenously as a single dose.

C. **Prostheses (penile implants, artificial sphincters)**
   1. Administer hexachlorophene or povidone-iodine (Betadine) skin scrubs for 2 days before surgery.
   2. Give 1 g of cefazolin (or equivalent first-generation cephalosporin) intramuscularly or intravenously 1/2 to 1 hour before surgery and repeated every 6 hours for 24 hours postoperatively.
   3. Soak prosthesis in antibiotic solution before implantation (bacitracin, Aerosporin, neomycin).
   4. Irrigate the wound with antibiotic solution before closure.

D. **Prophylaxis for bacterial endocarditis.** Patients at risk for bacterial endocarditis (Table 17-6) include those with valvular heart disease, prosthetic heart valves, most forms of congenital heart disease, idiopathic subaortic stenosis, mitral valve prolapse, history of prior infective endocarditis, and transvenous cardiac pacemakers.

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Chapter 18 Management of Genitourinary Trauma

Raymond McGoldrick and Gennaro Carpinito

Recent advances in intensive care technology and radiologic imaging have greatly improved diagnosis and survival in serious trauma. All medical personnel involved in the care of the trauma patient should be well versed in the basic principles of airway management, cardiopulmonary resuscitation, and protection of the spine. As a member of the trauma team, it is the responsibility of the urologist to provide proper interpretation of urologic imaging and intervene surgically when necessary.

I. General Principles

Approximately 10% of all trauma involves the genitourinary tract, but only 2% involves the genitourinary tract exclusively. Trauma patients presenting to the emergency room may have (a) unstable vital signs and require immediate surgical intervention, (b) penetrating trauma and stable vital signs, or (c) blunt trauma and stable vital signs.

A. **History.** Attempt to obtain a detailed history of the trauma from the patient or from witnesses and emergency personnel. Loss of consciousness is a rough indicator of the force of trauma and the possible presence of head injury. In falls, the height from which the victim has fallen and the nature of the landing surface are important. In motor vehicle accidents, the speed of the vehicle, location of the victim within the automobile, and use of seat belts are important. In gunshot wounds, the type of weapon, caliber of the projectile, and distance from the victim at which the shot was fired can be used to estimate the extent of tissue damage.
B. **Physical examination** is performed during the generalized trauma evaluation. Hemodynamic instability requires aggressive resuscitation and emergent surgical exploration in many cases. Physical findings of tenderness, ecchymosis, or penetrating injuries in the flank, suprapubic region, pelvis, or external genitalia strongly suggest an underlying urologic injury. Pelvic bony instability indicates a likely pelvic fracture and should alert the trauma team to the possibility of urethral or bladder injury. Likewise, gross blood at the urethral meatus and superior displacement of the prostate on rectal examination are indicative of possible urethral injury.
C. **Diagnostic tests** begin with routine urinalysis to look for the presence and extent of hematuria and should be performed on all patients. The urethra should be catheterized **unless urethral injury is suspected**. If blood is seen at the urethral meatus or a significant pelvic fracture is present, urethral injury must first be ruled out by retrograde urethrography (see below).
D. **Radiologic examination**
    1. **Plain films of the abdomen** may reveal bony fractures of the pelvis, ribs, or vertebrae. Loss of the perirenal outline, loss of the psoas shadow, or displacement of bowel gas may indicate retroperitoneal hematoma or urinoma. A “ground-glass” appearance on plain film may be caused by intraperitoneal urinary extravasation.
    2. **Retrograde urethrogram** is indicated whenever urethral injury is suggested by the presence of blood at the meatus, superior displacement of the prostate on digital rectal examination, pelvic fracture, or inability to pass a urethral catheter. The study may be performed easily by using either a Brodney clamp that fits to the glans penis or a 12F (French) Foley catheter inserted into the fossa navicularis. The balloon is inflated only enough to hold the catheter gently in place. After the patient is placed in the 30-degree oblique position, 15 mL of radiographic contrast agent is injected gently. The presence of extravasation is indicative of urethral injury. The posterior portion of the urethra above the pelvic floor is difficult to interpret on retrograde urethrography, as the external sphincter is often closed.
    3. **Cystography** (opacification of the bladder) is indicated to rule out bladder injury in all patients with blunt or penetrating trauma who manifest gross or microscopic hematuria. In patients who have penetrating trauma without hematuria, the indications for cystography depend on the nature and location of the wound. Ideally, cystography should be performed in a radiologic suite with fluoroscopic capacity to obtain oblique and real-time images. Some centers have advocated computed tomographic (CT) cystogram as their study of choice. Regardless of the technique used, it is essential that the bladder be completely filled with contrast to demonstrate small amounts of extravasation. Minor extravasation from the bladder is often missed on intravenous urogram (IVU) because the bladder is incompletely distended. Allow contrast to flow through the urethral catheter under gravity until the bladder is full; at least 250 mL is often required. After the bladder is emptied, a postvoid film is vital to assess extravasation located behind the bladder.
    4. **CT with intravenous contrast** has become the “gold standard” of trauma evaluation and is the preferred study in the initial assessment of renal trauma. Scanning in the spiral (helical) mode may be done in less than 5 minutes and provides an excellent assessment of renal parenchymal integrity, injury to other organs in the abdomen, and the presence of hematomas or urinomas. CT can also establish the presence of both kidneys and their function.
    5. **IVU** has been replaced by CT as the initial screening examination in most centers for patients with suspected renal injury. IVU is indicated in all patients with traumatic hematuria if CT is not available. In the case of the unstable patient who is brought straight to the operating room, a “one-shot” IVU is essential before any exploration of the kidneys to evaluate the contralateral side. After a scout film of the abdomen has been obtained, contrast (Renografin-60 in a dose of 1 mL/kg) is injected intravenously by hand during 3 to 5 minutes. A film is taken at 5 to 10 minutes after injection of contrast. Adequate visualization of the kidneys may not be obtained on IVU unless the patient has a stable systolic blood pressure above 90 mm Hg.
    6. **Renal arteriography** may be indicated in instances of renal vascular injury, a diagnosis suggested by nonvisualization of the kidney on CT or IVU. In selected patients, it also may be useful in identifying the source of persistent renal bleeding following trauma. If a source of bleeding is clearly identified, arteriographic embolization may be performed at the same time.
    7. **Ultrasonography (US)** permits noninvasive assessment of perirenal and subcapsular hematomas and is useful in following patients with renal trauma who are being managed nonsurgically.
    8. **Radionuclide studies** may be useful in the follow-up care of patients with trauma in whom hypertension develops.

II. Renal Trauma

A. **Mechanism.** Located high in the retroperitoneum, the kidneys are relatively well protected by the bony rib cage, lumbar spine, and vertebral muscles. However, trauma sufficient to fracture a rib or vertebral process often damages the kidneys. Renal trauma accounts for approximately 50% of all cases of genitourinary trauma, and more than 50% of cases involve patients under the age of 30. There is a male-to-female predominance of 4:1.
    1. **Blunt trauma** to the abdomen, flank, or back accounts for more than 80% of all renal injuries. The most common causes are motor vehicle accidents, falls, sports accidents, and assaults. Rapid deceleration such as commonly occurs in motor vehicle accidents or falls may cause intimal tears in the renal artery or even complete avulsion. In adult patients with blunt trauma, gross hematuria, shock, or direct trauma to the flank are associated with an increased risk for major renal injury (about 25%).
    2. **Penetrating trauma** is most commonly caused by knife and bullet wounds. Approximately 85% of instances of penetrating trauma involving the kidney are associated with injury to other intraabdominal organs (Table 18-1). Children are especially prone to renal injury because of the underdevelopment of the back muscles and rib cage and because the kidneys are relatively larger than in adults. In addition, the kidneys in children are not as well protected by perirenal fat and Gerota's fascia, which can act as a buffer against trauma. Renal injury is more likely in the presence of preexisting conditions such as hydronephrosis or tumors.

Liver	45
Stomach	25
Pancreas	25
Small bowel	25
Spleen	20
Right colon	20
Left colon	15
Major vessels	15
Duodenum	15

Table 18-1. Percentages of intraabdominal injuries associated with penetrating renal trauma

B. **Classification of renal injury**

Please see Fig. 18-1.

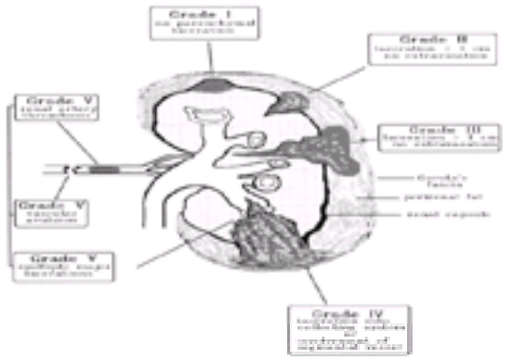

FIG. 18-1. Staging system for renal trauma.

1. **Grade 1 injury**, also called **renal contusion**, is bruising of the renal parenchyma without true parenchymal disruption. An associated subcapsular or perinephric hematoma may be present, but the kidney is intact. Such injuries account for the majority of cases of blunt renal trauma.
2. **Grade 2** involves ruptures or tears of the renal capsule and parenchyma that are less than 1 cm in length. The injury does not involve the collecting system or the medulla of the kidney. Grade 1 and 2 injuries are classified as minor injuries and account for 85% of all renal injuries.
3. **Grade 3** injury is the same as grade 2 injury but extends more than 1 cm.
4. **Grade 4** injury is a major laceration that extends into the collecting system and produces extravasation of urine. Involvement of a segmental vessel also qualifies as a grade 4 injury.
5. **Grade 5** indicates the most extensive renal injury. Severe multiple lacerations, fracture, or shattering of the kidney and renal vascular injury are all examples of grade 5 injury. Grade 3, 4, and 5 injuries are classified as major injuries. **Renal lacerations** account for approximately 15% of blunt renal injuries and 30% of penetrating injuries. **Renal vascular injury** includes occlusion, thrombosis, or avulsion of the renal artery, renal vein, or one of their branch vessels; it occurs in fewer than 1% of instances of blunt renal trauma but up to 10% of instances of penetrating trauma. Renal vascular injuries are difficult to diagnose quickly enough to prevent renal loss because significant and irreversible renal injury occurs within 1 hour if significant ischemia is present.

C. **Diagnosis.** The approach to patients with suspected renal trauma is outlined in Fig. 18-2.

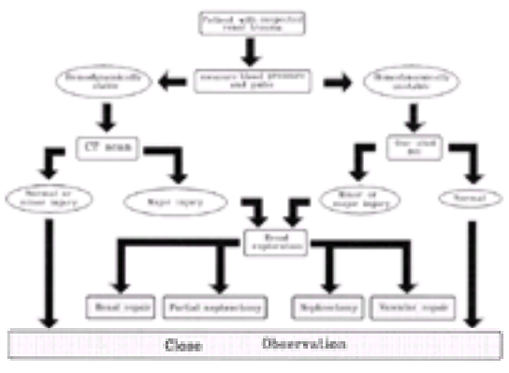

FIG. 18-2. Approach to the patient with suspected renal trauma. *IVU*, intravenous urogram.

1. Patients who are **hemodynamically unstable** will almost always need to be explored quickly. The urologist is often called to the operating room for consultation after the patient has been explored by the general surgeons and must determine whether both kidneys are present and functioning. This can be accomplished with a one-shot IVU performed on the operating table. If there is no evidence of renal injury, no exploration is needed. Major injuries should be explored. If only minor injury is noted on the IVU but retroperitoneal bleeding is present, the kidney should be explored and repaired.
2. In patients who are **hemodynamically stable**, CT is now the preferred initial radiologic examination.

D. **Treatment** of renal injury depends heavily on the nature and severity of injury, determined by the evaluation previously described (Table 18-2).

Absolute	Relative
Pulsatile or expanding retroperitoneal mass	Major renal injury
Hemodynamic instability from renal bleeding	Urinary extravasation
Renal vascular injury in solitary kidney	Laparotomy for associated injury
	Nonviable renal tissue needing debridement

Table 18-2. Indications for renal exploration

1. **Blunt trauma.** In general, the likelihood of urinary tract injury in patients with blunt trauma who are hemodynamically stable and have no hematuria is low. Patients with microscopic hematuria who are hemodynamically stable also have a low risk for significant renal injury, but they should be observed more closely if the mechanism of injury warrants it. Patients with hemodynamic instability or gross hematuria are more likely to have a significant injury and should therefore undergo a more aggressive radiologic assessment if time allows. These patients are monitored for signs of bleeding, such as a change in vital signs, decrease in the hematocrit, or expanding flank hematoma. Patients with fractured kidney or renal vascular injuries usually require prompt surgical

intervention for repair of the kidney or urgent nephrectomy. The management of **urinary extravasation** in blunt renal injury is controversial; some authorities favor conservative treatment, and others feel that early surgical intervention is preferable. Antibiotic therapy is usually indicated, especially if the urine is infected at time of injury, and serial US can be used to monitor the resolution of the urine collection. If signs of abscess formation or sepsis appear, the urinoma should be drained surgically or percutaneously. The proponents of early surgical exploration in patients with urinary extravasation argue that it results in decreased length of hospital stay and reduced incidence of complications, such as infected urinoma; however, the incidence of nephrectomy is increased in patients explored surgically.

2. **Penetrating trauma.** All patients with gunshot wounds and almost all patients with stab wounds should undergo surgical exploration (Table 18-2). The only exception is the patient with a stab wound of the flank, no hematuria, normal CT or IVU findings, and no abnormal physical findings. These patients can be managed nonoperatively. In other instances of penetrating trauma, abdominal exploration is required to repair associated injuries and the urologic injury. Surgical management of penetrating renal trauma consists of gaining control of the renal pedicle, obtaining adequate hemostasis, debriding devitalized tissue, repairing the collecting system, and providing adequate drainage (Table 18-3). When the severity of the injury makes this treatment impossible, nephrectomy is indicated, which occurs in approximately 10% of patients with stab wounds and in 40% of those with gunshot wounds.

Surgery	Blunt trauma (%)	Stab wound (%)	Gunshot wound (%)
Debridement and repair	35	60	40
Partial nephrectomy	15	15	20
Nephrectomy	10	7.5	15
Vascular repair	10	7.5	10
Pelvic repair	15	0	0
Exploration only	15	10	15

Modified from McAninch JW, et al. J Urol 1981;145:932

Table 18-3. Results of renal exploration

E. **Complications of renal injury** include delayed bleeding, hypertension, formation of arteriovenous fistulae, hydronephrosis, and loss of renal parenchyma. Delayed bleeding may occur during the first month after injury. Persistent hematuria may be an indication of a traumatic arteriovenous fistula and should prompt arteriography. The patient's blood pressure should be monitored carefully during the first 6 months after injury, and IVU, CT, or renal US should be performed at the end of that period.

III. Ureter

A. **Mechanisms.** Blunt trauma to the ureter is extremely rare and usually involves disruption of the ureteropelvic junction following rapid deceleration, a mechanism seen most commonly in children. Ureteral injury is almost exclusively caused by penetrating trauma. The most common cause is iatrogenic injury during pelvic surgery, in particular abdominal hysterectomy; however, ureteral injury has occurred in a wide variety of intraabdominal, pelvic, and retroperitoneal surgical procedures. The mechanism of iatrogenic injury is ligation or transection of the ureter with subsequent hydronephrosis, urinary extravasation, or both. The second most common cause of ureteral injury is gunshot wound, most commonly from low-velocity weapons. All portions of the ureter are at equal risk for penetrating trauma from gunshot wounds. Stab wounds involving the ureter are rare. With the recent development of endourologic techniques, ureteral injury (perforation or avulsion) during stone manipulation may be seen.

B. **Diagnosis**

1. **Iatrogenic injury.** Any patient in whom flank pain, fever, and paralytic ileus develop during the first 10 days following intraabdominal or pelvic surgery should be suspected of having ureteral injury. In female patients, a ureterovaginal fistula may develop after ligation of the ureter during hysterectomy. IVU or CT will demonstrate delayed excretion, hydronephrosis, and sometimes extravasation of contrast material.
2. **External penetrating injury.** Hematuria is present in approximately 80% of patients with penetrating injury of the ureter. Thus, the absence of hematuria does not rule out penetrating ureteral injury. The diagnosis is usually apparent on IVU. In patients with ureteral transection from penetrating trauma, there is little time for a urinary collection to develop, and the IVU may demonstrate no abnormality except for extravasation at the point of injury. In approximately 10% of patients, IVU findings will be completely normal. The injury can be well delineated with a retrograde pyelogram. To avoid the risk of contaminating the retroperitoneum, however, this study should be performed immediately before surgical exploration.

C. **Treatment** depends on whether the injury is recognized immediately or after some period of delay.

1. **Immediate recognition.** Injuries diagnosed within a few days should generally be treated with surgical exploration. Sepsis, abscess formation, and other injuries or medical problems may delay surgical exploration. Debridement and primary anastomosis should be performed whenever possible. Injuries involving the lower third of the ureter can generally be managed by reimplantation into the bladder, with or without the use of a bladder flap or psoas hitch. An internal stent should be provided until healing is complete (usually 3 to 4 weeks). At that time, the stent can be removed via cystoscopy.
2. **Delayed recognition.** In instances of delayed recognition, the presence of infection usually prevents primary reconstruction; urinary diversion by percutaneous nephrostomy and drainage of any urinary collection are the initial steps. Reconstructive surgery is undertaken after the hydronephrosis and infection have resolved.

E. **Complications of ureteral injury** include ureteral stricture, retroperitoneal fibrosis, pyelonephritis, and ureterocutaneous fistula.

IV. Bladder

A. **Mechanisms.** The bladder normally is protected from injury by the bony pelvis; however, the bladder and/or the urethra are frequently injured when the pelvis is fractured. The general approach to the patient with pelvic fracture and suspected genitourinary trauma is shown in Fig. 18-3. Severe blunt trauma to the lower abdomen may result in bladder rupture if the bladder is filled at the time of trauma. Penetrating trauma to the bladder may occur by the same mechanisms as to the ureter (see preceding discussion).

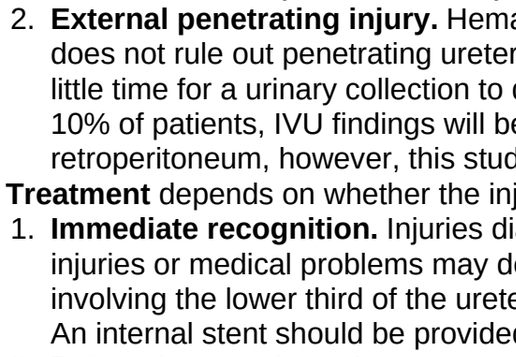

FIG. 18-3. Approach to the patient with pelvic fracture.

B. **Classification**

1. **Contusion** involves injury to the bladder wall resulting in hematuria and perivesical hematoma with no extravasation of urine demonstrated.
2. **Extraperitoneal rupture.** In this injury, the lateral wall or floor of the bladder is ruptured, leading to extravasation of urine into the pelvis and retroperitoneum. This type of injury accounts for approximately 50% of all bladder ruptures and is almost always associated with pelvic fracture. Conversely, approximately 15% of patients with pelvic fracture have bladder rupture.
3. **Intraperitoneal rupture** usually involves bladder rupture at the dome, leading to intraperitoneal extravasation of urine. This type of injury is almost always caused by blunt trauma to the lower abdomen and is often seen in intoxicated patients who fall with a full bladder or are involved in a motor vehicle accident.

4. **Spontaneous rupture.** Rarely, the bladder ruptures without external trauma, usually indicating underlying pathology such as bladder tumor.

C. **Diagnosis.** Acute bladder trauma rarely produces specific symptoms or signs. Extraperitoneal rupture is characterized by the presence of contrast outside the bladder in the pelvis and paracolic areas. The bladder may assume a “teardrop” appearance during compression by a pelvic hematoma. Intraperitoneal rupture is characterized by the presence of contrast in the peritoneal cavity outlining loops of small bowel. A small number of patients may have both kinds of injury. Even if bladder trauma is demonstrated by cystography, all trauma patients with hematuria should undergo IVU.

D. **Treatment** in almost all patients with bladder trauma involves exploration, debridement, surgical repair, drainage of the perivesical space, and diversion of urine, usually by a suprapubic catheter. Following repair, a low-pressure cystogram should be obtained to assess the integrity of the bladder before the catheter is removed.

1. **Extraperitoneal rupture.** Many patients may be successfully treated by urethral catheter drainage alone provided that (a) only a moderate degree of extraperitoneal extravasation is present, (b) there is no evidence of infected urine, and (c) the patient is carefully monitored for the development of clot retention and infected pelvic hematoma. All patients with significant extraperitoneal extravasation should undergo exploration, however. Extraperitoneal rupture of the bladder from blunt trauma usually is repaired transvesically.
2. **Intraperitoneal rupture** requires a transperitoneal approach to rule out associated injuries and to permit removal of extravasated urine from the peritoneal cavity. With penetrating trauma, concomitant injury to the rectum, iliac vessels, or ureters should be ruled out during surgical exploration.

E. **Complications of bladder injury** include cystitis, sepsis, pelvic collection, nephrogenic adenoma, and vesicovaginal fistula.

V. Urethra

Urethral injuries in male patients are usually divided into those involving the anterior portion (penile and bulbous urethra) and those involving the posterior portion (membranous and prostatic urethra).

A. **Mechanisms.** Anterior urethral injuries occur most often as a result of blunt trauma suffered during straddle-type falls in which the urethra is crushed against the pubic bones. If the urethra remains intact, the injury is a urethral contusion, whereas the presence of extravasation implies urethral laceration. Posterior urethral injuries are usually associated with pelvic fractures; the urethra is transected at the genitourinary diaphragm, resulting in superior displacement of the prostate.

B. **Diagnosis**

1. **Anterior urethral injuries.** The patient gives a history of trauma to the perineum followed by perineal pain and inability to void. Almost always a bloody urethral discharge is present. The bulbous urethra is extremely vascular, and both blood and urine will extravasate if the urethra is lacerated. This injury results in a characteristic ecchymosis, in which the pattern depends on the fascial planes of the genitalia and perineum. If Buck's fascia is not ruptured, the ecchymosis is limited to the penis. If Buck's fascia is ruptured, the extent of the ecchymosis is limited by Colles' fascia in the perineum and by Scarpa's fascia in the abdomen. This injury results in a “butterfly” ecchymosis in the perineum with possible extension along the anterior abdominal wall up to the clavicles.
2. **Posterior urethral injuries.** The patient presents with pelvic fracture and inability to void. Almost always there is bloody urethral discharge. In contrast to anterior urethral injuries, posterior urethral injuries are not characterized by ecchymosis. Rectal examination may reveal the prostate to be displaced superiorly, indicating complete transection of the posterior urethra. In instances of partial transection, however, the prostate may be normally located. Regardless of the presence or absence of bloody urethral discharge, retrograde urethrography should be the initial study in all male patients with pelvic fracture (Fig. 18-3). Attempts at instrumentation in these patients may convert a partial urethral tear into a complete transection and may introduce infection into the pelvic hematoma.

C. **Treatment**

1. **Anterior urethral contusion** may be treated nonoperatively. If the patient is able to void without significant hematuria, no treatment is needed. If there is significant bleeding, urethral catheterization for several days is usually sufficient.
2. **Anterior urethral laceration** is best treated by diverting the urine by suprapubic cystotomy (open or percutaneous). In the absence of significant extravasation, conservative treatment will result in spontaneous healing in most cases, although surgical repair may be considered in the acute setting or if warranted by the clinical situation. In patients in whom a urethral stricture develops, this complication can almost always be treated in a delayed fashion successfully by endoscopic means. In the presence of perineal or scrotal hematoma, drainage of the extravasated urine and blood is indicated in addition to suprapubic drainage.
3. **Posterior urethral transection** is best treated in a delayed fashion. Initial management should be suprapubic cystotomy drainage. Partial urethral tears heal spontaneously in about 3 weeks. Complete transection almost always results in severe stricture that requires surgical reconstruction. The patient should be informed that incontinence, erectile dysfunction, and recurrent urethral stricture are possible complications of urethral injuries and surgery.

D. **Complications of urethral injury** may be severe and include stricture, urethral fistula, periurethral abscess, incontinence, and impotence.

VI. Penis

Trauma to the penis may occur from gunshot wounds, stab wounds, machinery accidents, animal attacks, and self-mutilation. Penetrating injury to the penis is managed by debridement, hemostasis, and repair of the injured tissue along with systemic antibiotic therapy. Machinery accidents may result in partial or total avulsion of the genital skin. Such injuries require careful debridement and skin grafting. Urethral continuity may need to be assessed by retrograde urethrography. Spontaneous **penile fracture** may occur during intercourse and result in rupture of the tunica albuginea of the corpora; this injury should be repaired surgically.

VII. Testis

Severe blunt trauma to the testis may result in testicular rupture. The testis may also rupture spontaneously or with minimal trauma if underlying pathology, especially carcinoma, is present. Following rupture of the tunica albuginea, there is considerable bleeding into the space around the testis, resulting in a hematoma.

A. **Diagnosis.** The patient usually presents with a history of blunt trauma to the scrotum and the finding of a tender, swollen scrotal mass that does not transilluminate. US should be performed to delineate the injury.

B. **Treatment** depends on the degree of trauma and extent of the hematoma. When there is little or no trauma, an underlying carcinoma should be suspected, and the patient should undergo testis exploration by the inguinal approach. Patients with severe trauma and bleeding should undergo scrotal exploration and repair of the testis if possible. Patients in whom there is a clear history of trauma but minimal hematoma formation may be treated conservatively with analgesics, elevation, and ice packs applied to the scrotum.

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Chapter 19 Pediatric Urology

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I. Introduction

Pediatric urology requires a detailed understanding of embryology and pediatric physiology in addition to sensitivity toward the special emotional needs of sick children and their parents. With recent advances in surgery, intensive care technology, and chemotherapy, children are surviving conditions that were previously devastating and often fatal. Continuing advances in the field of reconstructive surgery offer the potential for highly successful management of these challenging diseases.

II. Wilms' Tumor (Nephroblastoma)

A. **Incidence.** Wilms' tumor accounts for approximately 10% of childhood cancers. There appear to be two variants—one that is sporadic and has a peak incidence at 3.5 years of age, and a hereditary form (autosomal dominant) that has a peak incidence of 2.5 years. The hereditary form accounts for approximately 15% of cases and is associated with aniridia, hemihypertrophy, macroglossia, polycystic kidney, and neurofibromatosis. Bilateral tumors occur in 5% to 10% of cases, but this incidence is increased when aniridia is present. **Mesoblastic nephroma** is a less malignant variant that has a peak incidence at less than 1 year of age.
B. **Histology** is the most important predictor of clinical outcome. A **favorable histology** is one without anaplastic features, clear cell sarcoma, or rhabdoid tumors; an **unfavorable histology** comprises any of these features. An unfavorable histology is seen in about 12% of patients with Wilms' tumor.
C. **Diagnosis.** The most common presentation is a large, firm, unilateral abdominal mass (80%). Less common are abdominal pain (30%) and nausea and vomiting (20%). Approximately 50% of patients may have hypertension, and half present with hematuria. Anemia may be present, and results of liver function tests may be abnormal with metastatic disease. Radiologically, the diagnosis is made by ultrasound (US) and confirmed by computed axial tomography (CT), which is also useful in clinical staging of the patient. Wilms' tumor must be differentiated from hydronephrosis, polycystic kidney, and neuroblastoma.
D. **Staging** is summarized in Table 19-1. About 12% of patients have distant metastases at presentation.

Stage	Description
I	Tumor confined to kidney
II	Tumor beyond kidney but completely excised
III	Residual disease in the abdomen
IV	Hematogenous metastases
V	Bilateral disease

Table 19-1. Summary of staging of Wilms' tumor

E. **Treatment** of Wilms' tumor involves a multimodal approach that includes surgical removal, chemotherapy, and radiotherapy. Survival approaching 100% can be achieved in earlier-stage disease.
   1. **Surgical removal** is the mainstay of treatment and provides important staging information. Complete lymphadenectomy is not necessary to achieve accurate staging. Vena caval thrombus does not necessarily carry a poor prognosis.
   2. **Chemotherapy** is indicated in all stages of Wilms' tumor regardless of histologic type (actinomycin D, cyclophosphamide, vincristine, doxorubicin, and *cis*-platinum are all active).
   3. **Radiotherapy.** In patients with favorable histology, radiotherapy is reserved for stage III or more advanced disease. With unfavorable histology, radiotherapy is also given in stage II disease.

III. Obstruction of the Upper Urinary Tract

A. **Obstruction of the ureteropelvic junction**
   1. **Incidence.** The ureteropelvic junction is the most common site of urinary tract obstruction in children. The vast majority of instances are congenital in origin. With routine prenatal US, obstruction of the ureteropelvic junction can be detected before birth. Children who escape diagnosis in infancy usually present later with either urinary infection or episodic abdominal pain. There is a predilection for the left side, and boys are affected twice as often as girls.
   2. **Associated findings** include contralateral obstruction of the ureteropelvic junction (10%), contralateral renal agenesis (5%), and vesico-ureteral reflux (10%).
   3. **Pathophysiology**
      a. An **intrinsic muscular defect** causing impaired peristalsis through the ureteropelvic junction is probably the most common cause.
      b. **Aberrant blood vessels** that cross the ureteropelvic junction anteriorly and supply the lower renal pole account for approximately one-third of cases.
      c. **Rare causes** include stenosis or stricture of the ureteropelvic junction, angulation, kinks, periureteral fibrosis, and external compression.
      d. **Secondary obstruction of the ureteropelvic junction** may occur with high-grade vesicoureteral reflux, which leads to the development of a tortuous ureter and kinking at the point of fixation.
   4. **Diagnosis**
      a. **Symptoms and signs.** Obstruction of the ureteropelvic junction occurs in varying degrees. Approximately 15% to 20% of patients present with urinary tract infection. Others may present with a palpable flank mass, intermittent pain, vomiting, or failure to thrive. The pain may be confused with pain arising from the gastrointestinal tract, especially because it is often exacerbated by fluid intake, which transiently increases the intrarenal pressure proximal to the point of obstruction. The patient may present with gross or microscopic hematuria with or without a history of antecedent trauma. In cases of bilateral obstruction of the ureteropelvic junction, a child may present with uremia.
      b. **Radiologic examination.** Increasingly, obstruction of the ureteropelvic junction is diagnosed antenatally by maternal US. In high-grade obstruction, the intravenous urogram (IVU) typically demonstrates a delayed nephrogram and delayed excretion of contrast. Obstruction of the ureteropelvic junction can be intermittent and may become evident only during periods of diuresis. Thus, many provocative tests have been devised, such as the diuretic IVU and diuretic renogram. US will show pelvic and calyceal dilatation with a ureter of normal caliber.
      c. **Antegrade perfusion of the kidney (Whitaker test).** Following percutaneous nephrostomy, the nephrostomy catheter is perfused at a rate of 10 mL/min while the perfusion pressure is measured. The intravesical pressure, monitored simultaneously with an intravesical catheter, is subtracted from the intrapelvic pressure. In the presence of obstruction of the upper urinary tract, a higher perfusion pressure is required to achieve a given perfusion rate. A differential intrapelvic pressure of more than 20 cm H_2O is considered diagnostic of obstruction. Although false-positive and false-negative results can occur, the overall accuracy of the test is approximately 90%. Its major disadvantage is the requirement for percutaneous nephrostomy.

5. **Treatment**
   a. **Conservative management** is indicated in patients with minimal objective evidence of obstruction, normal renal function, no symptoms, and no history of infection.
   b. **Surgical pyeloplasty** is indicated for children if caliectasis or symptoms that can be attributed to the obstruction are present. If the lower ureter is not well visualized, cystoscopy and retrograde pyelography should be performed in conjunction with pyeloplasty. The **Anderson-Hynes dismembered pyeloplasty**, the most commonly employed procedure to correct this anomaly, involves excision of the ureteropelvic junction segment, reanastomosis of the ureter to the pelvis, and repositioning of any associated or aberrant vessels posterior to the anastomosis.
   c. **Nephrectomy** should be considered in patients with complete or nearly complete absence of renal function.

B. **Duplication of the kidney, renal pelvis, and ureter.** A system of standardized terminology is presented in Table 19-2.

Term	Definition
Duplex kidney	Kidney with two pelvicalyceal systems
Bifid pelvis	Duplex kidney with a single ureter
Bifid ureter	Duplex kidney with two ureters that join before reaching the bladder; same as older term "incomplete duplication of ureter"
Double ureter	Duplex kidney with two ureters that drain separately into the urinary or genital tract; same as older term "complete duplication of ureter"
Ectopic ureter	Ureter that drains to an abnormal site
Lateral ectopia	Ureteral orifice lateral to the normal position
Caudal ectopia	Ureteral orifice at or distal to the bladder neck
Intravesical ureterocele	Ureterocele located entirely within the bladder
Ectopic ureterocele	Ureterocele located at least partially at or distal to the bladder neck

Table 19-2. Definition of terms in upper urinary tract duplication

1. **Incidence.** Duplication of the upper urinary tract is one of the most common congenital malformations. The female-to-male ratio is about 3:2, and 15% to 30% of instances are bilateral.
2. **Associated malformations.** Duplication of the ureter itself is usually of no clinical significance, but associated problems such as reflux or obstruction may require treatment. The ureteral orifice draining the upper pole segment will be located in the bladder in a position caudal and medial to the orifice draining the lower pole segment (Meyer-Weigert rule).
   a. **Vesicoureteral reflux** is the most common problem associated with complete duplication of the ureter. Reflux, which occurs in 30% of cases, is much more likely to occur into the lower pole ureter because it inserts laterally into the bladder and has a shortened intramural segment. Rarely, reflux occurs into the upper pole ureter alone, but reflux into both ureters may occur when the orifices are in close proximity.
   b. **Ureteral ectopia**. Any ureter that does not insert onto the trigone may be considered ectopic. Thus, lateral displacement is, strictly speaking, a form of ectopia; in practice, however, the term is reserved for insertion onto or distal to the bladder neck. Ureteral ectopia has a female-to-male predominance of 3:1, and about 10% of instances are bilateral.
      1. **Location.** If the ectopic ureter is located in the proximal female urethra, the result is usually obstruction, reflux, or both. These patients often present with recurrent urinary tract infections. If the location of the ureter is distal to the external sphincter, the patient invariably presents with continuous incontinence despite a normal voiding pattern. An ectopic ureter also may insert into the vestibule, vagina, or uterus. An ectopic ureter in male patients inserts most commonly into the prostatic urethra, although it may insert into the ejaculatory duct, seminal vesicle, or vas deferens/epididymis (Table 19-3). These patients can present with urinary tract infections or epididymitis but not incontinence, because the male ureter never inserts below (distal to) the external sphincter.

Male patients (%)		Female patients (%)	
Urethra	50	Urethra	35
Seminal vesicle	30	Vestibule	35
Ejaculatory duct	15	Vagina	25
Vas deferens	5	Uterus	5

Table 19-3. Location of orifice in ureteral ectopia

      2. **Association with duplication.** In female patients, an ectopic ureter is almost always part of a duplication anomaly and almost always affects the upper pole ureter. The converse is not true; only about 3% of completely duplicated ureters are ectopic. In male patients, ectopic ureter occurs more commonly with a single than with a duplicated system.
   c. **Ureterocele** is a term describing a cystic dilatation of the terminal or intramural portion of the ureter; it usually is associated with the upper pole ureter in a completely duplicated system. There is a female predominance. A ureterocele can also occur in a single ureter, and when it does, it is more commonly seen in boys than in girls. Approximately 10% of ureteroceles are bilateral. The ureteral orifice may be located entirely within the bladder (intravesical ureterocele), at the bladder neck, or within the urethra (ectopic ureterocele). In girls, an ectopic ureterocele can prolapse into the urethra, and as such it is one of the most common causes of infravesical obstruction in girls.
3. **Diagnosis.** US may demonstrate the presence of a dilated, dysplastic upper pole segment. If both segments of a duplicated kidney are functioning, the IVU usually demonstrates the ureteral duplication (Table 19-4). Not infrequently, however, the renal upper pole segment may have little or no function and will not be visualized on IVU. The presence of a duplication with nonfunction of the upper pole segment is suggested on IVU by (a) downward displacement of the lower pole calyces by the upper pole ("drooping lily" sign), (b) discrepancy between the size of the kidney and the small number of calyces seen, and (c) change in the renal axis, with the upper pole displaced laterally away from the vertebral bodies. This displacement results in an increased distance between the kidney and vertebral bodies on the affected side in comparison with the contralateral side. Radionuclide studies may demonstrate an upper pole segment not visualized by IVU. Bladder films on IVU may demonstrate a characteristic filling defect referred to as a “cobra head” deformity, suggestive of a ureterocele. A voiding cystourethrogram (VCUG) should be performed in every patient with duplication to rule out vesicoureteral reflux into the ipsilateral lower pole or contralateral ureters. Cystoscopy is needed to assess the location of the ureteral orifices and the extent and boundary of the ureterocele, but this may be performed at the time of planned corrective surgery. Retrograde contrast studies may be useful in some cases of ectopic ureter.

Radiologic finding	Upper pole (%)	Lower pole (%)
IVU: nonfunction	90	5
IVU: delayed function	10	75
VCUG: reflux	15	45

IVU, intravenous urogram; VCUG, voiding cystourethrogram.

Table 19-4. Radiologic findings in duplication with ureterocele

4. **Treatment** of ureteral duplication depends on the presence of reflux or obstruction and on the degree of impairment of renal function.
    a. **Reflux** is treated in the same manner whether or not the ureter is duplicated. In the absence of hydroureter, prophylactic antibiotics (to help prevent pyelonephritis) and frequent radiologic follow-up will demonstrate spontaneous resolution in about 50% of patients. In patients placed on such a regimen, breakthrough infections or progressive renal scarring are indications for surgical correction of the reflux. In patients with hydroureter or absence of an adequate submucosal tunnel, surgical correction should be the initial mode of therapy. In approximately 10% of patients, reflux may cause severe damage to the lower pole renal unit, sometimes making heminephrectomy necessary.
    b. **Ectopic ureter.** In patients who have an ectopic ureter, with or without associated ureterocele, treatment depends on the function of the upper pole segment. If upper pole function is poor or absent, upper pole heminephrectomy and ureterectomy are indicated. If upper pole renal function is good, a ureteropyelostomy from upper to lower pole may be performed. Alternatively, if reflux into the lower pole ureter is present, excision of the ureterocele and reimplantation of the common sheath should be performed.

C. **Megaureter** denotes a dilated ureter and may occur as a result of various conditions. Primary megaureter refers to a lesion at the ureterovesical junction, and secondary megaureter implies a problem elsewhere in the urinary tract (e.g., obstruction of the bladder outlet) that secondarily affects the ureterovesical junction. Some causes of megaureter, such as reflux, are discussed separately in the following sections.
    1. **Pathophysiology**
        a. **Primary obstructive megaureter** is thought to be caused by defective peristalsis in the intramural ureter. A catheter usually can be passed easily in a retrograde manner through the aperistaltic segment, which cannot be done in cases of true ureteral stenosis or extrinsic compression of the ureter. The lesion is bilateral in 25% of instances, affects the left ureter three times as often as the right, and affects boys three times as commonly as girls. The contralateral kidney is absent or dysplastic in 10% of instances. Children with primary obstructive megaureter may be asymptomatic or may present with recurrent urinary tract infection, hematuria (gross or microscopic), or flank pain.
        b. **Secondary obstructive megaureter** is often bilateral and results from obstruction of the bladder outlet secondary to posterior urethral valves, neurogenic bladder dysfunction (especially myelodysplasia), or functional voiding disorders. In such patients, hypertrophy of the bladder wall leads to secondary obstruction of the ureterovesical junction.
        c. **Vesicoureteral reflux** is a very common cause of ureteral dilatation. It may result from primary dysfunction of the ureterovesical junction or secondary incompetence of the ureterovesical junction caused by obstruction of bladder outflow, neurogenic dysfunction, or functional voiding disorders.
        d. **Other causes** of megaureter in the absence of obstruction or reflux include residual dilatation from obstruction or reflux in the past, high rates of urine flow (diabetes insipidus, polydipsia from any cause), and bacterial infection.
    2. **Diagnosis**. Megaureter is most commonly detected by IVU or US. There is a relatively greater dilatation of the distal ureter than of the proximal ureter or renal pelvis. In mild cases, only the distal third of the ureter is dilated, and the remainder of the upper tract remains normal. A VCUG should be performed in all cases to rule out reflux and to detect obstruction of bladder outflow. Endoscopy should be performed to assess the bladder trigone and permit retrograde studies of the ureter.
    3. **Treatment** is surgical in most instances. When reflux or obstruction of the ureterovesical junction is the cause, excision of the distal ureter, tapering, infolding, and reimplantation are usually required. When obstruction of bladder outflow is the cause, treatment of the primary lesion may lead to spontaneous resolution of the ureteral dilatation.

IV. Obstruction of the Lower Urinary Tract

Posterior urethral valves are the most common cause of obstruction of bladder outflow in male neonates and infants. These valves represent mucosal folds at the distal prostatic urethra that cause varying degrees of obstruction. Type I valves extend distally from the verumontanum and insert onto the lateral urethral wall. Type II valves extend proximally from the verumontanum to the bladder neck. A type III valve is a circular diaphragm in a location slightly proximal or distal to the verumontanum.

A. **Associated findings. Oligohydramnios** occurs because of low intrauterine production of urine and may be associated with **pulmonary hypoplasia**. High-pressure reflux during the prenatal period may lead to **renal dysplasia**, which is associated with posterior urethral valves.
B. **Diagnosis**. Symptoms include a poor urinary stream with dribbling and infection. In some newborns and infants, only nonspecific symptoms are present, such as failure to thrive, uremia, hypertension, or anemia. Electrolyte abnormalities may lead to seizures or cardiac arrhythmias. Older children may present with incontinence, vague abdominal complaints, urinary tract infection, or hematuria. A palpable mass representing the distended bladder may be found. Urinary extravasation (usually at the calyceal fornix) may result in urinary ascites. In neonates with severely obstructing valves, the IVU will show bilateral hydroureteronephrosis, but this is better imaged by US. The VCUG is the most important diagnostic examination and will typically show a heavily trabeculated bladder, prominence of the bladder neck, dilatation of the posterior urethra, and focal narrowing of the stream at the site of the valves. Vesicoureteral reflux may be present in 40% of patients. Endoscopy may demonstrate the valves if flow from the bladder is induced by suprapubic pressure.
C. **Treatment** of urethral valves is by endoscopic fulguration.
    1. In a **nonuremic child**, this can usually be accomplished successfully as primary treatment. In very young infants in whom the urethra is too small to permit endoscopic surgery, either suprapubic ablation via a transvesical approach or temporary diversion by cutaneous vesicostomy can be performed. When the child is older, valve ablation and closure of the vesicostomy are performed.
    2. **Azotemia, acidosis, or sepsis.** In children with metabolic abnormalities, temporary bladder drainage should be established by urethral catheter or suprapubic tube. After resolution of the azotemia, sepsis, and electrolyte abnormalities, transurethral fulguration of the valves can be performed. In the most severe instances of hydronephrosis, azotemia may not resolve completely after valve fulguration because of obstruction at the ureteropelvic junction, poor ureteral peristalsis, or permanent renal dysfunction. In such patients, temporary supravesical diversion by percutaneous nephrostomy or cutaneous loop ureterostomy is required to preserve as much renal function as possible. Approximately one-third of patients requiring diversion of the upper urinary tract progress to renal failure by puberty.
    3. **Reflux.** Valve ablation results in spontaneous resolution of vesicoureteral reflux in approximately one-third of patients. The remainder require surgical correction.

V. Maldescent of the Testis

Maldescent of the testis may manifest as an ectopic testis or cryptorchidism. Ectopy of the testis is a rare condition in which the testis is found outside its normal path of descent, such as in the superficial inguinal pouch (most common), femoral triangle, or perineum. In cryptorchidism, the testis remains somewhere along its normal path of descent from the renal fossa to an intrascrotal position. The cause may be an intrinsic testicular defect or lack of maternal gonadotropins. Approximately 10% of instances are bilateral. The most common location is at the external inguinal ring. Levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) can be used to distinguish between intraabdominal testes and bilateral anorchia, in that the levels are generally elevated if no testes are present.

A. **Incidence.** The testes normally descend into the scrotum at 7 months of gestation. The incidence of cryptorchidism decreases with age; it is 30% in premature infants, 2% in newborns, 1.5% at 1 month, and 0.75% at 1 year of age. A patent processus vaginalis is present in 90% of patients, and inguinal hernia is present in 25%.
B. **Associated findings.** Unilateral cryptorchidism in an otherwise normal child is generally an isolated finding; however, bilateral cryptorchidism, especially when associated with any degree of hypospadias, may be a sign of an intersexual state such as adrenogenital syndrome or one of the androgen-insensitivity syndromes. Bilateral cryptorchidism is also found in “prune-belly” syndrome, exstrophy of the bladder, pituitary disorders, and testicular feminization.
C. **Diagnosis.** In infants and newborns, absence of one or both testes is usually noted on routine physical examination. In true cryptorchidism, the scrotum on the affected side may be underdeveloped. A retractile testis is a normally descended testis that is pulled into the pubic area by the cremaster muscle. In such cases, the scrotum is normal and the testis can be manipulated gently back into the scrotum. Retractile testes do not require surgery and resolve spontaneously at puberty. The location of the ectopic testis is usually superficial to the inguinal canal, and the testis cannot be manipulated into the scrotum.
    1. **Radiology.** In instances of bilateral cryptorchidism or nonpalpable unilateral cryptorchidism, US or CT may demonstrate the presence and location of the testicle or testicles.
    2. The **human chorionic gonadotropin (hCG) stimulation test** can be used to distinguish bilateral cryptorchidism from bilateral anorchia. After the baseline serum testosterone has been measured, the child is given hCG intramuscularly daily for 4 days. On the fifth day, the serum testosterone level will be many times its baseline value if normally responsive testes are present. In addition to a diminished or absent response to exogenous hCG, patients with bilateral anorchia will demonstrate elevated levels of LH and FSH.
    3. **Diagnostic laparoscopy** may be very helpful in the evaluation and treatment of cryptorchidism. The finding of gonadal vessels with a blind ending effectively confirms the diagnosis of an absent testis. If a testis is found, the decision can be made at the time of laparoscopy whether to remove it or mobilize it to facilitate manipulation into the scrotum.
D. **Treatment**
    1. **Hormonal therapy** with hCG or luteinizing hormone-releasing hormone (LHRH) has been reported to cause descent of the cryptorchid testis in about 15% of

patients, although the recommended dosage varies widely.

2. **Orchidopexy** through an inguinal incision either with or without laparoscopy is currently the treatment of choice in most patients and should be carried out at about 8 to 12 months of age. It has been shown that cryptorchid testes do not develop normally if they remain undescended after about 18 months of age. The testis is freed on its vascular pedicle and placed in a dartos pouch in the scrotum. If the spermatic cord is too short, the testicular vessels may be divided without impairment of testicular viability (Fowler-Stephens technique), as collateralization via the vasal and cremasteric circulation may adequately nourish the testis. If the cryptorchid testis cannot be brought down and the opposite testis is normal, either orchiectomy or a two-stage procedure may be performed. If the testis is not found in the inguinal canal, the retroperitoneum should be explored.

E. **Complications and sequelae**

1. **Testicular neoplasia.** The prevalence of cryptorchidism in patients with germ cell tumors is 7.3%, compared with 0.75% in the general population. Thus, a carcinoma is about 10 times as likely to develop in a cryptorchid testis during the patient's lifetime as in a normally descended testis. The absolute risk is, of course, still low. Approximately 1 in 2,500 patients with cryptorchidism will have a tumor, compared with 1 in 25,000 patients without cryptorchidism. Intraabdominal testes seem to account for a disproportionate number of malignancies in cryptorchid testes. Orchidopexy does not seem to influence the risk for testicular cancer but does facilitate the ease of examining the testis over time. Of patients with unilateral cryptorchidism in whom neoplasia develops, about 20% will have a tumor in the contralateral, normally descended testis. In postpubertal male patients under the age of 35 years, the cryptorchid testis should be removed; in patients older than 35, the risk for development of testis cancer is less than the risk associated with anesthesia.
2. **Infertility.** Approximately 50% of men with a history of surgery for unilateral cryptorchidism and two-thirds with a history of bilateral cryptorchidism are infertile. Histologic evidence of diminished spermatogenesis is found in almost all cryptorchid testes that remain outside the scrotum after the age of 1 year. Abnormalities of the vas and epididymis are present in one-third of patients.
3. **Torsion of the testicle** may occur rarely in the cryptorchid testis.

VI. Vesicoureteral Reflux

Vesicoureteral reflux is caused by primary or secondary incompetence of the ureterovesical valve mechanism. The degree of reflux is classified according to an international system (Table 19-5).

Grade of reflux	Degree of reflux
1	Ureter only
2	Ureter and pelvis; no dilatation
3	Mild dilatation; no fornieeal blunting
4	Moderate dilatation; fornieeal blunting; preservation of papillary impressions
5	Gross dilatation; tortuosity of ureter; papillae obliterated

Table 19-5. International classification of vesicoureteral reflux

A. **Incidence.** Studies of asymptomatic children have shown that vesico-ureteral reflux occurs very rarely in healthy persons. In contrast, vesicoureteral reflux is present in 50% of children with urinary tract infection and in 8% of adults with urinary infection. More importantly, between 30% and 50% of children with reflux will have renal scarring.

B. **Etiology**

1. **Primary reflux** is caused by poorly developed trigonal musculature, resulting in lateral displacement of the orifice and poor muscular backing owing to a short intramural tunnel for the ureter.
2. **Ureteral duplication** is commonly associated with reflux into the lower pole ureter; this is caused by the abnormally short intramural tunnel associated with this ureter.
3. **Ureteral ectopia** without ureterocele may be associated with reflux.
4. **Abnormalities of the bladder wall**, such as diverticula, radiation cystitis, and cyclophosphamide (Cytoxan) cystitis, may predispose to vesicoureteral reflux. As mentioned previously, urinary tract infection may be associated with transient reflux.
5. **Elevated intravesical pressure** from any cause may lead to reflux. Common causes are posterior urethral valves, detrusor hyperreflexia, and prostatic enlargement in adults.
6. **Prune-belly syndrome** is a congenital condition characterized by deficient anterior abdominal musculature, bilateral cryptorchidism, and often bilateral vesicoureteral reflux.
7. **Iatrogenic reflux** may result from any surgical procedure that disrupts the trigonal muscle, such as prostatectomy. Resection of the ureteral orifice can also produce reflux.

C. **Diagnosis.** Vesicoureteral reflux rarely causes symptoms. Most instances of reflux present as recurrent urinary tract infections or pyelonephritis. In more advanced stages, the patient may present with uremia or hypertension. The IVU findings are usually normal in low grades of reflux. The VCUG is the definitive examination and must include the voiding phase. In this examination, the presence of vesicoureteral reflux during passive bladder filling is often termed low-pressure reflux, whereas vesicoureteral reflux detected only during voiding is called high-pressure reflux. In addition, the voiding phase of the VCUG may allow the diagnosis of outflow obstruction to be made. Endoscopy should always be performed to assess the outlet, bladder wall, and appearance and location of the ureteral orifices.

D. **Treatment**

1. **Medical management** is indicated in cases of low-grade vesicoureteral reflux without outlet obstruction or other abnormality. Good patient compliance is necessary. Long-term antibiotic suppression with a regimen of trimethoprim/sulfamethoxazole, amoxicillin, or nitrofurantoin at one-fourth to one-half the usual dose daily is commonly used. Depending on the grade of reflux as determined by VCUG, a considerable number of instances of vesicoureteral reflux will resolve spontaneously without surgical correction (Table 19-6). If the patient remains asymptomatic, urine cultures are obtained every 3 months during treatment. If acute ("breakthrough") infection occurs, a full course of appropriate antibiotics is given and a different prophylactic regimen is then instituted. A radionuclide cystogram should be obtained at yearly intervals.

Grade of reflux	Spontaneous resolution (%)
1	90
2	60
3	50
4	30
5	0

Table 19-6. Spontaneous resolution of vesicoureteral reflux with antibiotic prophylaxis

2. **Surgical therapy** is indicated in patients with high-grade primary reflux (grades 4 and 5), those with low-pressure reflux and significant hydroureter, and patients in whom medical management has failed. Although failure can be defined in various ways, most agree that persistence of reflux after 3 to 4 years of antibiotic prophylaxis, multiple “breakthrough” infections, new or increased renal scarring, deterioration of renal function, and noncompliance with medication are indications for surgical therapy. In patients with minimal hydroureter, creation of a ureteroneocystostomy with the Leadbetter-Politano, Cohen, or extra-vesical technique has a 98% cure rate. Approximately 1% of patients have obstruction of the ureterovesical junction after ureteral reimplantation that

requires reoperation. In patients with massive ureteral dilatation, tapering of the distal ureter may be necessary during reimplantation. Rarely, temporary supravesical diversion is necessary in patients who are severely uremic.

VII. Exstrophy of the Bladder

Exstrophy of the bladder is a congenital defect characterized by ventral herniation of the bladder through the anterior abdominal wall. The rectus muscles are widely separated (as is the pubic symphysis), and the posterior wall of the bladder fills the defect. There is a 3:1 male predominance. In male patients, complete epispadias (a condition in which the urethra opens onto the dorsal aspect of the penis) may be present, and the clitoris is bifid in female patients.

A. **Associated findings.** Undescended testes, inguinal hernias, and a bifid uterus are frequently associated with bladder exstrophy. The exstrophic bladder is associated with an increased risk for development of adenocarcinoma.
B. **Treatment** is initiated in the neonatal period by closing the bladder primarily and mobilizing the corpora for penile lengthening. In those with adequate bladder capacity at 1 to 2 years of age, a second procedure to correct reflux and reconstruct the bladder neck for continence is carried out. The final stage of treatment consists of epispadias repair. In those without adequate bladder capacity, the entire bladder may be rolled into a tube, the bladder augmented with a segment of bowel, and the ureters reimplanted into the bowel patch. Success rates approach 80% in terms of continence and preservation of renal function.

VIII. Hypospadias

Hypospadias is a congenital defect of the penis resulting in a proximal (ventral) urethral meatus, ventral curvature (chordee), and ventral deficiency of the foreskin. Hypospadias is classified by the location of the meatus as (a) glanular, (b) coronal, (c) penile, (d) penoscrotal, or (e) perineal.

A. **Inheritance.** Hypospadias has a multifactorial mode of inheritance that is not sex-linked. The incidence of hypospadias in subsequent offspring varies between O% and 25%, depending on the severity of the hypospadias in the index child and presence of hypospadias in other family members.
B. **Associated findings.** Undescended testis is found in 10% of all patients with hypospadias, but this incidence increases to 30% in patients with a penoscrotal or perineal opening. An intersexual state is found in approximately one-third of patients with hypospadias and undescended testicles. Such patients should be carefully evaluated. Karyotyping should be performed to be certain that these persons are not females with virilized genitalia.
C. **Treatment** involves the surgical repair of chordee when present and urethral reconstruction by one of many techniques, such as a meatus-based flap, an island pedicle flap, or a free skin graft from the dorsal foreskin. Patients with hypospadias should not be circumcised because the foreskin often is required for surgical reconstruction. In approximately 10% to 20% of patients, a urethrocutaneous fistula develops, which may require secondary closure. Overall results are excellent.

IX. Disorders of Sexual Differentiation

A. **Disorders of chromosomal sex** occur when the number or structure of the X or Y chromosome is abnormal.
    1. **Klinefelter's syndrome** is the most common major abnormality of sexual differentiation, with an incidence of approximately 1 in 500 males. Patients often present after the time of expected puberty and are diagnosed incidentally. Patients characteristically have small, firm testes, impaired sexual maturation, azoospermia, gynecomastia, and elevated levels of urinary gonadotropins. Hyalinization of the seminiferous tubules is a typical histologic finding. The common karyotype is either a 47,XXY pattern (classic form) or 46,XY/47,XXY (mosaic form). Plasma levels of LH and FSH are high, the latter being a consequence of damage to the seminiferous tubules. Mean plasma levels of estradiol are also elevated, leading to insufficient masculinization and enhanced feminization. Most patients benefit from injections of testosterone cypionate or testosterone enanthate. Surgery is the only available means to correct the gynecomastia.
    2. **XX male syndrome** is a rare disorder in which a 46,XX karyotype is present. Most patients appear to have the Y-linked testis-determining factor, presumably from translocation of a fragment of the Y chromosome to the X chromosome. This occurs in about 1 in 20,000 to 24,000 male births. Affected persons lack female internal genitalia and have a male psychosexual identification. Clinical features resemble those in Klinefelter's syndrome, including small testes, gynecomastia, azoospermia, and hyalinization of the seminiferous tubules. Plasma gonadotropin and estradiol levels are elevated and mean testosterone levels are low. Management is similar to that of Klinefelter's syndrome.
    3. **Turner's syndrome (gonadal dysgenesis)** is characterized by primary amenorrhea, sexual infantilism, short stature, multiple congenital anomalies, and bilateral streak gonads in phenotypic females, most commonly with a 45,XO karyotype. These somatic features and streak gonads result from loss of genetic material from the X chromosome. Typically, patients have immature female external genitalia and no breast development. Mosaicism with a normal chromosomal complement (46,XX/45,XO) lessens the severity of the gonadal abnormality, and the likelihood of menses and breast development is greater in such cases. Other somatic anomalies include a webbed neck, low hair line, and a shieldlike chest. Congenital cardiac anomalies occur in 10% to 20% of cases, the most common being aortic coarctation; 60% have renal abnormalities, especially horseshoe kidney, with or without duplication. Plasma gonadotropins are elevated from the neonatal period to 4 years of age, normalize until age 10, and then rise to abnormally high levels thereafter. Management involves administration of recombinant human growth hormone with the anabolic steroid oxandrolone during childhood in an effort to increase the final adult height. Estrogen replacement therapy should be given at the time of expected puberty to patients without spontaneous feminization.
    4. **Mixed gonadal dysgenesis** is a disorder in which phenotypic males or females have a testis on one side and a streak gonad on the other. Most have 45,X/46,XY mosaicism. After congenital adrenal hyperplasia, it is the most common cause of ambiguous genitalia reported in neonates. Two-thirds are raised as girls. In most cases, the testis is intraabdominal, and a uterus, vagina, and fallopian tube are present in all. Somatic features include short stature, shieldlike chest, webbed neck, multiple pigmented nevi, and cubitus valgus. Gonadal tumors occur in 25% of patients. In phenotypic females, prophylactic gonadectomy should be performed. In phenotypic males, all streak gonads should be removed and scrotal testes should be preserved.
    5. **True hermaphroditism** is a condition in which both an ovary and a testis or an ovotestis (gonad with histologic features of both) is present. Seventy percent of cases have a 46,XX karyotype, 10% have a 46,XY karyotype, and the remainder are mosaic. Three-fourths are sufficiently masculinized to be raised as boys. Most of these patients have hypospadias, and half have incomplete labioscrotal fusion. Most phenotypic females have an enlarged clitoris, a urogenital sinus, and a hypoplastic uterus. At puberty, a variable degree of feminization or masculinization occurs. Breast development occurs in three-fourths, and half menstruate. Sex assignment depends largely on anatomic findings in the newborn, and external genitalia should be modified accordingly. Gonadal tumors are rare, although gonadoblastoma has been recorded in a patient with an XY karyotype.
B. **Disorders of gonadal sex** are characterized by an abnormal differentiation of the gonads without a chromosomal abnormality.
    1. **Pure gonadal dysgenesis** is a syndrome in which phenotypic females have gonads and genitalia identical to those with gonadal dysgenesis. However, these patients have a normal height, few somatic anomalies, and either a 46,XX or 46,XY karyotype. Estrogen deficiency is variable, and feminization occurs in 40%. Management with estrogen replacement therapy is started at puberty and is maintained throughout life. Tumors, especially dysgerminoma and gonadoblastoma, may develop in the streak gonads of those with a 46,XY karyotype, and removal is therefore recommended.
    2. **Absent testis syndrome** occurs in 46,XY males with absent or rudimentary testes in whom endocrine function of the testis was variable during embryogenesis. The clinical features range from absent or incomplete virilization of the external genitalia to bilateral anorchia in otherwise normal-appearing males. The degree of virilization and müllerian regression depends on the timing of testicular failure during gestation—that is, whether it occurred before or after the development of the seminiferous tubules and the onset of Leydig's cell function. Management depends on the clinical features. Depending on the patient's phenotype, either estrogen or androgen replacement therapy is given to allow appropriate secondary sexual development.
C. **Disorders of phenotypic sex**
    1. **Female pseudohermaphroditism** is a disorder in which the ovaries and müllerian derivatives are normal but in which the feminization of the external genitalia is abnormal. Virilization of the female fetus is secondary to androgens from either the maternal circulation or the fetal adrenal gland.
        a. **Congenital adrenal hyperplasia** is the most common cause of ambiguous genitalia in the newborn. It is also the most common cause of female pseudohermaphroditism.
            1. **Pathophysiology.** The etiology of congenital adrenal hyperplasia is a deficiency in one of a number of hereditary enzymes in the adrenal steroidogenesis pathway. The end result is an overproduction of androgen and adrenocorticotropin (ACTH) levels to cause enhanced virilization of external genitalia, hyperpigmentation in females, and precocious puberty in males. The most common enzyme deficiency is that of is 21-hydroxylase, which accounts for 95% of cases. Congenital adrenal hyperplasia is an autosomal recessive disorder that occurs in 1 of 15,000 births in the United States.
            2. **Diagnosis.** Congenital adrenal hyperplasia usually presents in one of two forms, mild or severe. In the severe form, decreased mineralocorticoid production can lead to life-threatening salt wasting and dehydration. This usually happens in the first weeks of life. Failure to recognize this problem can result in severe hypotension and ultimately collapse of circulation. In addition to a complete history and physical examination, measurement of serum electrolytes, chromosomal analysis, and determination of serum levels of 17-hydroxyprogesterone and urinary levels of 17-ketosteroids and pregnanetriol should be performed. Abdominal and pelvic US are performed to look for intraabdominal gonads.
            3. **Management** of congenital adrenal hyperplasia should focus on the issues of salt-wasting crisis, degree of virilization, and psychosocial concerns

surrounding the sexual assignment of the child. Replacement therapy with cortisone and mineralocorticoids are essential to prevent salt wasting. Surgical intervention involves reconstruction of the genitalia, which can be performed either during the neonatal period or infancy.

b. **Exogenous androgens and progestogens** represent another cause of female pseudohermaphroditism. In the past, progestational agents with androgenic side effects were administered during pregnancy to prevent abortion, resulting in virilization of the female fetus. Female pseudohermaphroditism may also occur when the mother has a virilizing ovarian or adrenal tumor.

2. **Male pseudohermaphroditism** results from inadequate virilization of the male embryo.
   a. **Abnormalities in androgen synthesis** lead to incomplete virilization of the fetus. There are five known defects of testosterone synthesis within the adrenal gland, each involving a crucial enzymatic step in the conversion of cholesterol to testosterone. The enzymes 20,22-desmolase, 3b-hydroxysteroid dehydrogenase, and 17a-hydroxylase are common to the synthesis of other adrenal hormones in addition to androgens, and their deficiency leads to congenital adrenal hyperplasia and male pseudohermaphroditism. On the other hand, 17,20-desmolase and 17b-hydroxysteroid dehydrogenase are involved only in androgen synthesis. A deficiency in either leads solely to male pseudohermaphroditism.
   b. **Abnormalities of androgen action** may cause impaired male development as a result of resistance to androgen action in target cells. Deficiency of 5a-reductase is an autosomal recessive disorder associated with failure of dihydrotestosterone formation, resulting in normal male wolffian duct derivatives but defective masculinization. Patients typically have a severe **perineoscrotal hypospadias** and a blind vaginal pouch opening into the urogenital sinus or urethra. At puberty, variable degrees of masculinization occur. Androgen receptor disorders result in different phenotypes. The most common of these disorders is **complete testicular feminization**, resulting in male pseudohermaphroditism. Breast development, the general habitus, and distribution of body fat are female in character, giving the patient a truly feminine appearance. All internal genitalia are absent except for the gonads, which have the histologic appearance of undescended testes. The clitoris is normal or small, and the vagina is short with a blind ending, but the external genitalia are unambiguously female. Because of increased tumor formation in the undescended testis, orchiectomy is recommended after puberty.

Suggested Reading

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Chapter 20 Neuro-Urology and Urodynamic Testing

Mike B. Siroky and Robert J. Krane

I. Introduction

The function of the urinary bladder is the storage and expulsion of urine. The pelvic floor is a complex muscle system that acts to support the pelvic organs and promote continence. Neurologic disorders often produce profound dysfunction of the lower urinary tract that may result in urinary retention, urinary incontinence, or both. As a result of dysfunction of the lower urinary tract, the upper urinary tract is often adversely affected, resulting in hydroureteronephrosis, renal failure, urinary stones, or sepsis. Evaluation of voiding dysfunction is discussed in Chapter 6, and urinary incontinence is discussed in Chapter 11.

II. Vesicourethral Unit

The urinary bladder is composed primarily of smooth muscle (the **detrusor**). Normal emptying of the bladder is accomplished by contraction of the detrusor muscle accompanied by opening of the bladder neck (**internal sphincter**) and relaxation of the pelvic floor (striated **external sphincter**). Minute-to-minute urinary continence results primarily from closure of the internal urinary sphincter. The external sphincter functions as an auxiliary continence mechanism that is much stronger but much less efficient than the internal sphincter. It is active for short periods of time to prevent leakage of urine during involuntary bladder activity or increased intrabdominal pressure (coughing, straining, or Valsalva maneuver).

A. **Innervation** of the vesicourethral unit involves all three divisions of the peripheral nervous system (Fig. 20-1). The detrusor is innervated by the pelvic nerves, which arise from sacral segments S-2 through S-4. The sympathetic nerves arising from T-10 through T-12 innervate the bladder neck and urethral smooth musculature. The pudendal nerves are somatic nerves that supply the pelvic floor, including the striated external sphincter.

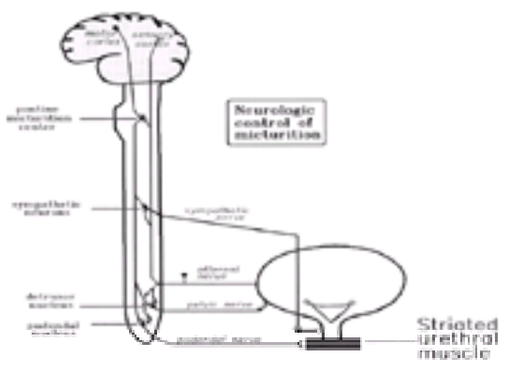

FIG. 20-1. Neurologic control of micturition involves parasympathetic (pelvic), somatic (pudendal), and sympathetic peripheral nerves. The cerebral cortex inhibits the pontine micturition center, which is responsible for coordinating the bladder and its sphincters during micturition.

B. **Central organization** of the micturition reflex is hierarchic, with centers located in the cerebrum, posterior hypothalamus, midbrain, pontine reticular formation, and sacral spinal cord (Fig. 20-1). The main function of the pontine center is coordination of the detrusor and its sphincters; suprapontine centers (mainly the cerebrum) act to inhibit the lower centers.
C. **Effects of neurologic lesions** vary with their level, extent, and completeness. As a rule, lesions of the cerebrum result in involuntary detrusor contractions that remain coordinated with the sphincters. Lesions of the high spinal cord have the effect of separating the vesicourethral unit from the pontine center, resulting in grossly uncoordinated voiding—**vesicosphincter dyssynergia**. Lesions of the sacral spinal cord and cauda equina tend to produce a paralyzed detrusor and denervated pelvic floor.

III. Diagnosis

The patient with symptoms of vesicourethral dysfunction requires a careful history and physical examination. Urodynamic testing may or may not be indicated.

A. **History.** Note any past history of enuresis, urinary infection, calculi, or surgery. In male patients, document the present level of sexual function and note any disturbance of bowel function. The medication history is important. A large number of commonly prescribed drugs may affect voiding function (Table 20-1). The voiding pattern should be elicited in detail, including any frequency (day and night), urgency, incontinence, pain on urination, hesitancy, weak stream, straining to void, dribbling, and incomplete emptying.

Class	Urinary dysfunction	Examples
Anticholinergic	Retention	Oxybutynin; tolterodine; antiparkinsonian drugs; phenothiazines
Antispasmodic	Retention	Oxybutynin; dicyclomine; flavoxate
Sympathomimetic	Retention	Pseudoephedrine; phenylephrine; phenylpropanolamine; ephedrine
Calcium-channel blocking	Retention	Nifedipine; terodiline
Adrenolytic	Incontinence	Reserpine; prazosin

Table 20-1. Medications associated with vesicourethral dysfunction

B. **Physical examination** should be focused on the sacral reflexes and sacral sensation. In male patients, perineal sensation is tested by pinprick of the scrotal, penile, and perianal skin. In female patients, the labial and perianal skin should be tested. **Anal tone** is assessed by digital rectal examination. Patients with normal anal tone can voluntarily contract the anal sphincter. Denervation of the perineal floor often manifests as a lax anal sphincter. The **bulbocavernosus reflex** may be tested in several ways. Squeezing the glans penis gently will elicit a contraction of the bulbocavernosus muscle, which can be palpated in the perineum. Alternatively, one may elicit the reflex during rectal examination and feel the contraction of the anal sphincter. A variation of this reflex is the “trigonal” reflex, which is elicited by gently tugging on an indwelling Foley catheter and observing the response of the perineal muscles or anal sphincter. The presence of the bulbocavernosus reflex implies that the innervation of the bladder and sphincters is grossly intact. In cases of partial denervation, the reflex may still be present.
C. **Urodynamic studies** include any objective assessment of lower urinary tract function that provides clinically useful information. Such studies generally

comprise measurements of pressure, flow, and electromyographic potentials and may or may not include radiographic examinations. It is ideal if the patient's symptoms can be reproduced during the urodynamic examination, but this is not always possible. It is also useful to ask patients whether the function observed during urodynamic examination approximates their usual voiding pattern.

1. The **cystometrogram** measures intravesical pressure during passive filling and active contraction (Fig. 20-2). The filling fluid may be either saline solution, water, radiographic contrast, or carbon dioxide. Cystometry may be considered a provocative test of bladder function wherein filling (stretch) is the stimulus and detrusor contraction is the evoked response. During cystometry, observations are made regarding bladder sensation, the slope of the filling curve, and detrusor contraction.

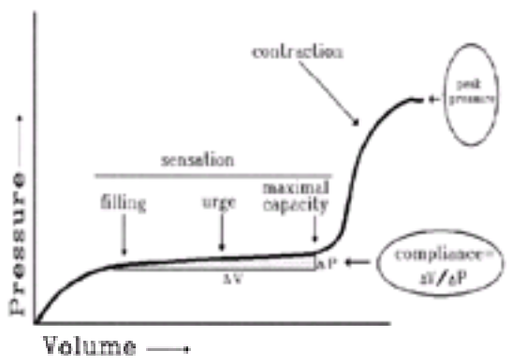

FIG. 20-2. Idealized cystometric curve showing important parameters, including sensation reported by patient, detrusor contraction, and definition of compliance.

   a. **Bladder sensation.** The great majority of normal persons report a sensation of filling at a bladder volume between 100 and 300 mL. This sensation is followed by an urge to void that is distinct from the filling sensation. Sensory abnormalities include absence of filling sensation and urge to void. Discomfort and urgency at low volumes is typical of inflammatory conditions such as lower urinary tract infections, radiation cystitis, and interstitial cystitis.
   b. **Filling phase.** The cystometrogram during the filling phase is nearly flat, demonstrating little increase in pressure with increasing bladder volume. The characteristics of this portion of the cystometrographic curve depend primarily on the physical properties (**compliance**) of the bladder wall. Increased compliance is seen after chronic urinary retention of any cause. Decreased compliance has many possible causes, including chronic inflammation, radiation cystitis, interstitial cystitis, and bladder carcinoma.
   c. **Contraction phase.** Detrusor contraction is characterized by a slow and sustained rise in pressure to a peak of 60 to 120 cm H_2O. Normal persons are aware of an urge to void before the contraction and can suppress the detrusor contraction if asked to do so.
      1. **Detrusor overactivity**, whether from neurogenic causes or not, is usually characterized by cystometric capacity of 200 mL or less. *More important than the capacity, however, is the inability to inhibit the detrusor contraction.* The term **detrusor hyperreflexia** is usually reserved for instances caused by a known neurologic lesion, whereas **detrusor instability** is commonly used to denote cases with nonneurogenic or unknown causes.
      2. **Acontractile detrusor** is characterized by lack of a detrusor contraction on filling of the bladder. The term **detrusor areflexia** should be reserved for cases in which a clearly defined neurologic condition is the cause; all other instances are more accurately termed acontractile detrusor. It is important to remember that approximately 10% of men and 50% of women without a voiding abnormality demonstrate no detrusor contraction on the cystometrogram because of psychological inhibition. This is one of the most common reasons for overinterpretation of cystometrographic tracings.
      3. **Impaired detrusor contractility** is characterized by a weak or short-lived detrusor contraction. This is a not uncommon finding in elderly patients of both sexes and may be caused by replacement of smooth muscle by collagen.
   d. **Bethanechol supersensitivity testing** may be indicated in some patients demonstrating acontractile bladder to determine whether the cause is neurogenic. This test is based on **Cannon's law**, which states that an exaggerated response to its natural neurotransmitter develops in a denervated organ (**denervation supersensitivity**).
      1. **Use of bethanechol chloride.** As originally described by Lapides, 2.5 mg of bethanechol chloride was used as the test agent, and an increase of 15 cm H_2O in bladder pressure was the test criterion. We have found improved sensitivity and specificity by using a dose of 5 mg in patients weighing more than 75 kg and a test criterion of 20 cm H_2O. Alternatively, one can use a weight-adjusted dose of 0.03 mg/kg. Bethanechol is contraindicated in patients with gastrointestinal obstruction, bronchial asthma, peptic ulcer, bradycardia, hypotension, or parkinsonism. Atropine (0.4 mg given intramuscularly) should always be available to reverse any adverse effects of the drug.
      2. **Cystometric pressure measurement.** After the bladder is filled slowly to 100 mL, the intravesical pressure is measured. The appropriate dose of bethanechol chloride is administered subcutaneously (not intradermally or intramuscularly, and never intravenously). The onset of cholinergic effect occurs after about 15 minutes and is indicated by flushing and increased salivation. Cystometry is repeated up to a volume of 100 mL.
      3. **Interpretation.** An increase of 20 cm H_2O in comparison with the baseline value is indicative of supersensitivity and suggests bladder denervation. **False-positive results** may occur in patients with inflammatory bladder disease or acute urinary tract infection. **False-negative** results may occur if the test is performed within the first 8 weeks after denervation, when the supersensitive response may not be fully developed. A supersensitive response to bethanechol does not imply a therapeutic benefit from oral use of the agent.
   e. **Ice water test.** Instillation of 50 to 100 mL of ice-cold water will provoke a bladder contraction in many patients with spinal cord injury, demonstrating that the sacral reflex arc is intact.

2. **Uroflowmetry** is among the most useful of all urodynamic studies (Fig. 20-3). The test requires only that the patient void an adequate amount into the flowmeter to permit measurement of the flow rate. The most important determinant of the normal flow rate is the initial bladder volume. The urinary flow increases as initial bladder volume increases. Table 20-2 lists minimal peak flow values for various patient groups. To compare flow rates before and after therapy or over a period of time, it is useful to refer to a flow rate nomogram (Fig. 20-4). The parameters used in uroflowmetry are shown in Fig. 20-3. The shape of the uroflow curve may also provide useful information; for example, an irregular flow curve may indicate abdominal straining or vesicosphincter dyssynergia.

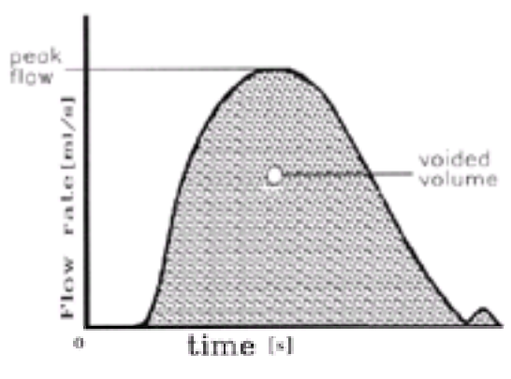

FIG. 20-3. Idealized uroflow curve.

Patient group	Age (y)	Normal peak flow rate (mL/s)
Men	<40	>22
	40–60	>18
	>60	>13
Women	<50	>25
	>50	>18
Children, adolescents	<10	>15
	10–20	>20

Table 20-2. Normal uroflow values for voided volumes greater than 150 mL

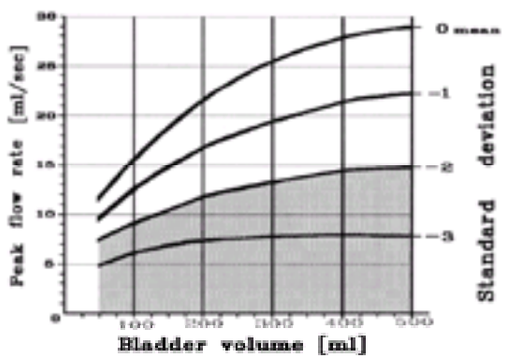

FIG. 20-4. Flow rate nomogram relating maximum flow rate to initial bladder volume.

3. **Electromyography** of the striated perineal musculature provides two kinds of information: (a) contractile activity and (b) state of innervation. Surface electrodes readily provide the first kind of information and are used widely in children because they are noninvasive. For more detailed studies of innervation, needle electrodes must be used. In male patients, a 50-mm concentric electrode is placed into the bulbocavernosus muscle or the external urethral sphincter. In female patients, a 30-mm electrode is placed into the external anal sphincter or the periurethral striated muscle. In normal persons, the electromyogram will show no evidence of denervation, normal sacral reflexes will be present, and the patient will be able to contract the perineal muscles voluntarily. With bladder filling, a gradual increase in electromyographic activity is noted, referred to as the **guarding reflex** (Fig. 20-5). With the onset of bladder contraction, electromyographic activity decreases or ceases for the entire voiding process. Failure of the perineal muscles to relax during a detrusor contraction is **vesicosphincter dyssynergia**. In some patients who use abdominal straining to void in the absence of a detrusor contraction, electromyographic activity may persist during straining; this is called **pseudodyssynergia**.

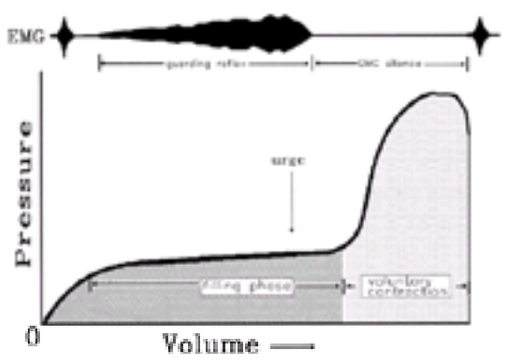

FIG. 20-5. Combined cystometrogram and perineal electromyogram showing normal voiding.

4. **Urethral pressure may be measured** by several different techniques. The primary indications for this examination are in the diagnosis of stress urinary incontinence, assessment of drug actions, and monitoring of antiincontinence devices.
   a. In the **Brown-Wickham technique**, a pressure-measuring catheter is withdrawn from the bladder through the urethra, providing a profile of the urethral pressure at each point. The examination is most commonly performed with a side-hole catheter, which is perfused with saline solution at a rate of about 2 mL/min while being withdrawn at 0.5 cm/s. An idealized curve showing the parameters of urethral profilometry is depicted in Fig. 20-6. The two most important parameters are the maximal urethral pressure (peak pressure) and the functional urethra length (Table 20-3). In women, maximal pressure tends to fall with age, whereas in men the functional length tends to increase with age. One can observe from Table 20-3 that the normal range is wide and overlaps considerably with abnormal values, which reduces the usefulness of profilometry as a diagnostic tool.

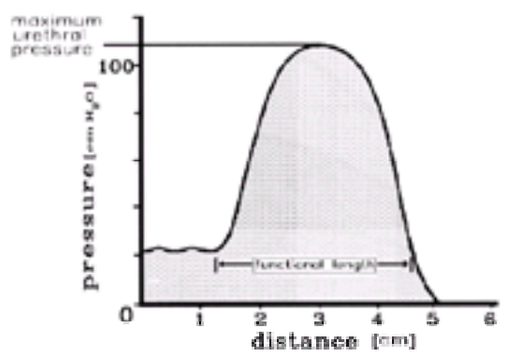

FIG. 20-6. Parameters of urethral profile measurement.

Patient group	Age (y)	Peak pressure (cm H_2O)	Functional length (cm)
Men	<50	65–105	3.5–4.5
	>50	65–105	4.0–5.5
Women	<50	60–90	2.0–3.5
	>50	50–80	2.0–3.5

Table 20-3. Normal values for Brown-Wickham urethral pressure profile

   b. **Abdominal leak point pressure**, measured during a fluoroscopic cystogram, is useful in determining the minimum pressure required to cause leakage. The bladder is gradually filled with contrast and monitored fluoroscopically. After a volume of at least 200 mL has been reached, the patient is placed in a sitting or upright position and asked to perform the Valsalva maneuver gradually. The lowest total bladder pressure at which leakage is detected is the abdominal leak point pressure. If no leakage occurs with the Valsalva maneuver, the patient is asked to cough several times, and fluoroscopic examination for the presence of leakage is repeated. Patients with a competent urethra typically have an abdominal leak point pressure above 120 cm H_2O; those with urethral incompetence have an abdominal leak point pressure below 60 cm H_2O.
5. **Pressure-flow studies and video urodynamics** are especially useful in the diagnosis and localization of outflow obstruction; however, they may be used in

all types of voiding dysfunction. The study is performed by filling the bladder and having the patient void around a 4F to 6F (French) catheter in the urethra. This allows simultaneous recording of the intravesical pressure and flow rate. High intravesical voiding pressures associated with low flow rates are indicative of outflow obstruction. The entire process may be filmed fluoroscopically and recorded on videotape (video urodynamics). The addition of video capability may permit more accurate localization of the site of outflow obstruction and is also very useful in patients with incontinence.

IV. Neurourologic Classification

Various systems of classifying urodynamic abnormalities have been proposed. The purpose of these systems is to provide commonly accepted terminology, promote communication, and aid in diagnosis and treatment. The commonly used classification systems are descriptive and do not indicate the cause of the dysfunction (Table 20-4).

Krane-Siroky	Wein	International Continence Society
Detrusor hyperreflexia Coordinated sphincters Striated sphincter dyssynergia Smooth-sphincter dyssynergia Detrusor areflexia Coordinated sphincters Nonrelaxing striated sphincter Nonrelaxing smooth sphincter Denervated striated muscle sphincter	Failure to store Because of bladder Because of outlet Failure to empty Because of bladder Because of outlet	Detrusor Normal Overactive Underactive Urethra Normal Overactive Incompetent Sensation Normal Hypersensitive Hyposensitive

Table 20-4. Classification systems used to describe voiding dysfunction

V. Effects of Neurologic Disease

A. **Spinal cord injury** can result from motor vehicle accidents, diving accidents, gunshot wounds, and contact sports. Men are affected much more frequently than women.
   1. **Pathophysiology.** Most spinal cord injuries are a combination of contusion, crush, ischemia, and swelling. Thus, some degree of recovery is common; about 50% of spinal cord injuries are ultimately incomplete. Immediately following suprasacral spinal cord injury, somatic reflexes below the level of injury are often completely abolished (**spinal shock**), including bladder reflexes. Spinal shock may last for 2 to 12 weeks. The bulbocavernosus reflex is one of the earliest to return. The patient's bladder should be emptied by intermittent catheterization during the period of spinal shock.
   2. **Classification of spinal cord injury**
      a. **Skeletal level of injury (SLI)** denotes the radiologic determination of the vertebral body with the greatest degree of fracture or injury.
      b. **Neurologic level of injury (NLI)** denotes the neurologic determination of the most caudal segment with good motor and sensory function. If dissociation is noted between the motor and sensory levels, both are given. In a **complete** lesion, no function can be elicited below this level. If any nonreflexive movement or sensation exists below the neurologic level of injury, the injury is **incomplete**. Frequently, lack of correlation is found between the neurologic and skeletal level of injury. Because the conus medullaris is located at the L-2 and L-3 vertebrae, the neurologic level is generally lower than the skeletal level.
      c. **Grading of motor function** is according to the following scale:

         0/5, no movement
         1/5, trace of movement
         2/5, full range of movement with gravity eliminated
         3/5, full range of movement against gravity
         4/5, full range of movement against resistance
         5/5, normal strength and movement
      d. **Frankel grading of completeness of injury** is as follows

         A, complete injury; no function below NLI
         B, incomplete injury; some sensation below NLI
         C, incomplete injury; minimal motor function below NLI
         D, incomplete injury; grade 3 movement below NLI
         E, normal motor and sensory function but reflexes remain abnormal

         Of all spinal cord injuries, 50% present as Frankel A injury and 30% present as Frankel D. Of patients presenting with Frankel A injuries, more than 90% are discharged from rehabilitation as Frankel A; 10% improve to Frankel B through D.
   3. **High spinal cord injuries (C-1 through C-8)** produce quadriplegia; a significant spinal cord segment is isolated from higher centers of control.
      a. **Vesicosphincter dyssynergia.** When complete, high spinal cord lesions are almost always associated with detrusor hyperreflexia and external sphincter dyssynergia.
      b. **Autonomic dysreflexia.** Of patients with lesions above T-6, autonomic dysreflexia may be a significant problem in anywhere from 30% to 85% (see Figure 4-4). Autonomic dysreflexia can be a life-threatening emergency, as systolic blood pressures occasionally exceed 200 mm Hg. Symptoms include headache, flushing, and sweating. Acute episodes of dysreflexia may be associated with bladder distention, fecal impaction, decubitus ulcer, or manipulation of the genito-urinary tract. The first step in managing an acute episode is removal of the inciting cause, if possible. See Chapter 4 for treatment recommendations.
   4. **Low spinal cord injuries (T-1 through L-5)** produce paraplegia. Detrusor hyperreflexia is common, with sphincter dyssynergia possible depending on completeness of the lesion.
   5. **Conus (S-1 through S-5) and cauda equina injury** produce bladder areflexia and denervated sphincter in about 75% of patients. The internal sphincter (bladder neck) may be also incompetent in these patients, making them prone to incontinence.

B. The effect of **cerebral lesions**, including those associated with cerebrovascular disease, Parkinson's disease, and brain injury or tumor, on urinary function depends on their location and extent. Cerebral lesions tend to produce detrusor hyperreflexia, with coordinated sphincters seen in the majority of patients. Patients with Parkinson's disease may have complex dysfunction caused by a combination of detrusor hyperreflexia, anticholinergic effects of medication, and impaired sphincter control.

C. **Multiple sclerosis** produces areas of demyelination in the spinal cord or brain. The site most commonly affected is the cervical spinal cord. Multiple sclerosis is the most important cause of disability in adults between 20 and 45 years old. About 80% of these patients have urologic symptoms. Urinary tract dysfunction tends to correlate with evidence of pyramidal tract dysfunction. Detrusor hyperreflexia is seen in 60% of patients, and about one-third of patients with detrusor hyperreflexia have vesicosphincter dyssynergia. About 20% have detrusor areflexia. The risk for deterioration of the upper tract is less than that in spinal cord-injured patients.

D. **Diabetes mellitus** is associated with peripheral neuropathy, which may affect the bladder and/or sphincters. About 80% of patients with diabetic bladder dysfunction also have other sequelae of diabetes (retinopathy, neuropathy, vascular disease). The classic urodynamic finding in diabetes is detrusor areflexia, but nearly 50% of patients with diabetes have detrusor hyperreflexia rather than areflexia. This may be caused by concomitant cerebrovascular disease. Patients with detrusor areflexia associated with diabetes also have impaired bladder sensation.

VI. Treatment

The goals of treatment in any type of voiding dysfunction are to (a) reverse the pathologic process whenever possible, (b) alleviate symptoms (especially incontinence) when reversal is not possible, and (c) preserve renal function. It is important to remember that a perfect therapeutic result is rarely obtained in treating voiding dysfunction. A practical treatment plan must take into consideration the underlying disease and its prognosis, the patient's desires, and the family support

available to the patient. In most cases, a combination of treatment modes is necessary to achieve satisfactory results.

A. **Detrusor overactivity** can be a debilitating problem, especially when it causes incontinence. Many options are available in treating the overactive detrusor, which suggests that none is completely effective.
   1. **Pharmacologic therapy.** See Table 6-4 for a summary of available agents.
      a. **Anticholinergic agents** continue to be the mainstay of treatment. Side effects common to this group of drugs are dry mouth, blurring of vision, constipation, and drowsiness. Anticholinergic agents may precipitate acute intraocular hypertension and are contraindicated in patients with angle-closure glaucoma. An ophthalmologic consultation should be obtained for all patients with glaucoma before anticholinergic medication is prescribed. The prototype agent is oxybutynin hydrochloride in oral doses of 5 mg three times daily. A 2-mg dose of tolterodine each day is effective, and the incidence of dry mouth is lower than with oxybutynin. **Intravesical oxybutynin** has been used in some patients who fail oral agents because of side effects. Intravesical instillation appears to produce a more tolerable side-effect profile. Five milligrams of oxybutynin is dissolved in 50 mg of saline solution and instilled via urethral catheter. The solution is left in the bladder until it is voided or removed by catheterization 4 hours later.
      b. **Tricyclic antidepressants** have a combination of anticholinergic and sympathomimetic actions. They may have central effects as well. The prototypic agent is imipramine, used in doses varying from 25 mg at bedtime to 25 mg four times daily. The drug may be used alone or in combination with anticholinergic agents. Imipramine is contraindicated in patients receiving monoamine oxidase inhibitors.
   2. **Biofeedback** may work well in motivated patients and can be used as an adjunct to pharmacologic therapy. In one simple biofeedback technique, the patient keeps a chart to record the timing of voiding and amounts voided. The patient receives rewards or encouragement for increasing the time between voiding, along with anticholinergic medication. This is often referred to as a Frewen regimen or “bladder drill.” More complex methods involve auditory or visual feedback to the patient when bladder contraction occurs to enable the patient to learn techniques to suppress contractile activity.
   3. **Electric stimulation** of the vaginal or rectal mucosa can promote urine storage by causing perineal muscle contraction and inhibiting detrusor activity. The stimulation is provided by intravaginal or intrarectal stimulating units.
   4. The use of **augmentation cystoplasty** in the treatment of storage failure has recently become widespread. Cystoplasty is most commonly achieved by placing detubularized ileum as a cap on the bladder to increase its capacity. Reported success rates range from 50% to 80%. Following this procedure, many patients will require intermittent self-catheterization.
   5. **Supravesical urinary diversion** should be considered in patients with intractable incontinence who demonstrate deterioration of the upper tracts from ureterovesical reflux or obstruction. Continent forms of diversion may be appropriate in some cases.

B. **Detrusor underactivity**
   1. **Pharmacologic therapy** of the acontractile detrusor is much less successful than therapy of the overactive bladder. Bethanechol chloride has been used for many years for this purpose because its action is somewhat selective for the bladder and gastrointestinal tract and because it can be given by mouth. Bethanechol is capable of increasing the tension in the bladder wall when given in doses of 50 to 100 mg orally four times daily. However, its ability to produce an effective bladder contraction capable of completely emptying the bladder has never been impressive. It may be useful as an adjunct to other methods, such as the Valsalva maneuver, in emptying the bladder. Side effects includes flushing, sweating, headache, diarrhea, gastrointestinal cramps, and bronchospasm.
   2. **Intermittent catheterization** has been very successful in managing the underactive detrusor. Originally described in patients with spinal cord injury, it may be used to treat a wide variety of voiding dysfunctions. Intermittent catheterization may be combined with anticholinergic agents to promote dryness. One of the most important factors in promoting patient acceptance of self-catheterization is a positive and supportive attitude on the part of physicians and nurses.
      a. **Clean technique.** Most patients can be taught to perform intermittent clean self-catheterization. In male patients, the head of the penis is cleansed with povidone-iodine, hexachlorophene, or plain soap, and a 14F straight catheter is inserted into the urethra. In female patients, the urethral meatus is cleansed and a short 12F female catheter is inserted. Any water-soluble lubricant can be used. The catheters may be cleaned and reused many times. Sterile gloves are not needed. For most patients, the clean technique is the most convenient and cost-effective method of emptying the bladder.
      b. **Sterile technique** is needed only for patients who are immunocompromised or prone to repeated infection. The only difference from clean technique is that a new, sterile catheter is inserted each time and sterile gloves are used to handle the catheter and prepare the skin.
   3. **Valsalva and Crede maneuver** is applicable in most paraplegic patients as long as no significant outflow obstruction is present.

C. **External sphincter dyssynergia** generally should be treated in male patients to prevent deterioration of the upper tract. Paraplegic patients may be treated with anticholinergic agents and intermittent self-catheterization. The same regimen may be used in quadriplegic patients if a family member or personal care attendant is available. For quadriplegic patients who cannot perform intermittent self-catheterization, other options may have to be considered.
   1. **Pharmacologic therapy** is generally not successful. Agents that have been used include baclofen, dantrolene, and diazepam. The use of intrathecal baclofen delivered with a subcutaneous pump has also been reported.
   2. **Urethral stents** have been implanted to treat external sphincter dyssynergia, but long-term results are not available.
   3. **External sphincterotomy** is performed by endoscopic resection of the external sphincter. Bladder neck and prostate resection may be required at the same time. Complications of external sphincterotomy include hemorrhage, stricture, and impotence (5% to 10%). About one-third of patients require a second sphincterotomy to correct poor bladder emptying.

D. **Urethral incompetence** in patients with neurologic disease is treated in much the same way as in other patients.
   1. **Pharmacologic therapy** includes pseudoephedrine hydrochloride in oral doses of 30 to 60 mg up to four times daily and phenylpropanolamine hydrochloride in oral doses of 50 mg three times daily. These drugs act to increase muscular tone at the bladder neck and in the urethra. If detrusor instability is present, an anticholinergic agent may be used concurrently. Sympathomimetic agents should be used with caution in the elderly and in those patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure, or bladder outlet obstruction from prostatic hyperplasia. Phenyl-propanolamine is contraindicated in patients receiving monoamine oxidase inhibitors.
   2. **Sling procedures** may be used in selected female patients with type III incontinence resulting from neurologic disease. The sling is composed of autologous rectus fascia, Marlex, Goretex, or Mersilene. In neurologic patients with bladder paralysis, the tension of the sling is adjusted so that urine will be retained, and the patient performs intermittent self-catheterization to empty the bladder. The major complications are operative injury to the urethra or bladder and delayed erosion of the sling into the urethra.
   3. The **artificial urinary sphincter** consists of a periurethral cuff, a pressure-regulating balloon inflated in the prevesical space, and a control valve. In male patients, the cuff can be placed around the urethra (most common) or around the bladder neck and the control valve implanted into the scrotum. In female patients, the cuff is placed around the bladder neck and the control valve is implanted into the labia. Detrusor instability, detrusor hyperreflexia, and diminished bladder compliance are relative contraindications. Approximately one-third of patients require revision of the device at some point. Like all prosthetics, these devices may be complicated by mechanical failure, erosion, displacement, or infection. To reduce the risk for urethral erosion, the device is activated 6 weeks after implantation, when healing has progressed.

Suggested Reading

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Chapter 21 Renal Failure and Dialysis

Ricardo Munarriz and Gennaro Carpinito

The urologist is frequently required to manage a patient with acute or chronic renal failure. Most commonly, the urologist is asked to evaluate a patient who has acute oliguria, increased serum creatinine, or both, and the role of the urologist is to rule out a correctable obstruction. Less often, urologic surgery is required in a patient known to have chronic renal insufficiency. In both circumstances, an understanding of acute and chronic renal failure is essential to proper patient management.

I. Renal Function Tests

A. **Glomerular filtration rate (GFR).** This is one of the best indicators of renal function and reflects the total filtration of all functioning nephrons. In a normal person, the GFR is about 120 mL/min. Although the best estimate of GFR is obtained by measuring inulin clearance, the creatinine clearance provides an approximate measure that is accurate enough for clinical use. The creatinine clearance overestimates GFR by as much as 20%, especially in the diseased kidney. Creatinine clearance tends to fall with aging, as skeletal muscle mass is reduced. Over relatively short periods of time, the plasma creatinine is inversely proportional to the creatinine clearance; thus, a rise in plasma creatinine from 0.8 to 1.6 mg/dL may indicate a fall of 50% in the GFR. The creatinine clearance C is measured by collecting urine over a predetermined time period (2 hours, 6 hours, 24 hours) and measuring the creatinine content of the urine U, urine volume V, and plasma creatinine P. The creatinine clearance is obtained from the following formula:

$$C(\text{mL/min}) = U(\text{mg/dl}) \times \frac{V\,(\text{mL/min})}{P\,(\text{mg/dL})}$$

To obtain the correct value for creatinine clearance, attention must be paid to the units in the preceding equation. If the laboratory does not report urine creatinine in milligrams per deciliter, the figure must be converted to these units. The total urine volume must be converted to milliliters per minute by dividing the volume (milliliters) by the collection period (minutes).

B. **Tubular function** is best evaluated by testing the concentrating and diluting ability of the kidney. Under conditions of water deprivation, the normal kidney can concentrate the urine to 1,200 mOsm or a specific gravity of 1.030. Concentrating ability tends to decline with age after 45 years. Under conditions of water diuresis, the urine can be diluted to 75 mOsm or a specific gravity of 1.003.

II. Acute Renal Failure

A. **Definition**. Acute renal failure is a sudden renal deterioration over a period of hours to days, resulting in the failure to maintain fluid and electrolyte homeostasis and excrete nitrogenous waste products. Acute renal failure can also be defined as an increase in serum creatinine of more than 0.5 mg/dL, an increase of more than 50% over the baseline value, or a decrease in creatinine clearance of 50%.

B. **Oliguria** is defined as a urine output of 400 mL/24 h or less; it typically occurs in acute renal failure but is not an invariable finding. **Anuria** (total cessation of urine output) is rare. It is important to remember that oliguria is a relative state that depends on the patient's fluid intake and renal concentrating ability. In the face of poor concentrating ability, even a rate of 1,000 mL/24 h may not be sufficient to remove body wastes. Urine volumes of 500 mL/24 h or more are noted in about 25% of patients with acute renal failure.

C. **Classification**. The most useful classification system recognizes acute renal failure caused by prerenal, renal, and postrenal factors (Table 21-1).

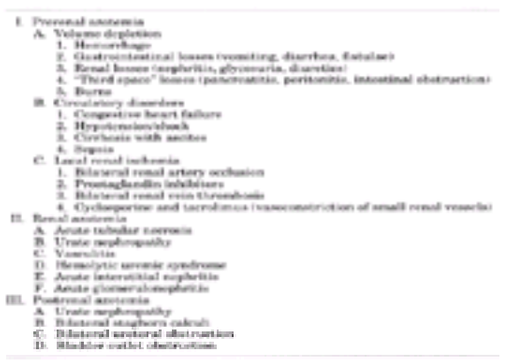
I. Prerenal azotemia
A. Volume depletion
1. Hemorrhage
2. Gastrointestinal losses (vomiting, diarrhea, fistulae)
3. Renal losses (nephritis, glycosuria, diuretics)
4. "Third space" losses (pancreatitis, peritonitis, intestinal obstruction)
5. Burns
B. Circulatory disorders
1. Congestive heart failure
2. Hypotension/shock
3. Cirrhosis with ascites
4. Sepsis
C. Local renal ischemia
1. Bilateral renal artery occlusion
2. Prostaglandin inhibitors
3. Bilateral renal vein thrombosis
4. Cyclosporine and tacrolimus (vasoconstriction of small renal vessels)
II. Renal azotemia
A. Acute tubular necrosis
B. Urate nephropathy
C. Vasculitis
D. Hemolytic uremic syndrome
E. Acute interstitial nephritis
F. Acute glomerulonephritis
III. Postrenal azotemia
A. Urate nephropathy
B. Bilateral staghorn calculi
C. Bilateral ureteral obstruction
D. Bladder outlet obstruction

Table 21-1. Causes of acute renal failure

1. **Prerenal azotemia** results from hypoperfusion of the kidneys and may be caused by a wide variety of conditions (Table 21-1). A fall in systemic blood pressure or plasma volume from any cause leads to the release of norepinephrine and angiotensin in an attempt to maintain the perfusion of vital organs such as the heart and brain. Renal vasoconstriction leads in turn to a decreased GFR and azotemia. Thus, it is important to realize that renal ischemia may be present even in the face of normal systemic blood pressure. A rise in blood urea nitrogen (BUN) and plasma creatinine may be the only manifestation of renal hypoperfusion. BUN may be elevated out of proportion to creatinine. The renal tubules respond to a lowered GFR by increasing the absorption of sodium and water. Renal hypoperfusion may also be present in cardiac failure and cirrhosis with ascites. In advanced hepatic cirrhosis, a progressive decline in renal function, termed hepatorenal syndrome, may occur.
2. **Renal azotemia.** The most common cause of acute renal failure from intrinsic renal disease is acute tubular necrosis. The pathophysiology of acute tubular necrosis is poorly understood, but it is known that necrosis of renal tubules with plugging of their lumina by necrotic debris plays a major role. The two most common causes of acute tubular necrosis are ischemia and nephrotoxic drugs (Table 21-2). Other causes of acute renal azotemia are listed in Table 21-1. Acute tubular necrosis is generally considered to have three phases:

Aminoglycosides
Anesthetics
Iodinated contrast media
Nonsteroidal antiinflammatory agents

Table 21-2. Drugs associated with acute renal failure

a. The **oliguric phase** usually begins within 24 hours after an acute renal insult, such as ischemia or administration of nephrotoxic agents. The onset of acute tubular necrosis is much more insidious with aminoglycoside toxicity; typically, a rise in plasma creatinine becomes apparent only after 7 or more days of drug administration. Patients who continue to produce reasonable amounts of urine despite a progressive rise in plasma creatinine and BUN are said to have nonoliguric acute tubular necrosis. The maintenance of normal urine output in some patients with acute tubular necrosis may be caused by a less marked fall in GFR or an increased degree of tubular dysfunction leading to diminished concentrating ability. The first appears more likely; patients with nonoliguric acute tubular necrosis have been shown to have a better prognosis overall than patients with oliguria. The average duration of the oliguric phase is about 10 days but is extremely variable.
b. The **diuretic phase** heralds the start of recovery of renal tubular function. A noticeable increase in daily urine output is accompanied by a stabilization or slow fall in plasma creatinine. Although urine output improves, renal concentrating ability and resorption are far from normal, and large losses of sodium, potassium, or both can occur, but this is rare.
c. The **recovery phase** may last from 3 to 12 months, during which GFR and tubular function gradually improve to nearly baseline levels.

3. **Postrenal azotemia** refers to obstruction in the collecting ducts, renal pelvis, ureter, or bladder outlet. A variety of causes must be considered, depending on the age and sex of the patient (Table 21-3). With acute obstruction, hydrostatic pressure in the collecting system rises and leads to a fall in GFR. Initially, tubular function tends to be preserved. After a period of about 4 weeks, the pressure in the collecting system gradually returns to normal as the GFR falls and lymphatic channels of egress from the renal pelvis become established. Despite the fall in intrapelvic pressure, dilatation of the collecting systems tends to persist, presumably because of loss of smooth-muscle tone from chronic overdistention. With established obstructive uropathy, tubular function becomes impaired, leading to renal salt wasting, decreased concentrating ability, and polyuria. Thus, partial obstruction may be associated with normal urine output accompanied by azotemia. Complete anuria occurs only in the presence of complete obstruction. In general, complete recovery of function occurs after obstruction lasting less than 2 weeks, and little or no recovery occurs after 12 weeks. In intermediate cases, the prognosis depends on the level of preexisting renal function and the presence of additional insults, such as infection.

Children
Posterior urethral valves
Bilateral ureteropelvic junction obstruction
Renal agenesis
Meatal stenosis
Neurogenic bladder (myelodysplasia)
Adults
Pregnancy
Retroperitoneal neoplasms
Bilateral calculi
Neurogenic bladder dysfunction
Impaired detrusor contractility
Benign prostatic hypertrophy
Prostate cancer
Gynecologic malignancies

Table 21-3. Major causes of postrenal azotemia

D. **Differential diagnosis of acute oliguria.** Acute or chronic urinary retention should be ruled out by physical examination or urethral catheterization. If urethral access to the bladder is not possible in a patient with bladder distention, ultrasonography (US) of the bladder can be performed. If no evidence of bladder distention is found, the diagnosis of prerenal azotemia and acute tubular necrosis should be considered, which together account for 75% of all patients with acute renal failure. Examination of the urine under the microscope and urine chemistry studies will allow differentiation of these two conditions in many instances (Table 21-4). These indices are most useful in patients with oliguria and less definitive in patients with nonoliguric renal failure. A therapeutic trial of fluid replacement is probably the most important test in this situation. If no diuresis is observed, renal causes (most likely acute tubular necrosis) or bilateral ureteral obstruction should be considered. A plain film of the abdomen may reveal the presence of urinary calculi. Renal US is extremely useful in identifying the presence of obstruction. Retrograde pyelography is sometimes indicated, even in the presence of normal renal US results, if ureteral obstruction is suspected clinically. This is because the fornix may rupture in an acutely obstructed kidney and reduce the degree of hydronephrosis.

	Sodium (mEq/L)	Osmolality (mOsm)	Urine/plasma creatinine (mg/dl)
Prerenal	<20	>500	>20
Renal	>40	<350	<20
Postrenal			
Acute	<20	>500	>20
Chronic	>40	<350	<20

Table 21-4. Differential diagnosis of acute renal failure

E. **Treatment of acute renal failure.** In many patients, it is not possible to establish whether acute renal failure is caused by hypovolemia or acute tubular necrosis before treatment is started. The treatment of acute renal failure should be focused on reversing the underlying cause, preventing further renal injury, correcting fluid and electrolyte imbalances, and providing supportive measures until renal recovery has occurred. Whether renal failure is caused by hypovolemia or acute tubular necrosis, the initial therapy in acutely oliguric patients should be aggressive fluid repletion. In patients with normal serum sodium levels and no evidence of congestive heart failure, it is generally safe to give half-normal saline solution at a rate of 500 mL/h. If oliguria persists after administration of 500 to 1,000 mL of fluids, a loop diuretic such as furosemide (200 mg intravenously) or an osmotic diuretic such as mannitol (25 gm intravenously) should be given. A presumptive diagnosis of prerenal azotemia can be made if these maneuvers produce a persistent diuresis. It should be remembered, however, that a loop diuretic may also produce diuresis in some cases of acute tubular necrosis. The difference is that in prerenal azotemia, renal function should return to nearly normal levels within 48 to 72 hours after correction of hypovolemia. In acute tubular necrosis, no significant improvement in renal function will occur despite adequate fluid repletion or increased urine output. Treatment of established renal failure caused by acute tubular necrosis is largely supportive. Nephrotoxic drugs should be discontinued or avoided. Hyperkalemia can be treated with hydration, oral or rectal binding resins, or the intravenous administration of glucose and insulin. Metabolic renal acidosis may be corrected with sodium bicarbonate. A low-protein diet with additional calories is generally recommended in renal failure and should be ordered in consultation with the dietitian. Anemia is a common finding and is often secondary to decreased production of erythropoietin, decreased red blood cell survival, and phlebotomy. Bleeding disorders secondary to uremia can be reversed with blood products, estrogens, or vasopressin analogs. Patients with severe and prolonged acute renal failure are best treated by peritoneal dialysis or hemodialysis. The overall mortality rate of acute tubular necrosis is approximately 80% (Table 21-5). Continuous therapies with venovenous access and more permeable membranes may facilitate fluid removal in

critically ill patients with acute renal failure.

Type	Mortality (%)
Oliguric	
Postoperative	60
Medical disease	40
Nonoliguric	30

Table 21-5. Mortality rate of acute tubular necrosis

III. Chronic Renal Failure

A. **Definition.** Chronic renal failure is defined as an established, slowly progressive decrease in GFR and tubular function. Generally, the term chronic renal failure is applied in cases of renal failure of more than several months' duration. The most common causes are diabetic nephropathy, hypertension, and glomerulonephritis (Table 21-6).

Diabetic nephropathy
Hypertension (nephrosclerosis)
Glomerulonephritis
Hereditary renal disease
Polycystic kidney disease
Alport's syndrome
Obstructive uropathy
Interstitial nephritis
Chronic pyelonephritis

Table 21-6. Causes of chronic renal failure

B. **Clinical findings** in chronic renal failure are caused by uremia itself and by compensatory mechanisms that attempt to restore water and electrolyte balance.
   1. **Constitutional symptoms** are usually the first to appear in chronic renal failure. Patients often complain of fatigue, lack of energy, and insomnia.
   2. **Gastrointestinal symptoms** are common in chronic renal failure and include anorexia, nausea, and vomiting. These symptoms tend to improve with dialysis.
   3. **Cardiovascular changes** include pericarditis, congestive heart failure, and hypertension. Pericarditis is an indication for immediate, aggressive dialysis. Dialysis usually reverses pericarditis within 1 to 2 weeks. Cardiovascular complications are a common cause of death in dialysis patients; for example, cerebrovascular accidents account for 30% of deaths in dialysis patients under the age of 50.
   4. **Hematologic changes** are common in chronic renal failure and include anemia and coagulopathy. Both of these may complicate surgical therapy in uremic patients. Anemia is caused by a relative lack of erythropoietin, decreased red cell survival, and phlebotomy. A platelet dysfunction, usually correctable by dialysis, accounts for the bleeding tendency observed in 60% of patients with chronic renal failure.
   5. **Neurologic changes** include both encephalopathy and peripheral neuropathy. Early encephalopathy in uremia may manifest as impaired mental concentration, insomnia, and emotional lability. Later, disorientation and confusion may develop, progressing to coma. Uremic encephalopathy often is accompanied by tremor and asterixis. The mental changes disappear rapidly with dialysis. Uremic polyneuropathy usually presents as sensory changes, particularly paresthesias, and later progresses to motor weakness. The sensory changes are usually reversible by dialysis, but the motor neuropathy is less reversible. The appearance or worsening of motor neuropathy is usually considered an indication to begin or increase the frequency of dialysis. Autonomic neuropathy is common in chronic renal failure, accounting for postural hypotension and erectile dysfunction. Dialysis does not restore potency, however, which suggests that other factors, such as vascular disease and decreased libido, are involved.
   6. **Endocrine changes.** Depression of plasma testosterone, oligospermia, and elevation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are common in male dialysis patients and consistent with primary testicular failure. Amenorrhea is very common in female patients. Successful renal transplantation often reverses these changes.
   7. **Renal osteodystrophy** is a consequence of either (a) secondary hyperparathyroidism induced by hyperphosphatemia, hypocalcemia, deficient production of calcitriol, and skeletal resistance to parathyroid hormone or (b) low-turnover bone disease generally associated with aluminum retention from aluminum-containing binders. Renal osteodystrophy manifests radiologically as subperiosteal bone resorption, best seen in the bones of the fingers. Clinical findings include bone pain and pathologic fractures. Metastatic calcification may occur in dialysis patients and lead to calcium deposits in peripheral vessels, around joints, and in the myocardium.
   8. **Acquired cystic kidney disease** is a disorder recently recognized to occur in up to 40% of patients with chronic renal failure, especially but not exclusively in those undergoing hemodialysis for longer than 3 years. Small, multiple cysts develop in both kidneys and may cause hematuria or retroperitoneal hemorrhage. More importantly, the incidence of renal adenocarcinoma is increased in patients with acquired cystic kidney disease to between 4% and 10%. Although most of these tumors are of low malignant potential and rarely metastasize, patients with acquired cystic kidney disease should be followed with yearly renal US to detect any new growths.
   9. **Erectile dysfunction** may be secondary to hormonal or vascular changes and to anemia.

C. **Treatment of chronic renal failure.** Only selected aspects of treatment that are relevant to urologic practice are discussed.
   1. **Anemia.** A normochromic, normocytic anemia is very common in chronic renal failure. In most dialysis patients, the hematocrit is between 15% and 30%; however, only about 25% of patients are symptomatic and require regular transfusions. Patients with angina pectoris or other signs of ischemia should be treated with transfusions of packed red cells until adequate oxygen-carrying capacity is restored. Treatment with recombinant human erythropoietin, a newer form of therapy now widely available, often increases the hematocrit within a few weeks.
   2. **Coagulopathy.** The bleeding time is prolonged in approximately 50% of patients with chronic renal failure. Although there is no simple relationship between the degree of azotemia and the degree of coagulopathy, circulating antibodies that interfere with platelet function are probably present. Another factor is the anemia commonly present in chronic renal failure. Simply raising the hematocrit to 30% will improve the bleeding time in many patients, presumably by increasing platelet-endothelial cell interaction. Several treatment options are available for patients being prepared for surgery or other invasive procedures.
      a. **Dialysis** is effective in more than two-thirds of patients. Either hemodialysis or peritoneal dialysis may be used. In patients already undergoing dialysis, increased frequency of treatment may be indicated. The efficacy of dialysis is one of the arguments supporting the presence of a circulating platelet toxin.
      b. **Administration** of 1-deamino-8-d-argininevasopressin (desmopressin) improves bleeding time within 1 hour of infusion, and the effect lasts up to 8 hours. The dose is 0.3 µg/kg dissolved in 50 mL of normal saline solution given intravenously over 30 minutes. The mechanism appears to involve release of factor VIII from endothelial cells.
      c. **Cryoprecipitate** appears to act by improving platelet adhesion to endothelial cells. The onset of action is at 12 to 24 hours and the effect lasts up to 24 hours. The usefulness of this mode of therapy is limited by the risk for transmitting hepatitis and acquired immuno-deficiency syndrome (AIDS).
      d. **Transfusions** may correct the coagulopathy if the hematocrit remains above 30%. This form of therapy carries risks for transmission of infectious disease and requires at least several hours to accomplish in most cases.
      e. **Estrogens.** Conjugated estrogens given intravenously in a dosage of 0.6 mg/kg per day for 5 days may be used if a delay in onset of action is acceptable. The onset occurs within 6 hours, but the effect does not reach a peak until the fifth day. The duration may be as long as 2 weeks. The mechanism of action is unknown.
   3. **Protein restriction** (0.6 to 0.7 g/kg per day) will reduce the accumulation of nitrogenous waste products. Adequate caloric intake (30 to 50 kcal/kg per day) is strongly recommended to avoid catabolism of endogenous protein. Consultation with a dietitian is beneficial in the management of these patients.

4. **Potassium** should be restricted to 40 mEq/d when the GFR falls below 20 mL/min.
5. **Sodium restriction** should be individualized, but in general a diet with “no added salt” is adequate.
6. **Fluid intake** in stable patients should equal the daily urine output plus 500 mL for insensible losses.
7. **Acidosis** may be treated when indicated with oral sodium bicarbonate (300 to 600 mg three times daily).
8. **Renal osteodystrophy** is a complex problem and may require correction of hyperphosphatemia and hypocalcemia, management of aluminum toxicity, and (occasionally) parathyroidectomy.

IV. Dialysis

A. **Definition.** Dialysis is any process that changes the concentration of solutes in the plasma by exposure to a second solution (the dialysis solution) across a semipermeable membrane.

B. **Indications for dialysis** are summarized in Table 21-7. In many instances, clinical judgment must be used in deciding whether it is appropriate to initiate dialysis. In contrast-induced acute tubular necrosis, for example, dialysis is usually not necessary, even in symptomatic patients, because renal function typically begins to recover within 5 days. In postischemic acute tubular necrosis, however, many feel that dialysis should be started even in asymptomatic patients when the BUN reaches 100 mg/dL because many weeks may pass before recovery occurs.

Indications	Contraindications
Pericarditis	Irreversible dementia or coma
Altered mental status	Hepatorenal syndrome
Prolonged bleeding time	Advanced malignancy
Neuropathy	
Hyperkalemia	
Acidosis	
Fluid overload	
Drug overdose	
Urea nitrogen >100 mg/dL or	
Creatinine clearance <0.10 mL/min/kg body weight	

Table 21-7. Indications and contraindications for dialysis

C. **Peritoneal dialysis versus hemodialysis.** Both forms of dialysis are effective when properly used. Hemodialysis achieves more rapid clearance of the plasma and is especially useful in treating hyperkalemia, fluid overload, and drug overdoses. Peritoneal dialysis is preferred in patients who cannot tolerate hypotensive episodes or the heparinization required to perform hemo-dialysis. In many cases, the choice is a matter of patient preference based on the significant advantages of peritoneal dialysis over hemodialysis (Table 21-8). Contraindications for peritoneal dialysis are listed in Table 21-9.

Advantages
Portability, safety
Fewer symptoms
Fewer medications
Higher hematocrit
No routine anticoagulation
Better control of parathyroid hormone levels
Disadvantages
Increased risk of infection, malnutrition, hypertriglyceridemia
Less efficacious
Catheter-related problems
Potential pulmonary complications

Table 21-8. Advantages and disadvantages of peritoneal dialysis

Absolute
Peritoneal fibrosis
Pleuroperitoneal fistula
Relative
Presence of colostomy or nephrostomy
Cardiac prosthesis (e.g., valve)
Fungal or tuberculous peritonitis
Inguinal or abdominal hernias
Obesity
Peripheral vascular disease
Hyperlipidemia
Diverticulosis
Polycystic kidney disease
Mental or physical incapacity

Table 21-9. Contraindications for peritoneal dialysis

D. **Peritoneal dialysis** is performed by introducing 1 to 8 L of a dextrose-containing dialysis solution into the peritoneal cavity. The peritoneum acts as a semipermeable membrane, and the dextrose creates an osmotic gradient with respect to plasma. The length of time the dialysate remains in the peritoneal cavity is called the **dwell time**. Access to the peritoneal cavity is most commonly achieved via a surgically implanted catheter. As in hemodialysis, small molecules such as urea diffuse rapidly, whereas larger protein molecules diffuse slowly, if at all. Hemodialysis membranes are more efficient at excluding proteins, and in general more protein is lost in peritoneal dialysis than in hemodialysis.

1. **Peritoneal dialysis solutions** closely approximate normal plasma in respect to electrolyte concentrations. Although many commercial solutions are available, most contain sodium chloride, sodium lactate, calcium chloride, and magnesium chloride. Dextrose is added to provide an osmotic gradient, and lactate or acetate is added as a source of bicarbonate (Table 21-10).

	Hemodialysate	Peritoneal dialysate
Glucose (g/dL)	0–0.20	1.4–3.9
Sodium (mmol/L)	140	132
Potassium (mmol/L)	2.0	0
Calcium (mEq/L)	2.5	1.5–3.5
Magnesium (mEq/L)	0.5	0.5–1.5
Chloride (mEq/L)	105	96–102
Lactate (mEq/L)	—	35–40
Bicarbonate (mEq/L)	35–40	—

Table 21-10. Composition of hemodialysate and peritoneal dialysate solutions

2. **Dialysis schedules.** Peritoneal dialysis is commonly administered according to one of four schedules.
   a. **Acute dialysis** is achieved by instilling and draining dialysate every ½ to 2 hours over a 2- to 3-day period.

b. **Chronic intermittent peritoneal dialysis** involves a short dwell time (30 minutes) repeated over 8 to 10 hours per session. The dialysate is infused and drained with a cycle machine. Three to four sessions per week are usually required. The abdomen contains no dialysate between sessions.
c. **Continuous ambulatory peritoneal dialysis** is carried out by the patient by means of gravity infusion and drainage. Dialysate is always present in the abdomen and is exchanged three to five times daily.
d. **Continuous cycled assisted peritoneal dialysis** is similar to chronic intermittent dialysis except that dialysis takes place overnight while the patient sleeps. Fresh dialysate is left in the abdomen during the day.

3. **Complications**
   a. The most important complication of peritoneal dialysis is **peritonitis**, which should be suspected in any patient undergoing peritoneal dialysis in whom abdominal pain, nausea, vomiting, or diarrhea develops. The peritoneal fluid becomes cloudy, and Gram's stain will reveal the presence of bacteria. Approximately 70% of instances are caused by gram-positive organisms (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus* species), and coli-forms account for most of the remainder. Five percent of the infections are fungal and are caused by *Candida albicans*, *Nocardia asteroides*, *Aspergillus* species, and *Mycobacterium*. The treatment of these infections is based on immediate abdominal lavage with rapid flushes of dialysate fluid, empiric administration of intraperitoneal antibiotics (Table 21-11), and empiric administration of broad-spectrum systemic antibiotics depending on the results of peritoneal Gram's stain until definitive cultures and sensitivities are obtained. Generally, the peritoneal catheter can remain in place in cases of bacterial peritonitis, whereas fungal peritonitis almost always requires removal of the peritoneal catheter. Other indications for catheter removal are infection by *Pseudomonas* species, persistence of symptoms, and failure of dialysate cell count to decline.

Gram-positive	Vancomycin alone
Gram-negative	Aminoglycoside alone or third-generation cephalosporin
Mixed organisms	Vancomycin + aminoglycoside + metronidazole
Gram stain-negative	Vancomycin + aminoglycoside
Fungal infections	Fluconazole IP or amphotericin IPTV

Table 21-11. Empiric regimens for peritonitis

b. **Obesity** may result from absorption of glucose in the dialysis solution across the peritoneal membrane.
c. **Protein loss** averaging 9 g/d can occur in peritoneal dialysis. Both protein loss and hyperglycemia can be addressed by attention to dietary intake. Other metabolic complications include hyperosmolar nonketotic coma, hyperkalemia or hypokalemia, hyperlipidemia, metabolic alkalosis, and sodium imbalances.
d. **Mechanical problems** include pain with inflow or outflow, fluid leakage, poor outflow drainage, and scrotal edema.
e. Atelectasis, hydrothorax, and aspiration pneumonia are the most common pulmonary problems seen in patients undergoing peritoneal dialysis.
f. The most common cardiovascular complication is fluid overload, followed by hypertension and dysrhythmias.

E. **Hemodialysis** requires access to the bloodstream and use of a hemodialysis machine. The hemodialysis machine pumps blood from the patient through a dialysis cartridge. In the dialyzer, the patient's blood is exposed to the dialysis solution across a semipermeable membrane. The blood is then pumped back to the patient through a return circuit. Treatment schedules are typically 3 to 5 hours three times a week. Despite the many technical advances in hemodialysis technology, patients undergoing this treatment continue to have a mortality rate of 5% to 10% while on maintenance dialysis.
   1. **Vascular access.** Temporary access for patients requiring acute dialysis may be obtained through a percutaneous venous cannula placed into the subclavian, jugular, or femoral vein. This form of access should be replaced by a more permanent form as soon as possible. The two most common forms of permanent vascular access are the arteriovenous fistula and the prosthetic shunt (Fig. 21-1).

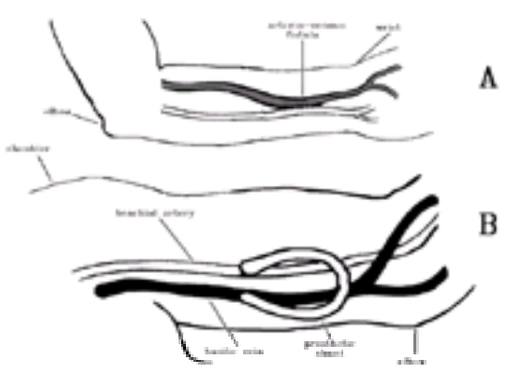

FIG. 21-1. Two common forms of vascular access for dialysis.

   a. **Arteriovenous (Cimino-Brescia) fistula** involves anastomosis of the cephalic vein and radial artery. Such a fistula usually requires 3 to 6 weeks to mature before it can be used for dialysis. The long-term patency rate is high (75% at 2 years), although revisions and declotting of the fistula may be required periodically in many patients. In many cases, permanent vascular access becomes difficult or impossible once all the veins in the forearm have been used.
   b. A **prosthetic fistula or shunt** made with a Goretex graft can be used to connect an artery and vein in the upper arm. Such artificial grafts can be used for dialysis immediately if necessary, but a period of maturation and healing should be allowed whenever possible. Such a shunt has a patency rate of 30% at 2 years; the most common cause of shunt failure is intimal hyperplasia, resulting in stenosis of the venous anastomosis.
   c. **Occlusion and thrombosis of vascular access** is suspected by loss of pulsation in an arteriovenous fistula or high pressure in the venous line during dialysis. Fistulography may be performed to identify the site of occlusion. A percutaneous transluminal angioplasty may be successful in correcting the problem. A thrombosed access site may be cleared with urokinase injection. If these maneuvers are unsuccessful, surgical reconstruction of the site is necessary.
   d. **Infection of vascular access site** is usually manifested by fever with little or no sign of local inflammation. Broad-spectrum antibiotics should be administered until the results of blood culture are available. If a rapid response is not obtained, the vascular access should be removed or ligated.

   2. **Dialysis solutions** typically contain sodium, potassium, calcium, magnesium, chloride, and bicarbonate or acetate (Table 21-10). The potassium concentration is somewhat lower than in plasma, phosphorus is absent, and bicarbonate is higher than in plasma, resulting in removal of potassium and phosphorus from the bloodstream with the addition of bicarbonate. In instances of acute hyperkalemia, solutions containing little or no potassium can be used to hasten removal of potassium from the bloodstream.
   3. **Complications**
      a. The **disequilibrium syndrome** consists of headache, nausea, confusion, or seizures during or soon after hemodialysis. It is thought to be caused by removal of urea more rapidly from the extracellular fluid than from the brain, leading to cerebral edema. The problem can be managed by infusion of mannitol or reduction of the rate of dialysis.
      b. **Hypotension** occurs during up to 50% of dialysis treatments and is usually caused by volume depletion; it can be corrected by administration of intravenous fluids.
      c. **Muscle cramps** are common during high-volume hemodialysis. Common therapeutic approaches include fluid restriction, stretching exercises, and administration of quinine sulfate.
      d. **Arrhythmias** are generally seen in predisposed patients and are often secondary to a combination of factors such as hypoxemia, removal of antiarrhythmic drugs during dialysis, and rapid changes of bicarbonate, sodium, potassium, calcium, and magnesium concentrations.
      e. **Acquired renal cystic disease** develops in approximately 80% of patients with end-stage renal disease who undergo dialysis for more than 3 years.
      f. **Other complications** are bleeding, anemia, transfusion-related diseases, metabolic bone disease, and pericarditis.

F. **Hemofiltration**, first described in 1977, relies on ultrafiltration of solutes across a highly porous, semipermeable membrane. It is occasionally used as a method for treatment of overly hydrated patients who are resistant to diuretics. Large volumes of ultrafiltrate can be generated and replaced by a desired fluid. If

additional clearance is desired, a dialysis circuit can be added to the hemofilter.

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Chapter 22 Renal Transplantation

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Currently, the optimal treatment of end-stage renal disease is renal transplantation. Approximately 200,000 patients are receiving dialysis in the United States while awaiting renal transplantation. Nearly 11,000 kidney transplants are performed annually, of which 4,000 are from living donors and the remainder from cadaveric sources.

I. History of Renal Transplantation

The first successful human renal transplant was performed in 1953. Initially, radiation was used for immunosuppression, followed by 6-mercaptopurine. In the early 1960s, tissue typing was introduced to allow better donor selection.In 1967, Belzer demonstrated the feasibility of organ preservation. In 1978, cyclosporine was first used, and its significant impact on graft survival was demonstrated. Further research in the field of both humoral and cellular immunology has accounted for most of the recent progress in renal transplantation.

II. Immunology of Transplantation

Transplant immunology involves understanding the complex response of the host to an antigen. The initial process requires recognition of the antigen by specific receptors of B cells and T cells. The antigen is presented to a cell, known as a helper T cell, by the antigen-presenting cells of the host. The major histocompatibility (MHC) antigens are responsible for allowing the host to recognize the graft as foreign. These antigens are located on the short arm of chromosome 6 and encode polymorphic cell surface molecules called human leukocyte antigens (HLA). The HLA type is inherited in a mendelian fashion. The HLA types are divided into class I and class II according to cellular location and their structure. The MHC antigens are involved in forming complexes of foreign proteins that can be recognized by T cells.

III. Rejection

The rejection of an allograft is a complex and incompletely understood process. Activation of alloreactive T cells and antigen-presenting cells is crucial. Acute graft rejection is a T cell-dependent process that occurs through either a direct or an indirect pathway. In the direct pathway, cytotoxic T cells, referred to as CD8+ T cells, are involved and lead to early graft rejection by direct cell contact, during which cytoplasmic granules containing cytotoxic substances are released. In the indirect pathway, cells known as CD4+ T cells recognize the donor MHC allopeptides presented by the antigen-presenting cells. Once activated, these cells initiate rejection and destroy the graft by recruiting B cells, which bind to the cell surface of the allograft and destroy the cells by complement-mediated lysis. In addition, cells known as natural killer (NK) cells participate in tissue destruction by producing cytokines and phospholipases.

IV. Etiology of End-stage Renal Disease

In 1995, the prevalence of end-stage renal disease was 967 per million and the incidence was about 253 per million population. The number of patients receiving dialysis increases by 8% to 10% annually. In the United States, 50% of patients are over the age of 65. The common causes of end-stage renal disease are shown in Fig. 22-1. It is important for the transplant surgeon to be aware of the specific original disease leading to end-stage renal disease, as this may affect the long-term survival of the graft and patient (Table 22-1).

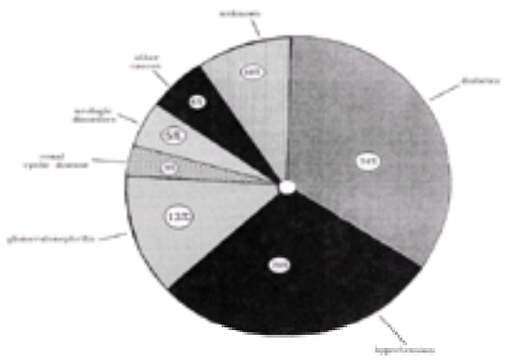

FIG. 22-1. The most common causes of end-stage renal disease.

Glomerulonephritis:	idiopathic Post-infectious Membranous Mesangiocapillary types I and II IgA nephropathy Antiglomerular basement membrane disease Focal glomerulosclerosis Henoch-Schönlein purpura
Metabolic:	diabetes mellitus Hyperoxaluria Cystinosis Fabry's disease Amyloidosis Gout Porphyria
Hereditary:	polycystic kidney disease Medullary cystic disease Alport's syndrome Tuberous sclerosis
Toxic:	analgesic nephropathy Opiate abuse
Systemic:	hypertension Amyloidosis Systemic lupus erythematosis Vasculitis Systemic sclerosis
Tumors:	Wilms' tumor Renal cell carcinoma Urothelial carcinoma Multiple myeloma
Congenital:	Renal hypoplasia Horseshoe kidney Congenital renal absence
Chronic pyelonephritis	
Obstructive uropathy	
Trauma	

Table 22-1. Common indications for renal transplantation

V. Evaluation of the Recipient

The selection of candidates for renal transplantation has recently become more lenient. Today, with advances in critical care and significant reduction in acute and chronic rejection consequent to newer immunosuppressive therapies, the number of potential renal transplant recipients has increased. The accepted age range of recipients is approximately 1 to 70 years.

A. The **pretransplantation workup** of recipients begins with a detailed history and physical examination. Laboratory studies should include a complete blood cell count with differential; measurement of serum electrolytes; liver function tests; determination of prothrombin and partial thromboplastin time and levels of calcium, magnesium, and phosphorus; ABO blood typing; and viral serologies, including titers for toxoplasmosis, rubella, cytomega-lovirus infection, and herpes (TORCH). In addition, the patient should be screened for hepatitis and infection with human immunodeficiency virus (HIV). If the patient is not anuric, a urine specimen should be obtained for analysis and culture. Tissue typing, chest roentgenography, and electrocardiography complete the routine initial evaluation. In certain cases, an echocardiogram, exercise or thallium cardiac stress test, pulmonary function test, and coronary angiogram may be appropriate. A dental evaluation and psychosocial assessment may be indicated. Evaluation of the lower urinary tract is crucial, as the success of the transplant depends on appropriate bladder function and the absence of obstruction (e.g., obstructing prostate, urethral strictures, congenital urethral valves). A voiding cystourethrogram (VCUG) and urodynamic studies are performed to rule out obstruction and determine bladder capacity and compliance. Cystoscopy may be useful as well in selected patients if bladder tumors are suspected. A VCUG is generally avoided in the presence of polycystic kidney disease, for fear of introducing infection.
B. **Immunologic evaluation.** Because the histocompatibility system is based on the ABO blood group and HLA systems, the donor and recipient should be ABO-compatible. ABO incompatibility may result in hyperacute rejection. However, studies have shown that successful transplantation of kidneys from both living and cadaveric sources without ABO compatibility have been performed. This requires removal of anti-A and anti-B antibodies by immunoadsorption, plasmapheresis, or splenectomy. HLA matching is routinely performed to assess the degree of compatibility between donor and recipient. Through the years, it has been observed that transplants between HLA-identical siblings have the longest survival in comparison with mismatched transplants. The survival of one haplotype-matched grafts is second best. Studies have demonstrated the relevance of HLA matching in cadaveric kidney transplants. The rate of loss of allograft is constant after the first year of transplantation. At 8 years, approximately one-half of cadaveric renal transplants are still viable. Perfectly HLA-matched transplants represent only about 7% of cases, but half are still viable at 19 years. However, it has also been observed that the rate of graft survival varies among the different centers, from 60% to 90%. With the development of newer immunosuppressive agents, graft survival will continue to improve.

VI. Preparations for Renal Transplant

A. **Exclusion criteria.** Active malignancy, sepsis, active tuberculosis, severe vasculitis, significant vascular disease, acquired immune deficiency syndrome (AIDS), active hepatitis, recent myocardial infarction, active lupus, extremes of age (less than 1 year and generally over 70 years), and impaired mental function generally preclude transplantation.
B. **Nephrectomy.** Indications for pretransplant nephrectomy include uncontrolled hypertension, renal infection, renal calculi, obstruction of the upper tract, severe ureteral reflux, and renal malignancy. Polycystic kidney disease may require nephrectomy if persistent infection is present or if the sheer size of the native kidneys precludes implantation of the allograft.
C. **Urologic procedures.** Vesicoureteral reflux remains the most common abnormality of the lower urinary tract. This condition may predispose the patient to infection in the native kidneys, especially after transplantation. Reflux can be treated by injecting Teflon or collagen at the ureteral orifice, or by ureteral reimplantation. In cases of prior cystectomy, the ureter of the transplanted kidney may be anastomosed to the existing urinary diversion. Obstructing conditions such as benign prostatic hyperplasia or congenital urethral valves should be corrected surgically.

VII. Living Related Kidney Donor

Living renal transplants offer significant advantages over cadaveric grafts. Living related kidney allografts have been shown to have better survival during the first year. The average “half-life” of a fully matched living related transplant is 25 years. With the advent of newer immunosuppressive agents, however, the gap between cadaveric and living related graft survival continues to narrow. Unfortunately, there is a considerable shortage of cadaveric allografts. On average, it takes 3 to 4 years for a patient on dialysis to receive a kidney allograft. The graft survival of spousal living unrelated transplants is comparable with that of one haplotype-matched living related grafts. In the United States, living related transplants represent 35% of all renal transplants.

A. **Evaluation.** A potential living donor is extensively evaluated (Table 22-2). The evaluation closely parallels that of the recipient, with the addition of a test called a mixed lymphocyte culture, in which lymphocytes from the proposed donor are incubated in serum from the recipient to anticipate a possible rejection episode. Further, imaging of the aorta and renal vessels with angiography allows the surgeon to select the more technically appropriate kidney. Magnetic resonance angiography may soon replace conventional angiography. The left kidney is often chosen because of the extra length of the renal vein.

Complete history and physical examination	
Laboratory:	complete blood count
	HIV, VDRL, CMV, hepatitis C
	glucose tolerance test (if diabetic family history exists)
	urinalysis and urine culture
	pregnancy test (for women)
	24-hour urine for protein and creatinine clearance
Radiologic:	intravenous pyelogram
	renal angiogram
	renal MRI

HIV, human immunodeficiency virus; CMV, cytomegalovirus; VDRL, venereal disease research laboratory; MRI, magnetic resonance imaging.

Table 22-2. Evaluation of living-related kidney donors

B. **Inclusion criteria.** Qualified living donors must have two normally functioning kidneys and are usually between 18 and 65 years of age. One of the most important aspects is the donor's willingness to donate an organ. Every patient should understand the inherent risks of undergoing a nephrectomy under general anesthesia. With 20 years of follow-up, the life expectancy of a donor and that of a person with two native kidneys have not been found to differ.
C. **Exclusion criteria.** Potential donors are excluded if there is any history of hypertension, renal disease, diabetes mellitus, hepatitis, HIV infection, or malignancy (Table 22-3).

Age	<18 or >65 years
Hypertension	>140/90 mmHg
Diabetes	abnormal glucose tolerance test
Urine protein	>250 mg/24 h
Renal stones	positive history
Creatinine clearance	<80 mL/min
Hematuria	present
Obesity	>30% above ideal weight
Medical illness	malignancy, pulmonary or cardiac disease, HIV, hepatitis

HIV, human immunodeficiency virus.

Table 22-3. Exclusion criteria for living-related donors

D. **Living donor nephrectomy.** A flank or transabdominal approach is usually chosen. Recently, laparascopically assisted donor nephrectomy has been reported

to decrease postoperative discomfort and shorten hospital stay. During the operation, great care is taken to preserve even the smallest accessory renal arteries (e.g., branches of the lower pole). Length of the renal vein is maximized to facilitate reimplantation. Careful preservation of the periureteral adventitia helps maintain the ureteral blood supply. Often, diuresis is induced with mannitol and furosemide just before division of the main renal vessels to help avoid acute tubular necrosis.

VIII. Cadaveric Renal Donors

Cadaveric renal transplants account for approximately 65% of all transplants performed.

A. **Criteria for brain death.** Although the laws defining brain death vary from state to state, it is usually defined as the complete and irreversible loss of all cerebral and brainstem functions (Table 22-4). This determination is usually based on a thorough physical examination followed by results of confirmatory diagnostic tests, such as the absence of any response to noxious stimuli. An observation period of 24 hours is often required before the declaration is made. An apnea test is performed by ventilating the patient with 100% oxygen for 10 minutes and then disconnecting the ventilator for 3 to 5 minutes, with oxygen supplied passively through a tracheal cannula. This normally results in hypercarbia, which in turn stimulates spontaneous breathing. After 5 minutes, arterial blood gases are measured and the patient is reconnected to the ventilator. The test result is considered positive if the arterial carbon dioxide tension is greater than 60 mm Hg and no spontaneous respiration is observed during the test. On occasion, an electroencephalogram or measurement of cerebral blood flow (nuclear scan or cerebral angiogram) may be performed. Donor acceptance criteria vary between transplant centers but are usually based on parameters as such as age, weight, ABO compatibility, serology, results of liver function tests, and general health status of the potential donor.

Cerebral unresponsiveness
No response to painful stimuli
Apnea
No spontaneous respiration
Absent brainstem reflexes
Pupillary, corneal, oculocephalic, oculovestibular, oropharyngeal
Confirmatory tests
Electroencephalography, radionuclide brain scan, cerebral angiography

Table 22-4. Criteria for brain death

B. **Preparation of donor.** The donor should be carefully maintained in a hemo-dynamically stable state to facilitate adequate perfusion of the organs. The serum osmolarity is measured at frequent intervals to assess fluid status. An arterial line for continuous monitoring of blood pressure and a central or pulmonary artery catheter can be used to monitor the patient further. The ventilator parameters are monitored by arterial blood gas measurements, and the oxygen saturation is maintained at 100%. As hypothalamic control is lost, wide variations in body temperature may be seen. The core temperature should be maintained above 34°C. Any coagulopathy should be corrected by the use of fresh frozen plasma.
C. **Surgical technique.** A long midline incision from sternal notch to pubis is routinely used. The kidneys are often harvested at the same time that other teams harvest the eyes, heart, pancreas, and liver. The peritoneal contents are examined to rule out any intraabdominal sepsis or neoplasm. The abdominal aorta and inferior vena cava are then exposed by mobilization of the right side of the colon. The pancreas along with the duodenum is retracted upward and the celiac axis exposed. The proximal aorta is freed from surrounding structures for cross-clamping at this segment. The aorta and vena cava are cannulated at a point proximal to their bifurcation (Fig. 22-2), and 300 U of heparin per kilogram of body weight is given intravenously. The aorta and vena cava are cross-clamped. The cold preservation solution is infused through the cannulas. The kidneys are removed *en bloc* with Gerota's fascia intact. The ureter is bluntly dissected along its course and divided at the bladder. The vena cava and aorta are divided in the midline, and the kidneys are separated. Currently, the kidneys are preserved by simple static cold storage.

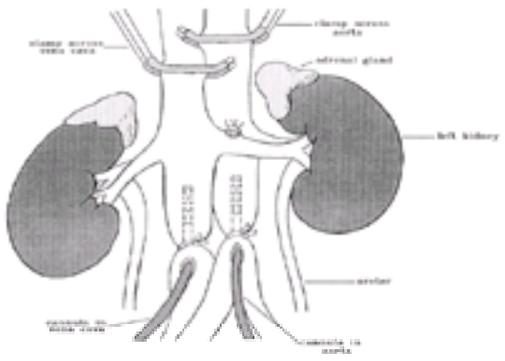

FIG. 22-2. Technique of *en bloc* kidney harvest in cadaveric donor.

IX. Technique of Transplantation

After induction of general anesthesia, the bladder is distended with 100 to 150 mL of a solution containing bacitracin (50,000 U) and 1 g of kanamycin per liter to improve intraoperative identification. A Gibson incision is made either in the right or left lower quadrant. The subcutaneous tissue and the external oblique, internal oblique, and transverse muscles are divided with an electrocautery. The inferior epigastric vessels are divided and ligated. In women, the round ligament can be divided and ligated. The spermatic cord is identified and preserved. The retroperitoneum is entered and the lymphatics over the iliac vessels are ligated and divided to prevent a lymphocele. The transplant kidney is inspected and the vessels prepared for anastomosis. Generally, the renal vein is anastomosed to the external iliac vein, then the renal artery to the internal iliac artery (Fig. 22-3). At completion of the vascular anastomosis, 40 mg of furosemide and 12.5 mg of mannitol is given to initiate diuresis. On release of the cross-clamp, the kidney is expected to be perfused homogeneously and become firm. The ureter is then passed posteriorly to the spermatic cord and anastomosed to the bladder by an extravesical or intravesical (less commonly performed) method. A submucosal tunnel is created by using the overlying detrusor muscle and perivesical pad of fat to prevent reflux. Postoperatively, hemodynamic monitoring is essential to optimize graft function and fluid management. Monitoring of blood pressure is critical, as the initial arterial blood flow to the graft depends on the mean systemic arterial pressure. A pulmonary artery catheter may be required in some patients for the initial 48 hours. Managing blood pressure in these patients is somewhat complicated, as most have long-standing systemic hypertension. High systolic blood pressure in the immediate postoperative period increases the risk for cerebrovascular accidents. On the other hand, reduced arterial blood pressure may increase the risk for acute tubular necrosis in the graft and vascular thrombosis. If the systolic blood pressure is consistently elevated, pharmacologic intervention is required.

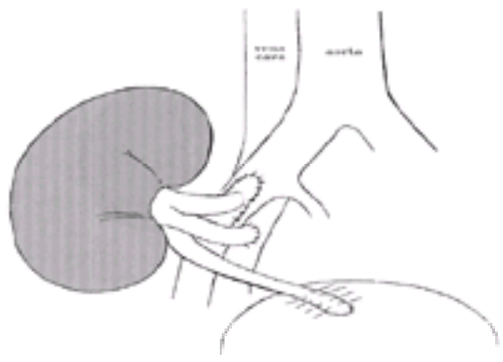

FIG. 22-3. Technique of vascular and ureteral anastomosis in renal transplantation.

A. **Postoperative orders.** Typical postoperative orders are as follows:
   1. Bed rest for 48 hours (patient supine or lying on same side as transplant).
   2. Measure vital signs and input and output every hour for the first 24 hours, then every 4 hours from the second postoperative day.
   3. Nothing by mouth.
   4. Obtain body weight every morning.
   5. Replace fluids intravenously. If urine output less than 200 mL/h, replace hourly output and insensible water loss (5% dextrose in 1/2 normal saline solution at 30 mL/h). If output greater than 200 mL/h, replace 200 mL plus two-thirds of amount of output in excess of 200 mL.
   6. Irrigate Foley catheter with normal saline solution as needed if blood clots are noted in urine or if acute drop in urine output occurs.
   7. Check dialysis fistula every 4 hours.
   8. No blood pressure measurement or intravenous line in extremity with fistula.
   9. Obtain complete blood cell count and measure electrolytes (chem 7) every 6 hours, then every morning.
   10. Determine cyclosporine level every other day.
   11. Perform urine culture twice a week.
   12. Obtain nuclear renal scan on postoperative day 1.
   13. Obtain renal ultrasonogram (US) on postoperative day 5.
   14. Obtain cystogram on postoperative day 5.
   15. Immunosuppression as ordered.

B. **Postoperative care.** The insensible fluid loss is replaced with dextrose solution, and urine replacement should be with 1/2 normal saline solution. A bolus of saline solution can be given to those patients who are assessed to be hypovolemic or euvolemic to increase the urine output. If the urine output declines or stops abruptly, the Foley catheter should be flushed to clear any blood clots. If the patient remains oliguric or anuric, the fluid status should be assessed carefully. If the patient fails to respond to furosemide or volume challenge, further studies are required, including a Doppler scan and US of the graft to assess blood flow and rule out extravasation of urine. The nuclear scan is performed routinely on postoperative day 1 and may be repeated to assess renal function. In patients who become hypotensive, after assessment of fluid status, early postoperative bleeding should be considered. Most hematomas resolve spontaneously and do not require surgical intervention. If generalized bleeding develops secondary to uremia-induced platelet dysfunction, desmopressin acetate can be used. In oliguric patients, postoperative dialysis may be required until the kidney functions. Persistently hyperkalemic patients may also require dialysis. A nuclear scan with ^{99m}Tc-MAG3 (mercaptoacetyltriglycine) is obtained on day 1 to assess the perfusion and function of the graft. A cystogram and US are obtained on day 5. If the cystogram is unremarkable, the Foley catheter is removed. Most patients are discharged to home by postoperative day 6. About 30% to 50% of the cadaveric kidneys function immediately. When graft function is delayed, some studies report that 1-year graft survival is reduced by 20%. Various factors, such as donor age above 55 years, acute tubular necrosis, prolonged duration of graft ischemia, intraoperative hypotension, previous transplants, early use of the monoclonal antibody muromanab-CD3 (OKT3), and high doses of cyclosporine, play a role in delayed graft function. Rejection episodes are managed as described in the section on immunosuppression.

X. Complications

The frequency of complications following renal transplantation has been declining during the last two decades. Improvements in surgical technique, diagnostic methods to identify these problems, and better immunosuppressive agents are likely responsible.

A. **Vascular complications.** The overall reported incidence ranges between 6% and 30%. Arterial complications are more frequent than venous complications.

   The incidence of renal artery thrombosis, which manifests by abrupt anuria in a previously well-functioning allograft, is about 1%. Other causes, such as an occluded Foley catheter or prerenal azotemia, should be excluded before a renal scan is obtained. Delay in diagnosis results in a 50% to 60% mortality rate secondary to occult sepsis. Renal artery thrombosis is attributed to technical problems such as dissection or an intimal flap, occlusion resulting from technique or atherosclerotic vessels, or kinking or torsion of the vessels.

   Renal artery stenosis may be caused by occlusive atherosclerotic disease or intimal hyperplasia of the recipient or donor artery. The reported incidence varies from 2% to 10%. Renal artery stenosis manifests by refractory hypertension, decline in renal function of the allograft, and an audible bruit over the allograft. Several imaging modalities are available to evaluate and diagnose the stenosis. These include a duplex scan, captopril scan, and digital subtraction angiography. The sensitivity of these studies varies from 50% to 80%. Arteriography remains the gold standard for confirming the diagnosis. Treatment options include percutaneous transluminal angioplasty and surgical revision.

   Renal vein thrombosis is a rare complication following renal transplantation, with a reported incidence of 0.3% to 4%. Thrombosis of the renal vein results in irreversible graft damage. The signs and symptoms include graft swelling and pain or tenderness over the graft, hematuria, and oliguria. Diagnosis can be made by duplex sonography or renal scintigraphy. However, it is difficult to differentiate renal vein thrombosis from acute rejection based on these studies, as the findings are similar for both conditions. Most often, renal vein thrombosis is diagnosed at exploration. Successful recovery of graft function with infusion of streptokinase has been reported.

   Vascular anastomotic disruption is a rare complication following transplantation that may result from mycotic aneurysm or infection of the anastomosis. Technical factors such as overt tension on the anastomotic site, missed arterial or venous laceration, or disrupted ligature after the transplant may be responsible. This condition manifests with symptoms of hemorrhage and back pain. Operative exploration for possible salvage of the graft is required. However, repair is associated with a high rate of rebleeding, and most often nephrectomy is required. A mortality rate of 35% to 50% has been reported.

B. **Ureteral complications.** Ureteral complications can be classified according to whether they are caused by leakage or obstruction. The donor ureter depends solely on the hilar vasculature of the graft for its blood supply. The donor ureter should be handled with care to prevent devascularization, from the time of donation to the time of implantation. Ureteral leakage from the hilum or anastomotic site occurs in from 3% to 10% of cases. This is usually secondary to tension at the anastomosis, which causes ischemia of the distal segment. Less likely are changes in the ureter resulting from rejection. These patients usually have a wide variety of symptoms, such as pain and swelling of the graft, fever, oliguria, elevated serum creatinine, cutaneous drainage, or sepsis. US may identify peritransplant fluid collections in about 67% of patients. Percutaneous antegrade pyelography has a sensitivity of 85%. Management depends on the site and amount of the fluid collection. Percutaneous drainage with ureteral stenting may be adequate. Surgical exploration and correction of the problem ensure good drainage and reduce the risk for development of sepsis. Depending on the findings, either revision of the anastomosis with an indwelling stent or a diverting nephrostomy or creation of a flap by using the recipient's bladder to replace the necrotic ureter may be necessary. The stents are removed 2 weeks after a cystogram demonstrates no extravasation.

   Obstruction of the transplanted ureter without leakage may also be seen. During the early postoperative period, this may be caused by edema of the ureter, hematoma in the wall of the distal ureter, or malrotation or kinking. Obstruction that develops over time is related to fibrosis resulting from chronic ischemia or to extrinsic compression by a lymphocele or a mass. Patients present with oliguria, sepsis, rising creatinine, and graft tenderness. US is useful in making the diagnosis. Antegrade pyelography will delineate the actual site and degree of obstruction. The Whitaker test (see Chapter 19) can be useful in making the diagnosis. Surgical exploration with revision of the ureteroneocystostomy is preferable to percutaneous balloon dilatation.

C. **Bladder complications** usually appear soon after transplantation. Extravasation, a rise in serum creatinine, a palpable suprapubic mass, a tender graft, and dysuria are frequent signs and symptoms. US or cystogram can confirm the diagnosis. Complications are usually managed by surgical repair. Lymphoceles may occur in the pelvis following transplantation. The incidence ranges from 0.6% to 18%. Lymphoceles may develop as a result of inadequate ligation of the lymphatics over the recipient vessels during dissection, or as a result of decapsulation of the kidney transplant. Most lymphoceles are small and resolve spontaneously. Larger lymphoceles may exert pressure on adjacent structures such as the bladder, ureter, iliac vein, or lymphatics. The presence of lymphoceles can be confirmed by US. If resolution does not occur after a period of observation, intervention may be required. US-guided laparoscopic or open drainage is effective in managing lymphoceles.

   Pelvic hematoma may result from uremic coagulopathies, unrecognized minor trauma to the donor hilar vessels, or from the use of heparin intraoperatively and during preoperative dialysis. Symptoms may include pain over the graft site, a palpable mass, and a drop in hematocrit. US is useful in making the diagnosis.

Large, expanding hematomas require surgical intervention. Smaller hematomas may resolve spontaneously.

D. **Infectious and other complications.** Renal transplant patients are at a high risk for infection because of their immunocompromised status. The anti-inflammatory properties of steroids delay wound healing. Other risk factors that predispose to infection include diabetes mellitus, hepatitis B and C, leukopenia, splenectomy, and the use of cadaveric organs. The incidence of posttransplant infectious complications has decreased during the past several years. It is known that recipients are at a higher risk for common infections as well as opportunistic infections. Opportunistic infections occur from 1 to 6 months postoperatively. Unusual infections with bacteria and slow-growing fungi become clinically apparent between 6 months and 1 year after transplantation. Identification and prophylaxis of infection begin at the time of the transplant evaluation. Patients are screened for active infection and for exposure before transplant to any organisms that could become active following immunosuppression. As described in the section on preoperative evaluation, routine screening is performed for toxoplasmosis, hepatitis, herpes simplex, and infection with Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and HIV. All donors, both living and cadaveric, are screened in the same way. During the operative procedure, patients benefit from administration of intravenous antibiotics. Most commonly, a cephalosporin or penicillin antibiotic is administered to cover *Staphylococcus aureus*. Preoperative bladder washing or instillation has no proven value.

XI. Immunosuppression

At the present time, triple immunosuppression with cyclosporine (Neoral or Sandimmune), prednisone, and mycophenolate mofetil (Cellcept) comprises our standard regimen, although different centers may vary in this regard. Once routinely used, azothioprine has now been largely replaced with Cellcept. The following is a brief overview of the most commonly used immunosuppressive agents.

A. **Cyclosporine.** Derived from a fungus, cyclosporine is available in two forms, Sandimmune and the newer microemulsion form called Neoral. Cyclosporine acts by forming a complex with its cytoplasmic receptor protein cyclophilin, which in turn binds with calcineurin. This impairs expression of critical T-cell activation genes, including those coding for interleukin-2 and its receptor and for the protooncogenes H- *ras* and c-*myc*. The expression of transforming growth factor-b is enhanced by cyclosporine, which again inhibits interleukin-2 and the production of cytotoxic T lymphocytes. Cyclosporine leaves the phagocytic activity of neutrophils intact and does not affect antigen recognition. Cyclosporine is available in both liquid and capsule form. Absorption of cyclosporine is incomplete and varies from patient to patient. Bioavailability is about 35% to 45%. Oral absorption is bile-dependent and therefore varies in patients with diabetic gastroparesis, cholestasis, and malabsorption and in patients who have undergone surgical procedures such as biliary diversion. A steady blood level is reached in about 4 to 8 weeks.

   Neoral is formulated in a microemulsion form and is found to have improved bioavailability. Trough concentrations are more reliable and correlate better with tissue levels. Several studies indicate a 15% reduction in the rate of rejection with cyclosporine. The half-life of cyclosporine is 8 hours, and it is metabolized by the cytochrome P-450 microsomal enzyme system in the liver and gastrointestinal system. It is primarily excreted in bile and does not require dose alteration in the case of renal dysfunction resulting from acute tubular necrosis or rejection. The dose does need to be reduced in the presence of liver disease. Trough levels should be monitored to help avoid toxicity.

B. **Drug interactions.** Drugs that may reduce cyclosporine levels include rifampin, isoniazid, barbiturates, phenytoin, carbamazepine, nafcillin, trimethoprim, sulfadimidine (intravenous), cephalosporins, and imipenem. Drugs that may increase cyclosporine levels include calcium-channel blockers (verapamil, diltiazem, nicardipine). Use of these drugs for hypertension control in the posttransplant period may help to reduce the dosage up to 40%. The antifungal drugs ketoconazole, fluconazole, and itraconazole increase cyclosporine levels significantly. Some centers use this combination routinely to reduce the cost of cyclosporine, and it is possible to reduce the dose up to 80%. Erythromycin, histamine blockers, and hormones (corticosteroids, testosterone, oral contraceptives, norethindrone) all may increase cyclosporine levels. Amphotericin, aminoglycosides, nonsteroidal antiinflammatory drugs, enalapril, metoclopramide, colchicine, cholestyramine, and lovastatin should be used with caution, as they may increase the nephrotoxicity of cyclosporine.

C. **Toxicity.** Nephrotoxicity induced by cyclosporine may be manifested by a wide variety of syndromes (Table 22-5), including acute and chronic decreases in glomerular filtration, acute microvascular disease, worsening of early graft dysfunction, hypertension, hypomagnesemia, hyperchloremic acidosis, hyperuricemia, and gout. It may be difficult to differentiate cyclosporine toxicity from acute rejection (Table 22-6). Other complications may include hepatotoxicity, cholelithiasis, hypertrichosis, hyperlipidemia, impairment of glucose tolerance, tremor, bone pain, headache, and deep venous thrombosis.

Nephrotoxicity
Hypertension
Biochemical effects
Hyperbilirubinemia
Hyperkalemia
Hyperuricemia
Increased alkaline phosphatase
Neurologic effects
Seizure
Tremor
Paresthesias
Miscellaneous
Hirsutism
Anorexia
Nausea
Gingival hypertrophy
Breast fibroadenoma

Table 22-5. Toxicity of cyclosporin A

	Acute rejection	Cyclosporin A
Serum creatinine	>60% rapid increase	<25% slow increase
Intrarenal pressure	elevated	normal
Fever	may be present	usually absent
CsA level	<100 ng/mL	>250 ng/mL

CsA, cyclosporin A.

Table 22-6. Differentiating acute rejection from cyclosporin A nephrotoxicity

D. **Mycophenolate (Cellcept).** Approved in 1995, this drug is a fermentation product of a group of *Penicillium* species. The drug reversibly inhibits the enzyme inosine monophosphate dehydrogenase and exerts a selective antiproliferative effect on lymphocytes. Mycophenolate is found to be effective in treating ongoing rejection and is able to prevent rejection episodes effectively when used in conjunction with cyclosporine and steroids. Diarrhea occurs in about one-third of patients receiving mycophenolate. Esophagitis, gastritis, and gastrointestinal bleeding are observed in 4% to 5% of treated patients. Leukopenia, anemia, and rarely lymphomas occur in fewer than 1% of patients.

E. **Polyclonal antibodies.** Antithymocyte globulin is the only polyclonal antibody currently available in the United States. The monoclonal antibody muromanab-CD3 (OKT3) has been used for the past several years. Antithymocyte globulin is derived from immunizing either horses or rabbits with human lymphoid tissue and then harvesting the g-globulin fractions. Once routinely administered for induction in the immediate posttransplant period, antithymocyte globulin is now used mostly for treating rejection. When it is given intravenously, a drop in the total lymphocyte count is noted as T cells are lysed and driven into the reticuloendothelial system. The usual dose of 10 to 20 mg/kg per day is given for 7 to 14 days through a central vein. The patient will require premedication with 30 mg of prednisone, 50 mg of intravenous diphenhydramine (Benadryl), and 650 mg of oral acetaminophen (Tylenol) 30 minutes before administration of antithymocyte globulin. Vital signs should be monitored every 15 minutes for the first hour and hourly during the infusion. Patients require blood counts every day during the course of treatment. If thrombocytopenia occurs, the dose of antithymocyte globulin should be lowered. During treatment with antithymocyte globulin, cyclosporine can be withheld, and prednisone is given either orally or intravenously as methylprednisolone. Adverse effects may include fever, chills, and arthralgias. Anaphylaxis is rare; serum sickness-like syndromes may occur during the course of therapy. Infection with cytomegalovirus is commonly encountered, and patients will require prophylaxis based on their serology status.

F. **Monoclonal antibodies.** These are produced by the hybridization of murine antibody-secreting B lymphocytes with nonsecreting myeloma cell lines. Currently,

OKT3 is the only available agent approved for human therapeutic use. This drug attacks the CD3 antigen complex of mature T cells and is used most commonly for steroid-resistant rejection. It is also used less frequently for induction, primary rejection treatment, and rejection prophylaxis. The standard dose is 5 mg given intravenously through a Millipore filter. The usual course is for 10 days. Before the first dose of OKT3, patients should undergo chest roentgenography to rule out congestive heart failure. Patients in congestive heart failure may require dialysis. Patients may require premedication with 5 to 8 mg of methylprednisolone per kilogram, 50 mg of intravenous diphenhydramine, and 650 mg of oral acetaminophen. After the first dose, vital signs are monitored every 15 minutes for 2 hours and then every 30 minutes for the next 2 hours. Premedication is not required for subsequent doses. Acetaminophen is given for fever. Concurrent doses of cyclosporine should be reduced by half. During the course of treatment, CD3 panels should be monitored twice a week. Once diuresis is good, patients are encouraged to maintain hydration by taking adequate oral fluids after the second dose of OKT3. Adverse effects may include fever and chills. Pulmonary edema can occur after the first two doses. OKT3-induced renal dysfunction is usually transient and is often followed by a brisk diuretic response. Occasionally, neurologic complications such as aseptic meningitis can occur, which are also self-limiting. OKT3 should be discontinued in severe cases of encephalopathy. As with antithymocyte globulin, the risk for cytomegalovirus infection is increased with OKT3 use. There is also an increased incidence of rapidly fatal B-cell lymphoma within the first few months of repeated use of OKT3. Patients who are negative for Epstein-Barr virus and receive organs that are positive for the virus are at greatest risk for development of lymphoma.

XII. Management of Acute Rejection

Pulse steroids. The first episode of acute rejection can be managed successfully about 75% of the time with high doses of steroids. Often, 500 to 1,000 mg of intravenous methylprednisolone (Solu-Medrol) is given once a day for 3 days. Some centers use low-dose pulsing with 120 to 250 mg of oral prednisone for 3 to 5 days. The patients are then placed back on their usual immunosuppression regimen following pulsing. If patients fail to respond to pulsing with steroids alone, intravenous OKT3 is used for 10 to 14 days. About 90% of acute rejections can be treated successfully with OKT3. For patients with refractory rejection, a second course of OKT3 may be used. However long-term graft function is achieved only in about 40% to 50% of patients. High levels of OKT3 antibodies may develop, which limits the further use of this agent.

XIII. Long-term Management and Complications

Since the introduction of cyclosporine in the late 1970s, short-term graft survival has improved by 30%. However long-term survival has not improved markedly. Chronic rejection (24% to 67%), death (22% to 48%), and drug non-compliance (4% to 28%) are the most common causes of graft loss after the first posttransplant year. Recurrent disease accounts for about 2% to 9% of graft losses. Episodes of acute rejection have significantly affected long-term survival. Survival is halved from 13 years to 6 years for grafts with one rejection episode. Pathologically, changes are noticed as chronic persistent perivascular inflammation and arteriosclerosis. This process ultimately results in vasculopathy, fibrosis, and glomerulosclerosis. Chronic rejection is the most common cause of transplant nephrotoxic syndrome. Recurrence of the original disease in the allograft may occur in about 2% to 9% of cases. Membranoproliferative disease (type II) has the highest recurrence

A. **Hypertension** is one of the most common complications, with a prevalence of about 80% in the immediate posttransplant period; it may be of idiopathic causes or occur as a sign of rejection. Angiotensin-converting enzyme inhibitors are found to be useful in controlling the hypertension related to rejection. Renal artery stenosis of the graft with significant narrowing can occur in 12% of patients. It develops commonly during the initial 6 months. Renal artery stenosis is suspected when hypertension is poorly controlled with medication. Angiotensin-converting enzyme inhibitors can worsen renal function in these cases. Cardiovascular disease accounts for 50% of deaths in dialysis patients, and transplant recipients carry three to four times the risk for development of ischemic heart disease in comparison with the normal population.
B. **Hyperlipidemia** is common in patients with end-stage renal disease. Following transplantation, about 50% of patients will be shown to have **hypercholesterolemia**. Patients are encouraged to lose weight before transplantation and to maintain an ideal weight after surgery.
C. **Chronic liver disease** in transplant patients is one of the leading causes of late mortality and morbidity. Hepatitis C is the most common type of hepatitis in dialysis units and accounts for about 70% of cases of chronic liver disease in kidney transplant patients. Hepatitis C can cause membrano-proliferative glomerulonephritis or can present as mixed cryoglobulinemia in a few cases. After renal transplantation, cirrhosis develops in about one-third of patients with early active hepatitis C and two-thirds with advanced chronic hepatitis.
D. **Posttransplant carbohydrate intolerance** occurs in about 20% of the patients. Steroids alter glucose metabolism and may cause diabetes. In most cases, the condition is mild and resolves on reduction or withdrawal of steroids. Studies have shown that reducing the dose of cyclosporine in some patients may result in better glucose tolerance.
E. **Bone and mineral metabolism.** Kidney transplantation has several beneficial as well as a few untoward effects on bone and mineral metabolism. The beneficial effects may include relief of bone pain, improved subperiosteal bone resorption, reduction of serum alkaline phosphatase and phosphorus, better regulation of calcitriol and parathyroid hormone levels, and resolution of aluminum bone disease and amyloid osteoarthropathy resulting from dialysis. Osteopenia is a major problem, especially in postmenopausal women. Bone density is low in patients with end-stage renal disease, and it continues to decline for the first 2 years after transplantation. This is largely ascribed to use of steroids, which interfere with the intestinal absorption of calcium. Vitamin D supplements for children, calcium replacement for women at high risk, and reduction of steroids to minimal levels may be beneficial. Osteonecrosis occurs in about 15% of transplant patients and usually affects the femoral head. Magnetic resonance imaging (MRI) is very sensitive in detecting the disease early in its course. Based on the degree of damage, patients may require total hip arthroplasty.
    1. **Calcium levels.** Hypercalcemia occurs in about 10% of transplant patients and is attributed to hyperparathyroidism. Hypocalcemia resulting from urinary calcium loss in patients with pretransplant parathyroidectomy can be worsened by steroids, and intravenous replacement of calcium in addition to oral supplements of calcium and vitamin D may be required. Following transplantation, the hyperfunctioning gland involutes, and regulation of vitamin D metabolism and parathyroid hormone levels improves.
    2. **Phosphate levels.** One of the most common untoward effects is hypophosphatemia resulting from phosphaturia; dietary supplements may be necessary to prevent symptoms of hypophosphatemia.
    3. **Magnesium levels.** The use of cyclosporine can cause hypomagnesemia in transplant patients, who require oral supplements.
F. **Skin problems.** Warts are seen about 50% of transplant patients in areas of the skin that are exposed to the sun. Human papillomavirus (HPV) is the usual causative agent. A few subtypes, such as type 5, may predispose the patient to squamous cell cancer. HPV type 6 has been implicated in about 90% of cases of genital and verrucous warts. The incidence of condylomas is about 4% in transplant patients. Patients with condylomas should be treated aggressively, as these lesions multiply rapidly and tend to recur after various modes of treatment. Usual fungal infections of the skin are tinea rubrum and molluscum contagiosum. Infection with *Malasessezia furfur* or *Candida* is also seen. Skin lesions respond most often to topical chemotherapeutic agents.
G. **Malignancy in transplant patients** is an important issue. Some form of cancer will develop in about two-thirds of patients with transplants for more than 20 years.
    1. The incidence of **lymphoma** in renal transplant patients is about 1% to 2%; the most common type is non-Hodgkin's B-cell lymphoma. Epstein-Barr virus infection has been found to be a great risk factor, especially in seronegative patients who receive a seropositive organ. Epstein-Barr virus binds to epithelial oropharyngeal cells and replicates, inducing a latent infection. This results in transformation of B cells and production of lymphoblastoid cells. The mortality rate in transplanted patients is almost 50 times that of the general population. Polyclonal B-cell lesions respond to discontinuation of immunosuppression and antiviral therapy. Monoclonal lesions are malignant and may represent later stages of the disease; they sometimes respond to cessation of immunosuppression and chemotherapy. Patients with polyclonal B-cell lesions are most likely to respond to therapy with acyclovir. Unfortunately, discontinuation of immunosuppression usually leads to rapid loss of the graft.
    2. **Skin cancers** are about 20 times more common in transplant patients than in the general population. Male sex, mismatched transplants at the HLA-B locus, and recipient homozygosity for HLA-DR have been found to be associated with higher risk for development of squamous cell cancer. The incidence of squamous cell carcinoma is more common than that of basal cell carcinoma. Malignant melanomas account for about 5% of skin cancers in these patients. Kaposi's sarcoma is rare and tends to respond to withdrawal of immunosuppression coupled with chemotherapy and radiotherapy. Avoidance of excessive exposure to sun, use of topical sunscreens and low-dose retinoids, surgical excision of suspected lesions, and aggressive dermatologic surveillance are the keys to management and prevention of skin cancers in this patient population.
    3. **Other malignancies.** The incidence of cancers of the lung, prostate, colon, rectum, and breast in transplant patients is not increased in comparison with the incidence in the general population. Women with kidney transplants should undergo a pelvic examination and Papanicolaou smear every year. Those with a history of genital warts require more frequent examinations.
H. **Reproductive function**
    1. **Male patients.** Fertility improves in about 50% of transplant patients. In two-thirds of male patients, libido and sexual activity increase.
    2. **Female patients.** In women, improved regulation of the menstrual cycle and ovulation are expected to occur within 1 year of transplantation. Low doses of oral contraceptives are used with caution, as these may cause hypertension and thromboembolic events. If a patient has good allograft function 18 to 24 months after transplantation, minimal or no proteinuria, and normal findings on US examination, and if she is taking low doses of antihypertensive medications, less than 15 mg of prednisone daily, less than 2 mg of azathioprine (Imuran) per kilogram daily, and cyclosporine at therapeutic levels, she may conceive and continue the pregnancy. Pregnancy does not tend to have any adverse effect on long-term graft survival. Pregnant patients do, however,

require serology for cytomegalovirus, herpes simplex virus, and hepatitis B and C viruses and cervical cultures for herpes at 30 weeks of gestation. Vaginal delivery is preferred. Preterm delivery is common in about 50% of patients. Stress doses of steroid with hydrocortisone should be used in the perinatal period to prevent rejection. Patients should be followed closely for the first 3 months post partum. No increased incidence of fetal abnormalities has been reported.

XIV. Conclusion

Renal transplantation offers an excellent alternative to dialysis for patients with end-stage renal disease. With ongoing research to develop better immunosuppressive agents, the outlook for these patients will continue to improve.

Suggested Reading

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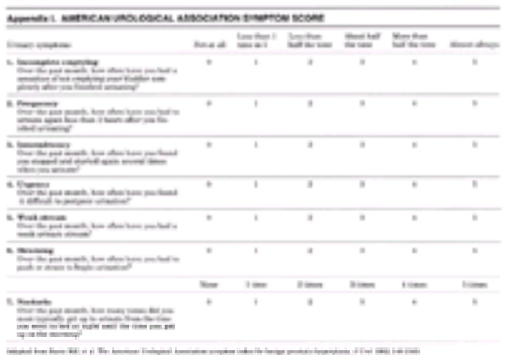
Appendix I. American Urological Association Symptom Score



Appendix I. AMERICAN UROLOGICAL ASSOCIATION SYMPTOM SCORE

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

Adapted from Barry MJ, et al. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 1992;148:1549.

Appendix II. Staging of Genitourinary Tumors[1]

I. Kidney (Fig. AII-1)

Definition of TNM

Primary tumor (T)

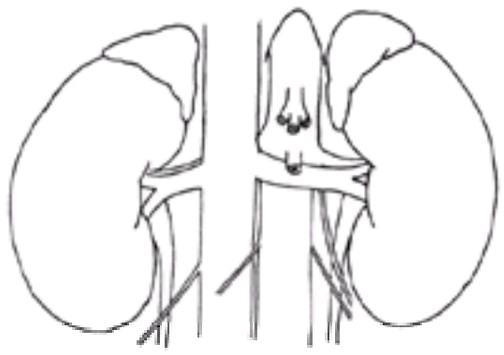


FIG. AII-1. Sketch in the extent of tumor by clinical criteria.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 7 cm or less in greatest dimension limited to kidney
T2 Tumor more than 7 cm in greatest dimension limited to kidney
T3 Tumor extends into major veins or invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia
T3a Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3b Tumor grossly extends into renal vein(s) or vena cava below diaphragm
T3c Tumor grossly extends into renal vein(s) or vena cava above diaphragm
T4 Tumor invades beyond Gerota's fascia

Regional lymph nodes (N)[2]

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in a single regional lymph node
N2 Metastasis in more than one regional lymph node

Distant metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

II. Renal Pelvis and Ureter

Definition of TNM

Primary tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Papillary noninvasive carcinoma
Tis Carcinoma *in situ*
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades muscularis
T3 (for renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma
T3 (for ureter only) Tumor invades beyond muscularis into periureteric fat
T4 Tumor invades adjacent organs, or through kidney into perinephric fat

Regional lymph nodes (N)[3]

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or in multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

III. Urinary Bladder (Fig. AII-2)

Definition of TNM

Primary tumor (T)

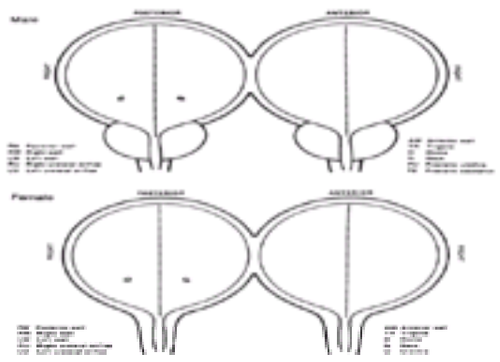


FIG. AII-2 A,B. Indicate on diagrams the primary tumor and regional nodes involved.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Noninvasive papillary carcinoma
Tis Carcinoma *in situ* (“flat tumor”)
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades muscle
T2a Tumor invades superficial muscle (inner half)
T2b Tumor invades deep muscle (outer half)
T3 Tumor invades perivesical tissue
T3a microscopically
T3b macroscopically (extravesical mass)
T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a Tumor invades prostate, uterus, vagina
T4b Tumor invades pelvic wall, abdominal wall

Regional lymph nodes (N)
Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or in multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

IV. Prostate (Fig. AII-3 and Fig. AII-4)

Definition of TNM
Primary tumor, clinical (T)

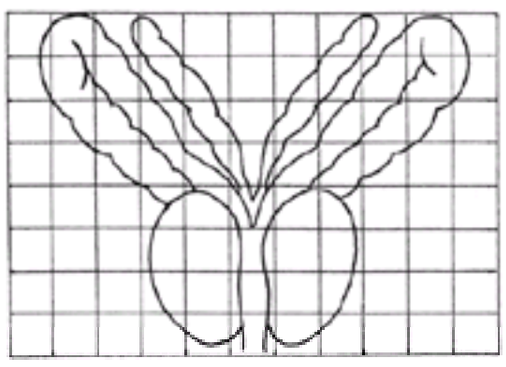


FIG. AII-3. Use the prostate diagram to indicate the extent of the primary tumor.

FIG. AII-4. Indicate on diagram the primary tumor and regional nodes involved.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor not palpable or visible by imaging
T1a Tumor incidental histologic finding in 5% or less of tissue resected
T1b Tumor incidental histologic finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated prostate-specific antigen)
T2 Tumor confined within prostate[4]
T2a Tumor involves one lobe
T2b Tumor involves both lobes
T3 Tumor extends through the prostate capsule[5]
T3a Extracapsular extension (unilateral or bilateral)

T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Primary tumor, pathologic (pT)

pT2[6] Confined to organ
pT2a Unilateral
pT2b Bilateral
pT3 Extraprostatic extension
pT3a Extraprostatic extension
pT3b Seminal vesicle invasion
pT4 Invasion of bladder, rectum

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node or nodes

Distant metastasis (M)[7]

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Nonregional lymph node(s)
M1b Bone(s)
M1c Other site(s)

V. Testis (Fig. AII-5)

Definition of TNM
Primary tumor (pT)
The extent of the primary tumor is classified after radical orchiectomy.

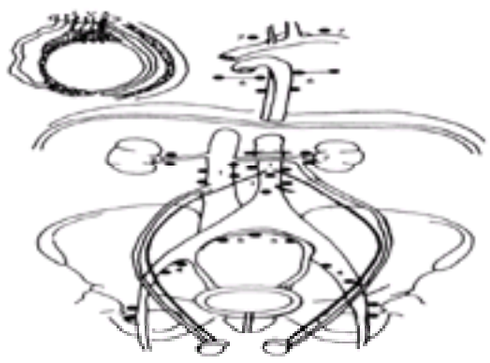


FIG. AII-5. Indicate on diagram the location of tumor and regional nodes involved.

pTX Primary tumor cannot be assessed (TX used if no radical orchiectomy performed)
pT0 No evidence of primary tumor (e.g., histologic scar in testis)
pTis Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1 Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis
pT2 Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3 Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4 Tumor invades scrotum with or without vascular/lymphatic invasion

Regional lymph nodes, clinical (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a lymph node mass, 2 cm or less in greatest dimension, or in multiple lymph nodes, none more than 2 cm in greatest dimension
N2 Metastasis in a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension, or in multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3 Metastasis in a lymph node mass more than 5 cm in greatest dimension

Regional lymph nodes, pathologic (pN)

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in a lymph node mass, 2 cm or less in greatest dimension, and 5 or fewer nodes positive, none more than 2 cm in greatest dimension
pN2 Metastasis in a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3 Metastasis in a lymph node mass more than 5 cm in greatest dimension

Distant metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Nonregional nodal or pulmonary metastasis
M1b Distant metastasis to other than nonregional lymph nodes and lungs

VI. Penis

Definition of TNM
Primary tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
Ta Noninvasive verrucous carcinoma

T1 Tumor invades subepithelial connective tissue
T2 Tumor invades corpus spongiosum or cavernosum
T3 Tumor invades urethra or prostate
T4 Tumor invades other adjacent structures

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single superficial inguinal lymph node
N2 Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3 Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral

Distant metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

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[1] *Used with permission of the American Joint Committee on Cancer (AJCC™), Chicago, Illinois. The original source for this material is the* AJCC™ Cancer Staging Manual, *5th ed. (1997), published by Lippincott-Raven Publishers, Philadelphia, Pennsylvania.*

[2] *Note: Laterality does not affect the N classification.*

[3] *Note: Laterality does not affect the N classification.*

[4] *Note: Tumor found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging is classified as T1c.*

[5] *Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2, not as T3.*

[6] *Note: There is no pathologic T1 classification.*

[7] *Note: When more than one site of metastasis is present, the most advanced category is used. M1c is the most advanced.*