

# Alterations in Renal Function

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More than 20 million North Americans have diseases of the kidneys and urinary tract. Each year, more than 8 million people receive diagnoses of acute urinary tract disorders, and approximately 50,000 die of these diseases.<sup>1</sup>

The kidneys are subject to many of the same types of disorders that affect other body structures, including developmental defects, infections, altered immune responses, and neoplasms. The kidneys filter blood from all parts of the body, and although many forms of kidney disease originate in the kidneys, others develop secondary to disorders such as hypertension, diabetes mellitus, and systemic lupus erythematosus (SLE).



## CONGENITAL AND HEREDITARY DISORDERS OF THE KIDNEY

Some abnormality of the kidneys and ureters occurs in approximately 3% to 4% of newborn infants.<sup>2</sup> Anomalies in shape and position are the most common. Less common are disorders involving a decrease in renal mass (*e.g.*, agenesis, hypogenesis) or a change in renal structure (*e.g.*, renal cysts). Many fetal anomalies can be detected before birth by ultrasonography. In the normal fetus, the kidneys can be visualized as early as 12 weeks.

## Agenesis and Hypoplasia

The kidneys begin to develop early in the fifth week of gestation and start to function approximately 3 weeks later. Formation of urine is thought to begin in the 9th to 12th weeks of gestation; by the 32nd week, fetal production of urine reaches approximately 28 mL/hour.<sup>3</sup> Urine is the main constituent of amniotic fluid. The relative amount of amniotic fluid can provide information about the status of fetal renal function.

The term *dysgenesis* refers to a failure of an organ to develop normally. *Agenesis* is the complete failure of an organ to develop. Total agenesis of both kidneys is incompatible with extrauterine life. Infants are stillborn or die shortly after birth of pulmonary hypoplasia. Newborns with renal agenesis often have characteristic facial features, termed *Potter's syndrome*.<sup>4</sup> The eyes are widely separated and have epicanthic folds, the ears are low set, the nose is broad and flat, the chin is receding, and limb defects often are present.<sup>4,5</sup> Other causes of neonatal renal failure with the Potter phenotype include cystic renal dysplasia, obstructive uropathy, and autosomal recessive polycystic disease. Unilateral agenesis is an uncommon anomaly that is compatible with life if no other abnormality is present. The opposite kidney usually is enlarged as a result of compensatory hypertrophy.

In *renal hypoplasia*, the kidneys do not develop to normal size. Like agenesis, hypoplasia more commonly affects only one kidney. When both kidneys are affected, there is progressive development of renal failure. It has been suggested that true hypoplasia is extremely rare; most cases probably represent acquired scarring caused by vascular, infectious, or other kidney diseases, rather than an underlying developmental failure.<sup>5,6</sup>

In pregnancies that involve infants with nonfunctional kidneys or outflow obstruction of the kidneys, the amount of amniotic fluid is small—a condition called *oligohydramnios*. The cause of fetal death in these infants is thought to be cord compression caused by the oligohydramnios.<sup>2</sup>

### Disorders of Kidney Position and Form

The development of the kidneys during embryonic life can result in kidneys that lie outside their normal position, usually just above the pelvic brim or within the pelvis. Because of the abnormal position, kinking of the ureters and obstruction of urine flow may occur.

One of the most common alterations in kidney form is an abnormality called a *horseshoe kidney*. This abnormality occurs in approximately 1 in every 500 to 1000 persons.<sup>4,5</sup> In this disorder, the upper or lower poles of the two kidneys are fused, producing a horseshoe-shape structure that is continuous along the midline of the body anterior to the great vessels. Most horseshoe kidneys are fused at the lower pole<sup>6</sup> (Fig. 23-1). The condition usually does not cause problems unless there is an associated defect in the renal pelvis or other urinary structures that obstruct urine flow.

### Polycystic Kidney Disease

Renal cysts are fluid-filled sacs or segments of a dilated nephron. The cysts may be single or multiple and can vary in size from microscopic to several centimeters in diameter. The most common form of renal cystic disease is polycystic kidney disease, which is the result of a hereditary trait. It is one of the most common hereditary diseases in the United States, affecting more than 600,000 Americans.<sup>1</sup> There are two types of inherited polycystic disease: autosomal recessive and autosomal dominant.

*Autosomal recessive polycystic kidney disease*, which is present at birth, is rare compared with the adult variety.<sup>5,6</sup> The disorder is inherited as a recessive trait, meaning that both parents are carriers of the gene and that there is a one in four chance of



■ **FIGURE 23-1** ■ Horseshoe kidney. The kidneys are fused at the lower poles. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 865]. Philadelphia: Lippincott Williams & Wilkins)

the parents having another child with the disorder. Because the condition is present at birth, it formerly was called *infantile* or *childhood polycystic disease*. The condition is bilateral, and significant renal dysfunction usually is present, accompanied by variable degrees of liver fibrosis and portal hypertension. The disorder can be diagnosed by ultrasonography. There is no known treatment for the disease. Approximately 75% of infants die during the perinatal period, often because the large kidneys compromise expansion of the lungs.<sup>6</sup> Some children may present with less severe kidney problems and more severe liver disease.

*Autosomal dominant polycystic kidney disease*, also called *adult polycystic kidney disease*, affects children and adults in the prime of life and accounts for 10% of persons who require treatment for end-stage renal disease. This disorder is transmitted as an autosomal dominant trait. There is considerable variability in gene expression, and many affected persons do not have clinical symptoms, or if they do, the symptoms occur later in life.

Three mutant genes have been implicated in the disorder.<sup>5-7</sup> A polycystic kidney disease gene called PKD1, located on chromosome 16, is responsible for approximately 85% of cases. It encodes a large membrane protein called *polycystin 1* that has domains similar to proteins involved in cell-to-cell and cell-to-extracellular matrix interactions.<sup>5,7</sup> A second gene, called PKD2, which is located on chromosome 4, is responsible for a milder form of the disease. It encodes for a product called *polycystin 2*, which is an integral membrane protein that is similar to certain calcium and sodium channel proteins as well as to a portion of polycystin 1. A third gene, PKD3, is responsible for a minority of cases and has yet to be mapped.

How the genetic defects in the polycystin proteins cause cyst formation is largely speculative. It is thought that the mem-

brane proteins may play a role in extracellular matrix interactions that are important in tubular epithelial cell growth and differentiation. In addition, cyst fluids have been shown to harbor mediators that enhance fluid secretion and induce inflammation, resulting in further enlargement of the cysts and the interstitial fibrosis that is characteristic of progressive polycystic kidney disease.

The disease is characterized by tubular dilatation with cyst formation interspersed between normally functioning nephrons. Fluid collects in the cyst while it is still part of the tubular lumen, or it is secreted into the cyst after it has separated from the tubule. As the fluid accumulates, the cysts gradually increase in size, with some becoming as large as 5 cm in diameter. The kidneys of persons with polycystic kidney disease eventually become enlarged because of the presence of multiple cysts (Fig. 23-2). Cysts also may be found in the liver and, less commonly, the pancreas and spleen. Mitral valve prolapse and other valvular heart diseases occur in 20% to 25% of persons, but are largely asymptomatic. Most persons with polycystic disease also have colonic diverticula. One of the most devastating extrarenal manifestations is a weakness in the walls of the cerebral arteries that can lead to aneurysm formation. Approximately 20% of persons with polycystic kidney disease have an associated aneurysm, and subarachnoid hemorrhage is a frequent cause of death.<sup>6</sup>

The manifestations of polycystic kidney disease include pain from the enlarging cysts that may reach debilitating levels, episodes of gross hematuria from bleeding into a cyst, infected cysts from ascending urinary tract infections, and hypertension resulting from compression of intrarenal blood vessels with activation of the renin-angiotensin mechanism.<sup>8</sup> Persons with polycystic kidney disease also are at risk for the development of renal cell carcinoma. The progress of the disease is slow, and end-stage renal failure is uncommon before 40 years of age.



■ **FIGURE 23-2** ■ Adult polycystic disease. The kidney is enlarged, and the parenchyma is almost entirely replaced by cysts of varying size. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 867]. Philadelphia: Lippincott Williams & Wilkins)

The diagnosis of autosomal polycystic kidney disease can be made by radiologic studies, ultrasonography, and computed tomography (CT). Ultrasonography is particularly useful as a screening test for the disease.

The treatment of polycystic kidney disease is largely supportive. Control of hypertension and prevention of ascending urinary tract infections are important. The cysts may be surgically decompressed in persons with severe, disabling pain.<sup>8</sup> The procedure permits removal of fluid from the cyst. Although affording pain relief, the procedure does not appear to alter the course of the disease.<sup>8</sup> Dialysis and kidney transplantation are reserved for those who have end-stage renal disease.

**In summary,** approximately 10% of infants are born with potentially significant malformations of the urinary system. These abnormalities can range from bilateral renal agenesis, which is incompatible with life, to hypogenesis of one kidney, which usually causes no problems unless the function of the remaining kidney is impaired. The developmental process can result in kidneys that lie outside their normal position. Because of the abnormal position, kinking of the ureters and obstruction of urine flow can occur.

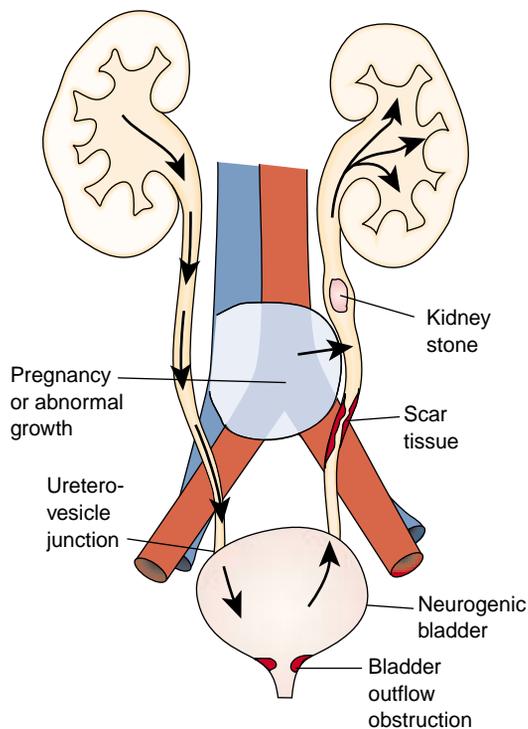
Renal cystic disease is a condition in which there is dilatation of tubular structures with cyst formation. Polycystic kidney disease is an inherited form of renal cystic disease; it can also be inherited as an autosomal recessive or an autosomal dominant trait. Autosomal recessive polycystic kidney disease is rare and usually presents as severe renal dysfunction during infancy. Autosomal dominant polycystic disease usually does not become symptomatic until later in life, often after 40 years of age.

## OBSTRUCTIVE DISORDERS

Urinary obstruction can occur in persons of any age and can involve any level of the urinary tract from the urethra to the renal pelvis (Fig. 23-3). The conditions that cause urinary tract obstruction include developmental defects, pregnancy, benign prostatic hyperplasia, tumors, and kidney stones. The causes of urinary tract obstructions are summarized in Table 23-1.

The two most damaging effects of urinary obstruction are stasis of urine, which predisposes to infection and stone formation, and development of backpressure, which interferes with renal blood flow, destroys kidney tissue, and predisposes to hydronephrosis. The destructive effects of urinary obstruction on kidney structures are determined by the degree (*i.e.*, partial vs. complete, unilateral vs. bilateral) and the duration of the obstruction.<sup>9</sup>

The manifestations of urinary obstruction depend on the site of obstruction, the cause, and the rapidity with which the condition developed. Most commonly, the person has pain, signs and symptoms of urinary tract infection, and manifestations of renal dysfunction, such as an impaired ability to concentrate urine. Changes in urine output may be misleading because output may be normal or even high in cases of partial obstruction.



■ **FIGURE 23-3** ■ Locations and causes of urinary tract obstruction.

Pain, which often is the factor that causes a person to seek medical attention, is the result of distention of the bladder, collecting system, or renal capsule. Its severity is related most closely to the rate, rather than the degree, of distention. Pain most often occurs with acute obstruction, in which the distention of urinary structures is rapid. This is in contrast to chronic obstruction, in which distention is gradual and may not cause pain. Instead, gradual obstruction may produce only vague abdominal or back discomfort. When pain occurs, it is related to the site of obstruction. Obstruction of the renal pelvis or upper ureter causes pain and tenderness over the flank area. With

lower levels of obstruction, the pain may radiate to the testes in the male or the labia in the female. With partial obstruction, particularly of the ureteropelvic junction, pain may occur during periods of high fluid intake, when a high rate of urine flow causes an acute distention of the renal pelvis. Because of its visceral innervation, ureteral obstruction may produce reflex impairment of gastrointestinal tract peristalsis and motility with abdominal distention and, in severe cases, paralytic ileus.

Hypertension is an occasional complication of urinary tract obstruction. It is more common in cases of unilateral obstruction in which renin secretion is enhanced, probably secondary to impaired renal blood flow. In these circumstances, removal of the obstruction often leads to a reduction in blood pressure. When hypertension accompanies bilateral obstruction, renin levels usually are normal, and the elevated blood pressure probably is volume related. The relief of bilateral obstruction leads to a loss of volume and a decrease in blood pressure. In some cases, relieving the obstruction does not correct the hypertension.

## Renal Calculi

The most common cause of upper urinary tract obstruction is urinary calculi. Although stones can form in any part of the urinary tract, most develop in the kidneys. Approximately 1 million North Americans are hospitalized each year with kidney stones, and an equal number are treated for stones without hospitalization.<sup>1</sup> Men are more frequently affected than women, with a ratio of 4:1.<sup>10</sup>

Kidney stones are crystalline structures made up of materials that the kidneys normally excrete in the urine. The etiology of urinary stone formation is complex, and not all aspects are well understood. It is thought to encompass a number of factors, including increases in blood and urinary levels of stone components and interactions among the components; anatomic changes in urinary tract structures; metabolic and endocrine influences; dietary and intestinal absorption factors; and urinary tract infections. To add to the mystery of stone formation is the fact that although both kidneys are exposed to the same urinary constituents, kidney stones tend to form in only one kidney. Three major theories are used to explain stone formation: the saturation theory, the matrix theory, and the inhibitor deficiency theory.<sup>11,12</sup> One or more of these theories may apply to stone formation in the same person.

Level of Obstruction	Cause
Renal pelvis	Renal calculi Papillary necrosis
Ureter	Renal calculi Pregnancy Tumors that compress the ureter Ureteral stricture Congenital disorders of the ureterovesical junction and ureteropelvic junction strictures
Bladder and urethra	Bladder cancer Neurogenic bladder Bladder stones Prostatic hyperplasia or cancer Urethral strictures Congenital urethral defects

## KEY CONCEPTS

### KIDNEY STONES

- Kidney stones are crystalline structures that form from components of the urine.
- Stones require a nidus to form and a urinary environment that supports continued crystallization of stone components.
- Stone formation is influenced by the concentration of stone components in the urine, the ability of the stone components to complex and form stones, and the presence of substances that inhibit stone formation.

Kidney stones require a nidus, or nucleus, to form and a urinary environment that supports continued precipitation of stone components to grow. The *saturation theory* states that the risk of stone formation is increased when the urine is supersaturated with stone components (e.g., calcium salts, uric acid, magnesium ammonium phosphate, cystine). Supersaturation depends on urinary pH, solute concentration, ionic strength, and complexation. The greater the concentration of two ions, the more likely they are to precipitate. Complexation influences the availability of specific ions. For example, sodium complexes with oxalate, decreasing its free ionic form and increasing the amount that is available to participate in stone formation.

The *matrix theory* proposes that organic materials, such as mucopolysaccharides derived from the epithelial cells that line the tubules, act as a nidus for stone formation. This theory is based on the observation that organic matrix materials can be found in all layers of kidney stones. It is not known whether the matrix material contributes to the initiation of stone formation or if the material is merely entrapped as the stone forms.

Kidney proteins inhibit all phases of crystallization. The *inhibitor theory* suggests that persons who have a deficiency of proteins that inhibit stone formation in their urine are at increased risk for stone formation. Kidney cells produce at least three proteins that are thought to slow the rate of calcium oxalate crystallization: nephrocalcin, Tamm-Horsfall mucoprotein, and uropontin.<sup>11,13</sup> Nephrocalcin inhibits nucleation, aggregation, and growth of calcium oxalate stones. *Tamm-Horsfall mucoprotein* is thought to exert a minor effect on crystal aggregation. Uropontin inhibits the growth of calcium oxalate crystals.

Urinary obstruction and stagnation of urine predisposes to infection. When present, urinary calculi serve as foreign bodies and contribute to the infection. Once established, the infection is difficult to treat. It often is caused by urea-splitting organisms (e.g., *Proteus*, staphylococci) that increase ammonia production and cause the urine to become alkaline.<sup>9</sup> Calcium salts precipitate

more readily in stagnant alkaline urine; thus, urinary tract obstructions also predispose to stone formation.

### Types of Stones

There are four basic types of kidney stones: calcium stones (i.e., oxalate or phosphate), magnesium ammonium phosphate stones, uric acid stones, and cystine stones. The causes and treatment measures for each of these types of renal stones are described in Table 23-2.

**Calcium Stones.** Most kidney stones (70% to 80%) are calcium stones—calcium oxalate, calcium phosphate, or a combination of the two materials. Calcium stones usually are associated with increased concentrations of calcium in the blood and urine. Excessive bone resorption caused by immobility, bone disease, hyperparathyroidism, and renal tubular acidosis all are contributing conditions. High oxalate concentrations in the blood and urine predispose to formation of calcium oxalate stones. A recent addition to the spectrum of kidney stones are those seen in persons with human immunodeficiency virus (HIV) infection who are being treated with indinavir, a protease inhibitor. The calcium-containing calculi develop in as many as 6% of persons treated with the drug.<sup>9</sup>

**Magnesium Ammonium Phosphate Stones.** Magnesium ammonium phosphate stones, also called *struvite stones*, form only in alkaline urine and in the presence of bacteria that possess an enzyme called *urease*, which splits the urea in the urine into ammonia and carbon dioxide. The ammonia that is formed takes up a hydrogen ion to become an ammonium ion, increasing the pH of the urine so that it becomes more alkaline. Because phosphate levels are increased in alkaline urine and because magnesium always is present in the urine, struvite stones form. These stones enlarge as the bacterial count grows, and they can increase in size until they fill an entire renal pelvis (Fig. 23-4). Because of their shape, they often are called *staghorn stones*. Staghorn stones almost always are associated with

**TABLE 23-2** Composition, Contributing Factors, and Treatment of Kidney Stones

Type of Stone	Contributing Factors	Treatment
Calcium (oxalate and phosphate)	Hypercalcemia and hypercalciuria Immobilization	Treatment of underlying conditions Increased fluid intake Thiazide diuretics
	Hyperparathyroidism Vitamin D intoxication Diffuse bone disease Milk-alkali syndrome Renal tubular acidosis Hyperoxaluria Intestinal bypass surgery	Dietary restriction of foods high in oxalate
Magnesium ammonium phosphate (struvite)	Urea-splitting urinary tract infections	Treatment of urinary tract infection Acidification of the urine Increased fluid intake
Uric acid (urate)	Formed in acid urine with pH of approximately 5.5 Gout	Increased fluid intake Allopurinol for hyperuricemia
Cystine	High-purine diet Cystinuria (inherited disorder of amino acid metabolism)	Alkalinization of urine Increased fluid intake Alkalinization of urine



■ **FIGURE 23-4** ■ Staghorn calculi. The kidney shows hydronephrosis and stones that are casts of the dilated calyces. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 909]. Philadelphia: Lippincott Williams & Wilkins)

urinary tract infections and persistently alkaline urine. Because these stones act as a foreign body, treatment of the infection often is difficult. Struvite stones usually are too large to be passed and require lithotripsy or surgical removal.

**Uric Acid Stones.** Uric acid stones develop in conditions of gout and high concentrations of uric acid in the urine. Hyperuricosuria also may contribute to calcium stone formation by acting as a nucleus for calcium oxalate stone formation. Unlike radiopaque calcium stones, uric acid stones are not visible on x-ray films. Uric acid stones form most readily in urine with a pH of 5.1 to 5.9.<sup>11</sup> Thus, these stones can be treated by raising the urinary pH to 6 to 6.5 with potassium alkali salts.

**Cystine Stones.** Cystine stones are rare. They are seen in cystinuria, which results from a genetic defect in renal transport of cystine. These stones resemble struvite stones except that infection is unlikely to be present.

### Manifestations

One of the major manifestations of kidney stones is pain. Depending on location, there are two types of pain associated with kidney stones: renal colic and noncolicky renal pain.<sup>9</sup> *Renal colic* is the term used to describe the colicky pain that accompanies stretching of the collecting system or ureter. The symptoms of renal colic are caused by stones 1 to 5 mm in diameter that can move into the ureter and obstruct flow. Classic ureteral colic is manifested by acute, intermittent, and excruciating pain in the flank and upper outer quadrant of the abdomen on the affected side. The pain may radiate to the lower

abdominal quadrant, bladder area, perineum, or scrotum in the male. The skin may be cool and clammy, and nausea and vomiting are common. Noncolicky pain is caused by stones that produce distention of the renal calices or renal pelvis. The pain usually is a dull, deep ache in flank or back that can vary in intensity from mild to severe. The pain may be exaggerated by drinking large amounts of fluid.<sup>9</sup>

### Diagnosis and Treatment

Persons with kidney stones often present with acute renal colic, and the diagnosis is based on symptomatology and diagnostic tests, which include urinalysis, abdominal radiographs, and excretory urography. Urinalysis provides information related to hematuria, infection, the presence of stone-forming crystals, and urine pH. At least 90% of stones are radiopaque and readily visible on a plain radiograph of the abdomen. Excretory urography uses an intravenously injected contrast medium that is filtered in the glomeruli to visualize the collecting system and the ureters of the kidneys. Retrograde urography, ultrasonography, and CT scanning also may be used.

Treatment of acute renal colic usually is supportive. Pain relief may be needed during acute phases of obstruction, and antibiotic therapy may be necessary to treat urinary infections. Most stones that are less than 5 mm in diameter pass spontaneously. All urine should be strained during an attack in the hope of retrieving the stone for chemical analysis and determination of stone type.

A major goal of treatment in persons who have passed kidney stones or have had them removed is to prevent their recurrence (see Table 23-2). Adequate fluid intake reduces the concentration of stone-forming crystals in the urine and needs to be encouraged. Depending on the type of stone that is formed, dietary changes, medications, or measures to change the pH of the urine may be used to alter the concentration of stone-forming elements in the urine.

In some cases, stone removal may be necessary. Several methods, including ureteroscopic removal and extracorporeal lithotripsy, are available for removing kidney stones. Ureteroscopic removal involves the passage of an instrument through the urethra into the bladder and then into the ureter. *Extracorporeal shock-wave lithotripsy* uses acoustic shock waves to break up the stones so they can be passed in the urine. All these procedures eliminate the need for an open surgical procedure. Open stone surgery may be required to remove large calculi or those that are resistant to other forms of removal.

### Hydronephrosis

Hydronephrosis refers to urine-filled dilatation of the renal pelvis and calices, with accompanying atrophy of renal tissue, caused by obstruction of urine flow. The obstruction may be sudden or insidious and may occur at any level of the urinary tract. The most common causes are congenital disorders of the urethra or ureters, kidney stones, tumors that compress the urethra or ureters, prostatitis, inflammatory conditions of the urethra, and neurogenic bladder.

In situations of marked or complete obstruction, backpressure develops because of a combination of continued glomerular filtration and obstruction of urine flow. Depending on the degree of obstruction, pressure builds up, beginning at the site of obstruction and moving backward from the ureter or renal

pelvis into the calices and collecting tubules. Typically, the most severe effects occur at the level of the papillae because these structures are subjected to the greatest pressure. Damage to the nephrons and other functional components of the kidney is caused by compression from increased intrapelvic pressure and ischemia from disturbances in blood flow.

The degree of hydronephrosis depends on the duration, degree, and site of obstruction. Bilateral hydronephrosis occurs only when the obstruction is below the level of the ureters. If the obstruction occurs at the level of the ureters or above, hydronephrosis is unilateral. Unfortunately, unilateral hydronephrosis may remain silent for long periods of time. Often the enlarged kidney is discovered on routine exam. If the obstruction is removed within a few weeks, return of function is possible. Prolonged or severe partial obstruction causes irreversible kidney damage. The kidney eventually is destroyed and appears as a thin-walled shell that is filled with fluid (Fig. 23-5).

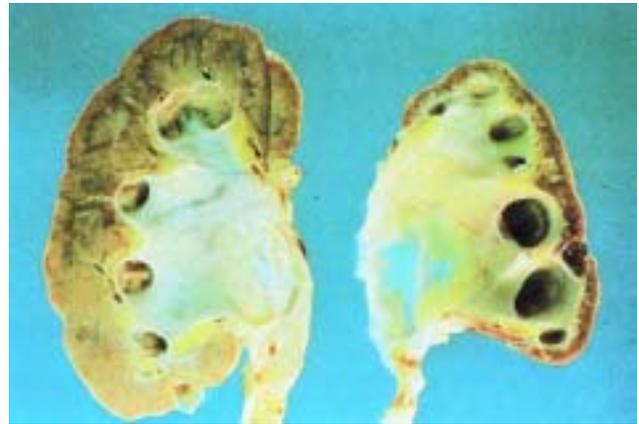
**In summary**, obstruction of urine flow can occur at any level of the urinary tract. Among the causes of urinary tract obstruction are developmental defects, pregnancy, infection and inflammation, kidney stones, neurologic defects, and prostatic hypertrophy. Obstructive disorders produce stasis of urine, increasing the risk of infection and calculi formation and resulting in back pressure that is damaging to kidney structures.

Kidney stones are a major cause of upper urinary tract obstruction. There are four types of kidney stones: calcium (*i.e.*, oxalate and phosphate) stones, which are associated with increased serum calcium levels; magnesium ammonium phosphate (*i.e.*, struvite) stones, which are associated with urinary tract infections; uric acid stones, which are related to elevated uric acid levels; and cystine stones, which are seen in cystinuria. A major goal of treatment for persons who have passed kidney stones or have had them removed is to identify stone composition and prevent their recurrence. Treatment measures depend on stone type and include adequate fluid intake to prevent urine saturation, dietary modification to decrease intake of stone-forming constituents, treatment of urinary tract infections, measures to change urine pH, and the use of diuretics that decrease the calcium concentration of urine.

Hydronephrosis refers to dilation of the renal pelvis and calices, with atrophy of renal tissue, that is caused by obstruction to the outflow of urine. The obstruction may be sudden or insidious in onset and may occur at any level of the urinary tract.

## URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are the second most common type of bacterial infections seen by health care providers (respiratory tract infections are first). UTIs can include several distinct entities, including asymptomatic bacteriuria, symptomatic infections, lower UTIs such as cystitis, and upper UTIs such as pyelonephritis. Because of their ability to cause renal damage, upper UTIs are considered more serious than lower UTIs.



**FIGURE 23-5** ■ Hydronephrosis. Bilateral urinary tract obstruction has led to conspicuous dilatation of the ureters, pelvis, and calyces. The kidney on the right shows severe cortical atrophy. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 910]. Philadelphia: Lippincott Williams & Wilkins)

## Etiologic Factors

Most UTIs are caused by *Escherichia coli*. Other common pathogens include *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Enterococcus* species.<sup>14–18</sup> Bacteria can enter the kidneys either through the bloodstream or as an ascending infection from the lower urinary tract. Most infections are of the ascending type. Although the distal portion of the urethra often contains pathogens, the urine formed in the kidneys and found in the bladder normally is sterile or free of bacteria. This is because of the *washout phenomenon*, in which urine from the bladder normally washes bacteria out of the urethra. When a UTI occurs, the bacteria that have colonized the urethra, vagina, or perineal area often are responsible.

There is an increased risk of UTI in persons with urinary obstruction and reflux; in people with neurogenic disorders that impair bladder emptying; in women who are sexually active, especially if they use a diaphragm or spermicide for contraception; in postmenopausal women; in men with diseases of the prostate; and in elderly persons. Instrumentation and urinary catheterization are the most common predisposing factors for nosocomial UTIs.

## KEY CONCEPTS

### URINARY TRACT INFECTIONS

- Urinary tract infections involve both the lower and upper urinary tract structures.
- In lower urinary tract infections, the infecting pathogens tend to propagate in the urine and cause irritative voiding symptoms, often with minimal systemic signs of infection.
- Upper urinary tract infections tend to invade the tissues of the kidney pelvis, inciting an acute inflammatory response with marked systemic manifestations of infection.

Because certain people tend to be predisposed to the development of UTIs, considerable interest has been focused on host-agent interactions and factors such as urinary tract obstruction and reflux that increase the risk of UTI.

### Host Defenses

In the development of a UTI, host defenses are matched against the virulence of the pathogen. The host defenses of the bladder have several components, including the washout phenomenon, in which bacteria are removed from the bladder and urethra during voiding; the protective mucin layer that lines the bladder and protects against bacterial invasion; and local immune responses. In the ureters, peristaltic movements facilitate the movement of urine from the renal pelvis through the ureters and into the bladder. Immune mechanisms, particularly secretory immunoglobulin A (IgA), appear to provide an important antibacterial defense. Phagocytic blood cells further assist in the removal of bacteria from the urinary tract.

There has been a growing appreciation of the protective function of the bladder's mucin layer.<sup>14</sup> It is thought that the epithelial cells that line the bladder synthesize protective substances that subsequently become incorporated into the mucin layer that adheres to the bladder wall. One theory proposes that the mucin layer acts by binding water, which then constitutes a protective barrier between the bacteria and the bladder epithelium. Elderly and postmenopausal women produce less mucin than younger women, suggesting that estrogen may play a role in mucin production in women.

### Pathogen Virulence

Investigations are focusing on the adherence properties of the bacteria that infect the urinary tract. These bacteria have fine protein filaments that help them adhere to receptors on the lining of urinary tract structures.<sup>14,15</sup> These filaments are called *fimbriae* or *pili*. Among the factors that contribute to bacterial virulence, the type of fimbriae that the bacteria possess may be the most important. Bacteria with certain types of fimbriae are associated primarily with cystitis, and those with other types are associated with a high incidence of pyelonephritis. The bacteria associated with pyelonephritis are thought to have fimbriae that bind to carbohydrates that are specific to the surfaces of epithelial cells in this part of the urinary tract.

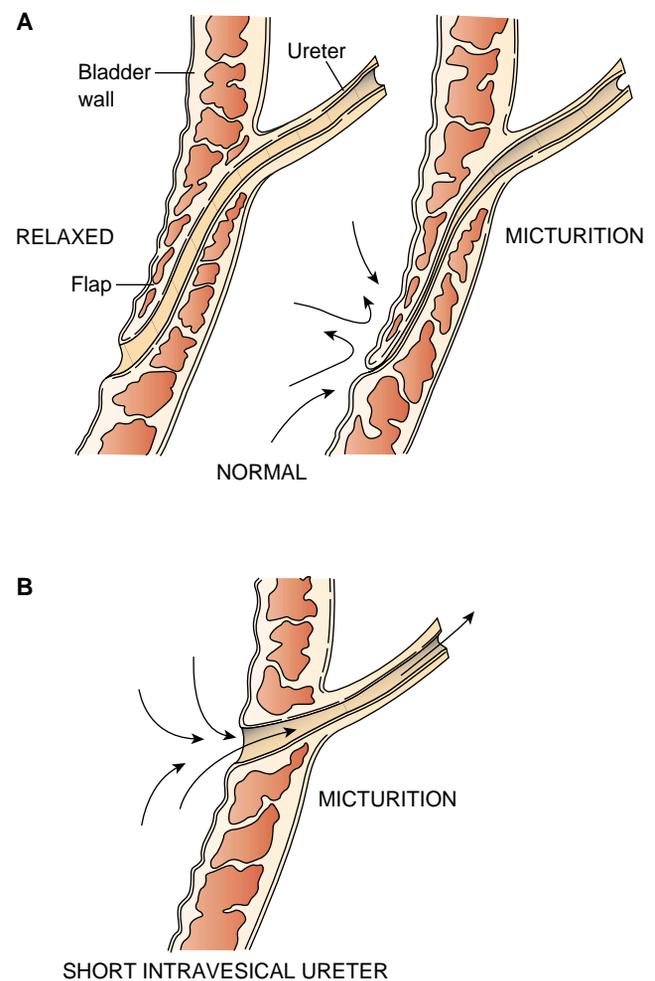
### Obstruction and Reflux

Obstruction and reflux are important contributing factors in the development of UTIs. Any microorganisms that enter the bladder normally are washed out during voiding. When outflow is obstructed, urine remains in the bladder and acts as a medium for microbial growth; the microorganisms in the contaminated urine can then ascend along the ureters to infect the kidneys. The presence of residual urine correlates closely with bacteriuria and with its recurrence after treatment. Another aspect of bladder outflow obstruction and bladder distention is increased intravesicular pressure, which compresses blood vessels in the bladder wall, leading to a decrease in the mucosal defenses of the bladder.

In UTIs associated with stasis of urine flow, the obstruction may be anatomic or functional. Anatomic obstructions include urinary tract stones, prostatic hyperplasia, pregnancy, and malformations of the ureterovesical junction. Functional obstructions include neurogenic bladder, infrequent voiding, detrusor (bladder) muscle instability, and constipation.

Reflux occurs when urine from the urethra moves into the bladder (*i.e.*, urethrovesical reflux) or from the bladder into the ureters (*i.e.*, vesicoureteral reflux). In women, *urethrovesical* reflux can occur during activities such as coughing or squatting, in which an increase in intra-abdominal pressure causes the urine to be squeezed into the urethra and then to flow back into the bladder as the pressure decreases. This also can happen when voiding is abruptly interrupted. Because the urethral orifice frequently is contaminated with bacteria, the reflux mechanism may cause bacteria to be drawn back into the bladder.

A second type of reflux mechanism, *vesicoureteral reflux*, occurs at the level of the bladder and ureter. Normally, the distal portion of the ureter courses between the muscle layer and the mucosal surface of the bladder wall, forming a flap. The flap is compressed against the bladder wall during micturition, preventing urine from being forced into the ureter (Fig. 23-6). In



■ **FIGURE 23-6** ■ Anatomic features of the bladder and kidney in pyelonephritis caused by vesicoureteral reflux. Bladder. (A) In the normal bladder, the distal portion of the intravesical ureter courses between the mucosa and the muscularis of the bladder. A mucosal flap is thus formed. On micturition, the elevated intravesicular pressure compresses the flap against the bladder wall, thereby occluding the lumen. (B) Persons with a congenitally short intravesical ureter have no mucosal flap, because the entry of the ureter into the bladder approaches a right angle. Thus, micturition forces urine into the ureter. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 903]. Philadelphia: Lippincott Williams & Wilkins.) (Courtesy of Dmitri Karetnikov, artist)

persons with vesicoureteral reflux, the ureter enters the bladder at an approximate right angle such that urine is forced into the ureter during micturition.<sup>6</sup> It is seen most commonly in children with UTIs and is believed to result from congenital defects in length, diameter, muscle structure, or innervation of the submucosal segment of the ureter. Vesicoureteral reflux also is seen in adults with obstruction to bladder outflow, primarily because of increased bladder volume and pressure.

### Catheter-Induced Infection

Urinary catheters are tubes made of latex or plastic. They are inserted through the urethra into the bladder for the purpose of draining urine. They are a source of urethral irritation and provide a means for entry of microorganisms into the urinary tract.

Catheter-associated bacteriuria remains the most frequent cause of gram-negative septicemia in hospitalized patients. Studies have shown that bacteria adhere to the surface of the catheter and initiate the growth of a biofilm that then covers the surface of the catheter.<sup>14</sup> The biofilm tends to protect the bacteria from the action of antibiotics and makes treatment difficult. A closed drainage system (*i.e.*, closed to air and other sources of contamination) and careful attention to perineal hygiene (*i.e.*, cleaning the area around the urethral meatus) help to prevent infections in persons who require an indwelling catheter. Careful hand washing and early detection and treatment of UTIs also are essential.

### Manifestations

The manifestations of UTI depend on whether the infection involves the lower or upper urinary tract. An acute episode of cystitis (bladder infection) or lower UTI is characterized by frequency of urination (sometimes as often as every 20 minutes), lower abdominal or back discomfort, and burning and pain on urination (*i.e.*, dysuria). Occasionally the urine is cloudy and foul smelling. In adults, fever and other signs of infection usually are absent. If there are no complications, the symptoms disappear within 48 hours of treatment. This type of UTI is common in younger women. The symptoms of cystitis also may represent urethritis caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus, or vaginitis attributable to *Trichomonas vaginalis* or *Candida* species.

Upper UTIs affect the parenchymal tissues of kidney pelvis (pyelonephritis). They tend to produce more systemic signs of infection than lower UTIs because of closer proximity to the vascular compartment and blood cells (*e.g.*, neutrophils) that incite the inflammatory response. Acute pyelonephritis tends to present with an abrupt onset of shaking chills, moderate to high fever, and constant ache in the loin area of the back that is unilateral or bilateral.<sup>13,14</sup> Lower urinary tract symptoms, including dysuria, frequency, and urgency, also are common. There may be significant malaise, and the person usually looks and feels ill. Nausea and vomiting may occur along with abdominal pain. Palpation or percussion over the costovertebral angle on the affected side usually causes pain. Pyelonephritis occurs more frequently in children and adults with urinary tract obstructions or other predisposing conditions.

### Diagnosis and Treatment

The diagnosis of UTI usually is based on symptoms and on examination of the urine for the presence of microorganisms. When necessary, x-ray films, ultrasonography, and CT and re-

nal scans are used to identify contributing factors, such as obstruction.

Microscopic urine tests are used to establish the presence of bacteria and blood cells in the urine.<sup>9</sup> A commonly accepted criterion for diagnosis of a UTI is the presence of  $10^5$  or more bacteria per milliliter of urine.<sup>9</sup> Colonization usually is defined as the multiplication of microorganisms in or on a host without apparent evidence of invasiveness or tissue injury. Pyuria (the presence of less than five to eight leukocytes per high-power field) indicates a host response to infection, rather than asymptomatic bacterial colonization. A Gram's stain may be done to determine the type of organism that is present (gram positive or gram negative).

Chemical screening (urine dipstick) for markers of infection may provide useful information but is less sensitive than microscopic analysis. A urine culture confirms the presence of pathogenic bacteria in urine specimens, allows for their identification, and permits the determination of their sensitivity to specific antibiotics.

The treatment of acute UTI is based on the type of infection that is present (lower or upper UTI), the pathogen causing the infection, and the presence of contributing host-agent factors. Other considerations include whether the infection is acute, recurrent, or chronic. Most acute lower UTIs are treated successfully with antimicrobial therapy and increased fluid intake. Because there is risk of permanent kidney damage, upper urinary tract infections (*e.g.*, pyelonephritis) are treated more aggressively. Hospitalization may be recommended during the early stages of infection until a response to treatment is observed.<sup>16</sup>

Recurrent lower UTIs are those that recur after treatment. They are attributable either to bacterial persistence or reinfection. Bacterial persistence usually is curable by removal of the infectious source (*e.g.*, urinary catheter or infected bladder stones).

Chronic UTIs are more difficult to treat. Because they often are associated with obstructive uropathy or reflux flow of urine, diagnostic tests usually are performed to detect such abnormalities. When possible, the condition causing the reflux flow or obstruction is corrected. Men in particular should be investigated for obstructive disorders or a prostatic focus of infection.

### Infections in Special Populations



#### Urinary Tract Infections in Women

In women, the urethra is short and close to the vagina and rectum, offering little protection against entry of microorganisms into the bladder. There is a peak incidence of these infections in the 15- to 24-year-old age group, suggesting that hormonal and anatomic changes associated with puberty and sexual activity contribute to UTIs.

The role of sexual activity in the development of urethritis and cystitis is a matter of controversy. The anterior urethra usually is colonized with bacteria; urethral massage or sexual intercourse can force these bacteria back into the bladder. Using a diaphragm and spermicide enhances the susceptibility to infection.<sup>17</sup> A nonpharmacologic approach to the treatment of frequent UTIs associated with sexual intercourse is to increase fluid intake before intercourse and to void soon after intercourse. This procedure uses the washout phenomenon to remove bacteria from the bladder.

Pregnant women are at increased risk for UTIs. Normal changes in the functioning of the urinary tract that occur during pregnancy predispose to UTIs.<sup>18</sup> These changes involve the collecting system of the kidneys and include dilatation of the renal calices, pelves, and ureters that begins during the first trimester and becomes most pronounced during the third trimester. This dilatation of the upper urinary system is accompanied by a reduction in the peristaltic activity of the ureters that is thought to result from the muscle-relaxing effects of progesterone-like hormones and mechanical obstruction from the enlarging uterus. In addition to the changes in the kidneys and ureters, the bladder becomes displaced from its pelvic position to a more abdominal position, producing further changes in ureteral position.

UTIs are commonly asymptomatic in pregnant women. The complications of asymptomatic UTIs during pregnancy include persistent bacteriuria, acute and chronic pyelonephritis, toxemia of pregnancy, and premature delivery. Evidence suggests that few women become bacteriuric during pregnancy. Rather, it appears that symptomatic UTIs during pregnancy reflect pre-existing asymptomatic bacteriuria, and that changes occurring during pregnancy simply permit the prior urinary colonization to lead to symptomatic infection and invasion of the kidneys.<sup>19</sup> Because bacteriuria may occur as an asymptomatic condition in pregnant women, the American College of Obstetricians and Gynecologists recommends that a urine culture be obtained at the first prenatal visit.<sup>18,19</sup> A repeat culture should be obtained during the third trimester. Women with bacteriuria should be followed up closely, and infections should be properly treated to prevent complications. The choice of antimicrobial agent should address the common infecting organisms and should be safe for the woman and fetus.



### Urinary Tract Infections in Children

Urinary tract infections occur in as many as 3% to 5% of female and 1% of male children.<sup>4</sup> In girls, the average age at first diagnosis is 3 years, which coincides with onset of toilet training. In boys, most UTIs occur during the first year of life; they are more common in uncircumcised than in circumcised boys. Children who are at increased risk for bacteriuria or symptomatic UTIs are premature infants discharged from neonatal intensive care units; children with systemic or immunologic disease or urinary tract abnormalities such as neurogenic bladder or vesicoureteral reflux; those with a family history of UTI or urinary tract anomalies with reflux; and girls younger than 5 years of age with a history of UTI.<sup>20</sup>

UTIs in children frequently involve the upper urinary tract (pyelonephritis). In children in whom renal development is not complete, pyelonephritis can lead to renal scarring and permanent kidney damage. It has been reported that more than 75% of children younger than 5 years of age with febrile UTIs have pyelonephritis, and that renal scarring occurs in 27% to 64% of children with pyelonephritis.<sup>20</sup> Most UTIs that lead to scarring and diminished kidney growth occur in children younger than 4 years, especially infants younger than 1 year of age. The incidence of scarring is greatest in children with gross vesicoureteral reflux or obstruction, in children with recurrent UTIs, and those with a delay in treatment.

Unlike adults, children frequently do not present with the typical signs of a UTI.<sup>20,21</sup> Many neonates with UTIs have bac-

teremia and may show signs and symptoms of septicemia, including fever, hypothermia, apneic spells, poor skin perfusion, abdominal distention, diarrhea, vomiting, lethargy, and irritability. Older infants may present with feeding problems, failure to thrive, diarrhea, vomiting, fever, and foul-smelling urine. Toddlers often present with abdominal pain, vomiting, diarrhea, abnormal voiding patterns, foul-smelling urine, fever, and poor growth. In older children with lower UTIs, the classic features—enuresis, frequency, dysuria, and suprapubic discomfort—are more common. Fever is a common sign of UTI in children, and the possibility of UTI should be considered in children with unexplained fever.

Diagnosis is based on a careful history of voiding patterns and symptomatology; physical examination to determine fever, hypertension, abdominal or suprapubic tenderness, and other manifestations of UTI; and urinalysis to determine bacteriuria, pyuria, proteinuria, and hematuria. A positive urine culture that is obtained correctly is essential for the diagnosis. Additional diagnostic methods may be needed to determine the cause of the disorder. Vesicoureteral reflux is the most commonly associated abnormality in UTIs, and reflux nephropathy is an important cause of end-stage renal disease in children and adolescents. Children with a relatively uncomplicated first UTI may turn out to have significant reflux. Therefore, even a single documented UTI in a child requires careful diagnosis. Urinary symptoms in the absence of bacteriuria suggest vaginitis, urethritis, sexual molestation, the use of irritating bubble baths, pinworms, or viral cystitis. In adolescent girls, a history of dysuria and vaginal discharge makes vaginitis or vulvitis a consideration.

The approach to treatment is based on the clinical severity of the infection, the site of infection (*i.e.*, lower vs. upper urinary tract), the risk of sepsis, and the presence of structural abnormalities. The immediate treatment of infants and young children is essential. Most infants with symptomatic UTIs and many children with clinical evidence of acute upper UTIs require hospitalization and intravenous antibiotic therapy. Follow-up is essential for children with febrile UTIs to ensure resolution of the infection. Follow-up urine cultures often are done at the end of treatment. Imaging studies often are recommended for all children after first UTIs to detect renal scarring, vesicoureteral reflux, or other abnormalities.<sup>20,21</sup>



### Urinary Tract Infections in the Elderly

Urinary tract infections are relatively common in elderly persons. It has been reported that 5% to 20% of the elderly living at home have bacteriuria. These numbers increase to 15% to 25% for the elderly living in nursing homes or extended-care facilities.<sup>22</sup>

Most of these infections follow invasion of the urinary tract by the ascending route. Several factors predispose elderly persons to UTIs: immobility resulting in poor bladder emptying, bladder outflow obstruction caused by prostatic hyperplasia or kidney stones, bladder ischemia caused by urine retention, senile vaginitis, constipation, and diminished bactericidal activity of urine and prostatic secretions. Added to these risks are other health problems that necessitate instrumentation of the urinary tract. UTIs develop in 1% of ambulatory patients after a single catheterization and within 3 to 4 days in essentially all patients with indwelling catheters.<sup>23</sup>

Elderly persons with bacteriuria have varying symptoms, ranging from the absence of symptoms to the presence of typ-

ical UTI symptoms. Even when symptoms of lower UTIs are present, they may be difficult to interpret because elderly persons without UTIs commonly experience urgency, frequency, and incontinence. Alternatively, elderly persons may have vague symptoms such as anorexia, fatigue, weakness, or change in mental status. Even with more serious upper UTIs (*e.g.*, pyelonephritis), the classic signs of infection such as fever, chills, flank pain, and tenderness may be altered or absent in elderly persons.<sup>22</sup> Sometimes, no symptoms occur until the infection is far advanced.

**In summary,** UTI is the second most common type of bacterial infection seen by health care professionals. Infections can range from simple bacteriuria to severe kidney infections that cause irreversible kidney damage. Predisposition to infection is determined by host defenses and pathogen virulence. Host defenses include the washout phenomenon associated with voiding, the protective mucin lining of the bladder, and local immune defenses. Pathogen virulence is enhanced by the presence of fimbriae that facilitate adherence to structures in the urinary tract.

Most UTIs ascend from the urethra and bladder. A number of factors interact in determining the predisposition to development of UTIs, including urinary tract obstruction, urine stasis and reflux, pregnancy-induced changes in urinary tract function, age-related changes in the urinary tract, changes in the protective mechanisms of the bladder and ureters, impaired immune function, and virulence of the pathogen. Urinary tract catheters and urinary instrumentation contribute to the incidence of UTIs. Early diagnosis and treatment of UTIs are essential to preventing permanent kidney damage.

## DISORDERS OF GLOMERULAR FUNCTION

The glomeruli are tufts of capillaries that lie between the afferent and efferent arterioles. The capillaries of the glomeruli are arranged in lobules and supported by a stalk consisting of mesangial cells and a basement membrane-like extracellular matrix (Fig. 23-7). The glomerular membrane is composed of three layers: an endothelial layer lining the capillary, a basement membrane, and a layer of epithelial cells forming the outer surface of the capillary and lining Bowman's capsule (see Chapter 22, Fig. 22-5). The epithelial cells are attached to the basement membrane by discrete cytoplasmic extensions, the foot processes (*i.e.*, podocytes). In the glomeruli, blood is filtered, and the urine filtrate formed. The capillary membrane is selectively permeable: it allows water, electrolytes, and dissolved particles, such as glucose and amino acids, to leave the capillary and enter Bowman's space and prevents larger particles, such as plasma proteins and blood cells, from leaving the blood.

### Mechanisms of Glomerular Injury

Glomerulonephritis, an inflammatory process that involves glomerular structures, is the leading cause of chronic renal failure in the United States, accounting for one half of persons with end-stage renal disease.<sup>24</sup> There are many causes of

## KEY CONCEPTS

### GLOMERULAR DISEASE

- Glomerular disorders affect the glomerular capillary membrane structures that filter materials from the blood.
- Nephritic syndromes are caused by diseases that produce proliferative inflammatory responses that decrease the permeability of the glomerular capillary membrane.
- The nephrotic syndrome is caused by disorders that increase the permeability of the glomerular capillary membrane, causing massive loss of protein in the urine.

glomerular disease. The disease may occur as a primary condition in which the glomerular abnormality is the only disease present, or it may occur as a secondary condition in which the glomerular abnormality results from another disease, such as diabetes mellitus or SLE. An understanding of the various forms of glomerular disease has emerged only recently. Much of this knowledge can be attributed to advances in immunobiology and electron microscopy, development of animal models, and increased use of renal biopsy during the early stages of glomerular disease.

Although little is known about the causative agents or triggering events that produce glomerular disease, most cases of primary and many cases of secondary glomerular disease probably have an immune origin.<sup>5,6,24</sup> Two types of immune mechanisms have been implicated in the development of glomerular disease: injury resulting from antibodies reacting with fixed glomerular antigens, and injury resulting from circulating antigen-antibody complexes that become trapped in the glomerular membrane (Fig. 23-8). Antigens responsible for development of the immune response may be of endogenous origin, such as DNA in SLE, or they may be of exogenous origin, such as streptococcal membrane antigens in poststreptococcal glomerulonephritis. Frequently, the source of the antigen is unknown.

The cellular changes that occur with glomerular disease include proliferative, sclerotic, and membranous changes. The term *proliferative* refers to an increase in the cellular components of the glomerulus, regardless of origin; *sclerotic* to an increase in the noncellular components of the glomerulus, primarily collagen; and *membranous* to an increase in the thickness of the glomerular capillary wall, often caused by immune complex deposition. Glomerular changes can be *diffuse*, involving all glomeruli and all parts of the glomeruli; *focal*, in which only some glomeruli are affected and others are essentially normal; *segmental*, involving only a certain segment of each glomeruli; or *mesangial*, affecting only the mesangial cell. Figure 23-8 shows changes associated with various types of glomerular disease.

Among the different types of glomerular diseases are the nephritic syndromes, which produce a proliferative inflammatory response; the nephrotic syndromes, which involve increased permeability of the glomerulus; and chronic glomerulonephritis, which represents the chronic phase of a number of glomerular disorders.

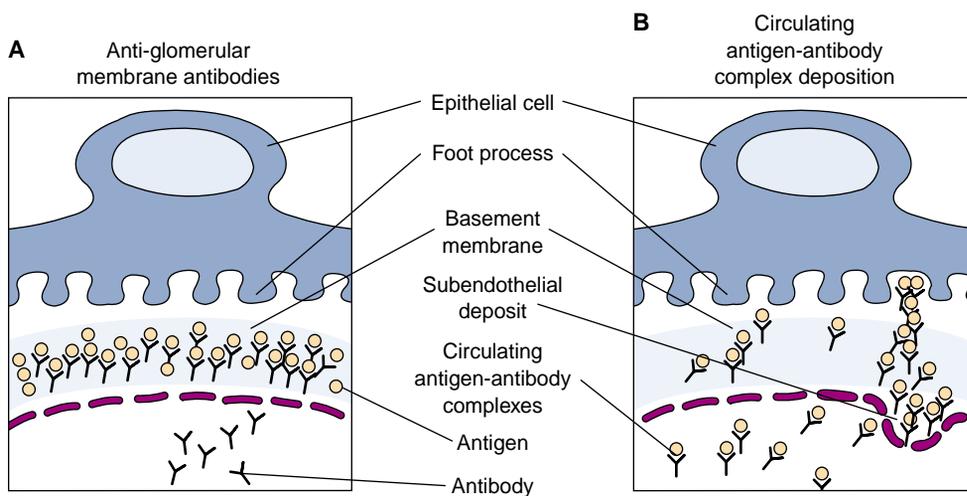
## Nephritic Syndromes

Glomerulonephritis is characterized by hematuria with red cell casts, a diminished glomerular filtration rate (GFR), azotemia (presence of nitrogenous wastes in the blood), oliguria, and hypertension. It is caused by diseases that provoke a proliferative inflammatory response of the endothelial, mesangial, or epithelial cells of the glomeruli. The inflammatory process damages the capillary wall, permitting red blood cells to escape into the urine and producing hemodynamic changes that decrease the GFR. The nephritic syndromes include acute proliferative glomerulonephritis and rapidly progressive glomerulonephritis.

### Acute Proliferative Glomerulonephritis

The most commonly recognized form of acute glomerulonephritis is diffuse proliferative glomerulonephritis, which follows infections caused by strains of group A  $\beta$ -hemolytic streptococci. Diffuse proliferative glomerulonephritis also may occur after infections by other organisms, including staphylococci and a number of viral agents, such as those responsible for mumps, measles, and chickenpox. With this type of nephritis, the inflammatory response is caused by an immune reaction that occurs when circulating immune complexes become entrapped in the glomerular membrane. Proliferation of the endothelial cells lining the glomerular capillary (*i.e.*, endocapillary form of the disease) and the mesangial cells lying between the endothelium and the epithelium follows (see Fig. 23-8). The capillary membrane swells and becomes permeable to plasma proteins and blood cells. Although the disease is seen primarily in children, adults of any age also can be affected.

The classic case of poststreptococcal glomerulonephritis follows a streptococcal infection by approximately 7 to 12 days—the time needed for the development of antibodies.<sup>24</sup> Oliguria, which develops as the GFR decreases, is one of the first symptoms. Proteinuria and hematuria follow because of increased glomerular capillary wall permeability. The blood is degraded by materials in the urine, and a cola-colored urine may be the first sign of the disorder. Sodium and water retention gives rise to edema, particularly of the face and hands, and hypertension. Important laboratory findings include an elevated streptococcal exoenzyme (antistreptolysin O) titer, a decline in C3 com-



**FIGURE 23-8** Immune mechanisms of glomerular disease. (A) Antiglomerular antibodies leave the circulation and interact with antigens that are present in the basement membrane of the glomerulus. (B) Antigen-antibody complexes circulating in the blood become trapped as they are filtered in the glomerulus.

plement (see Chapter 10), and cryoglobulins (*i.e.*, large immune complexes) in the serum.

Treatment for acute poststreptococcal glomerulonephritis is largely symptomatic. The acute symptoms usually begin to subside in approximately 10 days to 2 weeks, although in some children the proteinuria may persist for several months. The immediate prognosis is favorable, and approximately 95% of children recover spontaneously.<sup>5</sup> The outlook for adults is less favorable; approximately 60% recover completely. In the remainder of cases, the lesions eventually resolve, but there may be permanent kidney damage.

### Rapidly Progressive Glomerulonephritis

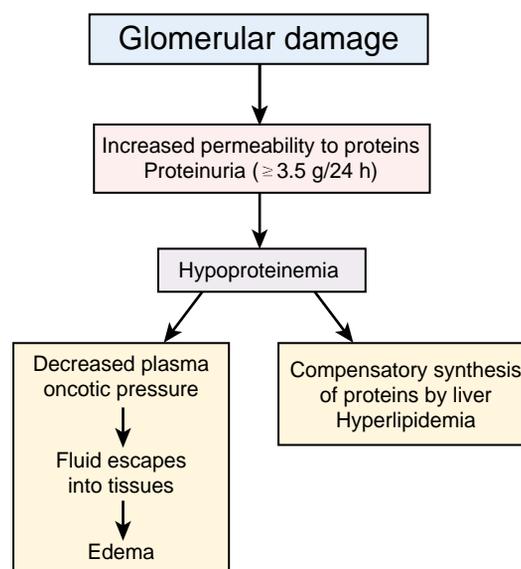
Rapidly progressive glomerulonephritis is a clinical syndrome characterized by signs of severe glomerular injury that does not have a specific cause. As its name indicates, this type of glomerulonephritis is rapidly progressive, often within a matter of months. The disorder involves focal and segmental proliferation of glomerular cells and recruitment of monocytes (macrophages) with formation of crescent-shaped structures that obliterate Bowman's space.<sup>5</sup> Rapidly proliferative glomerulonephritis may be caused by a number of immunologic disorders, some systemic and others restricted to the kidney. Among the diseases associated with this form of glomerulonephritis are immune complex disorders such as SLE, the small vessel vasculitides (*e.g.*, microscopic polyangiitis), and an immune disorder condition called *Goodpasture's syndrome*.

Goodpasture's syndrome, which is caused by antibodies to the glomerular basement membrane (GBM), accounts for approximately 5% of cases of rapidly progressive glomerulonephritis. It is a rare disease and is associated with a triad of pulmonary hemorrhage, iron-deficiency anemia, and glomerulonephritis. All of these manifestations result from anti-GBM antibody deposition in the lungs and glomeruli. The cause of the disorder is unknown, although influenza infection and exposure to hydrocarbon solvent (found in paints and dyes) have been implicated in some persons, as have various drugs and cancers. There is a high prevalence of certain human leukocyte antigen subtypes (*e.g.*, HLA-DRB1), suggesting a genetic predisposition.<sup>5</sup> Treatment includes plasmapheresis to remove circulating anti-GBM antibodies and immunosuppressive therapy (*i.e.*, corticosteroids and cyclophosphamide) to inhibit antibody production.

### Nephrotic Syndrome

Nephrotic syndrome is not a specific glomerular disease but a constellation of clinical findings that result from increased glomerular permeability to the plasma proteins (Fig. 23-9). The glomerular derangements that occur with nephrosis can develop as a primary disorder or secondary to changes caused by systemic diseases such as diabetes mellitus, amyloidosis, and SLE. Among the primary glomerular lesions leading to nephrotic syndrome are minimal change disease (lipoid nephrosis), focal segmental glomerulosclerosis, and membranous glomerulonephritis. The relative frequency of these causes varies with age. In children younger than 15 years of age, nephrotic syndrome almost always is caused by primary glomerular disease, whereas in adults it often is a secondary disorder.<sup>5</sup>

The nephrotic syndrome is characterized by massive proteinuria (>3.5 g/day) and lipiduria (*e.g.*, free fat, oval bodies,



■ FIGURE 23-9 ■ Pathophysiology of the nephrotic syndrome.

fatty casts), along with an associated hypoalbuminemia (<3 g/dL), generalized edema, and hyperlipidemia (cholesterol >300 mg/dL).<sup>6,25,26</sup> The initiating event in the development of nephrosis is a derangement in the glomerular membrane that causes increased permeability to plasma proteins. The glomerular membrane acts as a size and charge barrier through which the glomerular filtrate must pass. Any increased permeability allows protein to escape from the plasma into the glomerular filtrate.

Generalized edema, which is a hallmark of nephrosis, results from salt and water retention and a loss of serum albumin below that needed to maintain the colloid osmotic pressure of the vascular compartment.<sup>5</sup> The sodium and water retention appears to be caused by several factors, including a compensatory increase in aldosterone, stimulation of the sympathetic nervous system, and a reduction in secretion of natriuretic factors. Initially, the edema presents in dependent parts of the body, such as the lower extremities, but becomes more generalized as the disease progresses. Dyspnea caused by pulmonary edema, pleural effusions, and diaphragmatic compromise attributable to ascites can develop in persons with nephrotic syndrome.<sup>15</sup>

Although the largest proportion of plasma protein loss is in albumin, globulins also are lost. As a result, persons with nephrosis are particularly vulnerable to infections, particularly those caused by staphylococci and pneumococci.<sup>5</sup> This decreased resistance to infection probably is related to loss of both immunoglobulins and low-molecular-weight complement components in the urine. Many binding proteins also are lost in the urine. Consequently, the plasma levels of many ions (iron, copper, zinc), hormones (thyroid and sex hormones), and drugs may be low because of decreased binding proteins. Many drugs require protein binding for transport. Hypoalbuminemia reduces the number of available protein binding sites, thereby producing a potential increase in the amount of free (active) drug that is available.<sup>27</sup>

Thrombotic complications also have evolved as a risk in persons with nephrotic syndrome. These disorders are thought to be related to a disruption in the function of the coagulation

system brought about by a loss of coagulation and anticoagulation factors.<sup>15,27</sup> Renal vein thrombosis, once thought to be a cause of the disorder, is more likely a consequence of the hypercoagulable state.<sup>5</sup> Other thrombotic complications include deep vein thrombosis and pulmonary emboli.

The hyperlipidemia that occurs in persons with nephrosis is characterized by elevated levels of triglycerides and low-density lipoproteins (LDL). Levels of high-density lipoproteins (HDL) usually are normal. These abnormalities are thought to be related, in part, to increased synthesis of lipoproteins in the liver secondary to a compensatory increase in albumin production. Because of the elevated LDL levels, persons with nephrotic syndrome are at increased risk for development of atherosclerosis.

### Membranous Glomerulonephritis

Membranous glomerulonephritis is the most common cause of primary nephrosis in adults, most commonly people in their sixth or seventh decade. The disorders are caused by diffuse thickening of the GBM attributable to deposition of immune complexes. The disorder may be idiopathic or associated with a number of disorders, including autoimmune diseases such as SLE, infections such as chronic hepatitis B, metabolic disorders such as diabetes mellitus and thyroiditis, and use of certain drugs such as gold, penicillamine, and captopril.<sup>5</sup> Because of the presence of immunoglobulins and complement in the subendothelial deposits, it is thought that the disease represents a chronic antigen-antibody complex-mediated disorder.

The disorder is treated with corticosteroids. Cytotoxic drugs may be added to the treatment regimen. The progress of the disease is variable; approximately one half of persons sustain a slow but progressive loss of renal function.

### Minimal Change Disease (Lipoid Nephrosis)

Minimal change disease is characterized by diffuse loss (through fusion) of the foot processes from the epithelial layer of the glomerular membrane. The peak incidence is between 2 and 6 years of age. The cause of minimal change nephrosis is unknown; however, children in whom the disease develops often have a history of recent upper respiratory infections or of receiving routine immunizations.<sup>5</sup> Although minimal change disease does not progress to renal failure, it can cause significant complications, including predisposition to infection with gram-positive organisms, a tendency toward thromboembolic events, hyperlipidemia, and protein malnutrition. There usually is a dramatic response to corticosteroid therapy.<sup>5</sup>

### Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis is characterized by sclerosis (*i.e.*, increased collagen deposition) of some but not all glomeruli, and in the affected glomeruli, only a portion of the glomerular tuft is involved. Although focal segmental sclerosis often is an idiopathic syndrome, it may be associated with reduced oxygen in the blood (*e.g.*, sickle cell disease and cyanotic congenital heart disease), HIV infection, or intravenous drug abuse, or it may be a secondary event reflecting glomerular scarring caused by other forms of glomerulonephritis or reflux nephropathy.<sup>5,6</sup> The presence of hypertension and decreased renal function distinguishes focal sclerosis from minimal change disease. The disorder usually is treated with corticosteroids. Most persons with focal segmental glomerulosclerosis progress to end-stage renal disease within 5 to 10 years.

## Chronic Glomerulonephritis

Chronic glomerulonephritis represents the chronic phase of a number of specific types of glomerulonephritis.<sup>5</sup> Some forms of glomerulonephritis (*e.g.*, poststreptococcal glomerulonephritis) undergo complete resolution, whereas others progress at variable rates to chronic glomerulonephritis. Some persons who present with chronic glomerulonephritis have no history of glomerular disease. These cases may represent the end result of relatively asymptomatic forms of glomerulonephritis. Histologically, the condition is characterized by small kidneys with sclerosed glomeruli. In most cases, chronic glomerulonephritis develops insidiously and slowly progresses to end-stage renal disease over a period of years (see Chapter 24).

## Glomerular Lesions Associated With Systemic Disease

Many immunologic, metabolic, or hereditary systemic diseases are associated with glomerular injury. In some diseases, such as systemic lupus erythematosus and diabetes mellitus, the glomerular involvement may be a major clinical manifestation. The glomerular lesions associated with diabetes mellitus and hypertension are discussed in this chapter.

### Diabetic Glomerulosclerosis

Diabetic nephropathy, or kidney disease, is a major complication of diabetes mellitus. It affects approximately 30% of persons with type 1 diabetes and accounts for 20% of deaths in diabetic patients younger than 40 years of age.<sup>5</sup>

The glomerulus is the most commonly affected structure in diabetic nephropathy, evidenced by three glomerular syndromes: non-nephrotic proteinuria, nephrotic syndrome, and renal failure. Widespread thickening of the glomerular capillary basement membrane occurs in almost all persons with diabetes and can occur without evidence of proteinuria.<sup>5</sup> This is followed by a diffuse increase in mesangial matrix, with mild proliferation of mesangial cells. In nodular glomerulosclerosis, also known as *Kimmelstiel-Wilson syndrome*, there is nodular deposition of hyaline in the mesangial portion of the glomerulus. As the sclerotic process progresses in both the diffuse and nodular forms of glomerulosclerosis, there is complete obliteration of the glomerulus, with impairment of renal function.

Although the mechanisms of glomerular change in diabetes are uncertain, they are thought to represent enhanced or defective synthesis of the glomerular basement membrane and mesangial matrix with an inappropriate incorporation of glucose into the noncellular components of these glomerular structures. Alternatively, hemodynamic changes that occur secondary to elevated blood glucose levels may contribute to the initiation and progression of diabetic glomerulosclerosis. It has been hypothesized that elevations in blood glucose produce an increase in GFR and glomerular intracapillary pressure that leads to an enlargement of glomerular capillary pores by a mechanism that is at least partly mediated by angiotensin II. This enlargement impairs the size-selective function of the membrane so that the protein content of the glomerular filtrate increases, which in turn requires increased endocytosis of protein by the tubular endothelial cells, a process that ultimately leads to nephron destruction and progressive deterioration of renal function.<sup>28,29</sup>

The clinical manifestations of diabetic glomerulosclerosis are closely linked to those of diabetes. The increased GFR that occurs in persons with early alterations in renal function is associated with *microalbuminuria*, defined as urinary albumin excretion greater than 30 mg/24 hours and no more than 300 mg/24 hours.<sup>29</sup> Microalbuminuria is an important predictor of future diabetic nephropathies.<sup>5,29</sup> In many cases, these early changes in glomerular function can be reversed by careful control of blood glucose levels (see Chapter 32).<sup>29</sup> Inhibition of angiotensin by angiotensin-converting enzyme inhibitors (e.g., captopril) has been shown to have a beneficial effect, possibly by reversing increased glomerular pressure.<sup>6,29</sup> Hypertension and cigarette smoking have been implicated in the progression of diabetic nephropathy. Thus, control of high blood pressure and smoking cessation are recommended as primary and secondary prevention strategies in persons with diabetes.

### Hypertensive Glomerular Disease

Hypertension can be viewed as both a cause and an effect of kidney disease. Most persons with advanced kidney disease have hypertension, and many persons with long-standing hypertension eventually sustain changes in kidney function. Renal failure and azotemia occur in 1% to 5% of persons with long-standing hypertension (see Chapter 16). Hypertension is associated with a number of changes in glomerular structures, including sclerotic changes. As the glomerular vascular structures thicken and perfusion diminishes, the blood supply to the nephron decreases, causing the kidneys to lose some of their ability to concentrate the urine. This may be evidenced by nocturia. Blood urea nitrogen levels also may become elevated, particularly during periods of water deprivation. Proteinuria may occur as a result of changes in glomerular structure.

**In summary,** diseases of the glomerulus disrupt glomerular filtration and alter the permeability of glomerular capillary membrane to plasma proteins and blood cells. *Glomerulonephritis* is a term used to describe a group of diseases that result in inflammation and injury of the glomerulus. These diseases disrupt the capillary membrane and cause proteinuria, hematuria, pyuria, oliguria, edema, hypertension, and azotemia. Almost all types of glomerulonephritis are caused by immune mechanisms.

Glomerular diseases have been grouped into two categories: the nephritic and the nephrotic syndromes. The nephritic syndrome evokes an inflammatory response in the glomeruli and is characterized by hematuria with red cell casts in the urine, a diminished GFR, azotemia, oliguria, and hypertension. The nephrotic syndrome affects the integrity of the glomerular capillary membrane and is characterized by massive proteinuria, hypoalbuminemia, generalized edema, lipiduria, and hyperlipidemia. Both conditions can lead to progressive loss of glomerular function and eventual development of end-stage renal disease. Among the secondary causes of glomerular kidney disease are diabetes and hypertension. Kidney disease is a major complication of diabetes mellitus and is thought to be related to hemodynamic changes associated with defective synthesis of glomerular structures associated with increased blood glucose levels. Hypertension is closely linked with kidney disease, and kidney disease can be a cause or effect of elevated blood pressure.

## TUBULOINTERSTITIAL DISORDERS

Several disorders affect renal tubular structures, including the proximal and distal tubules. Most of these disorders also affect the interstitial tissue that surrounds the tubules. These disorders, which sometimes are referred to as *tubulointerstitial disorders*, include acute tubular necrosis (see Chapter 24), pyelonephritis, and drug-induced nephropathies.

Tubulointerstitial renal diseases may be divided into acute and chronic disorders. The acute disorders are characterized by their sudden onset and by signs and symptoms of interstitial edema; they include acute pyelonephritis and acute hypersensitivity reaction to drugs. The chronic disorders produce interstitial fibrosis, atrophy, and mononuclear infiltrates; most persons are asymptomatic until late in the course of the disease. In the early stages, tubulointerstitial diseases commonly are manifested by fluid and electrolyte imbalances that reflect subtle changes in tubular function. These manifestations can include the inability to concentrate urine, as evidenced by polyuria and nocturia; interference with acidification of urine, resulting in metabolic acidosis; and diminished tubular reabsorption of sodium and other substances.<sup>5</sup>

### Pyelonephritis

Acute pyelonephritis refers to an inflammation of the kidneys and renal pelves. There are two forms of pyelonephritis: acute and chronic. *Acute pyelonephritis* represents a patchy interstitial suppurative inflammatory process, with abscess formation and tubular necrosis. Infection may occur through bloodstream or ascend from the bladder. Factors that contribute to the development of acute pyelonephritis are catheterization and urinary tract instrumentation, vesicoureteral reflux, pregnancy, and neurogenic bladder. A second less frequent and more serious type of acute pyelonephritis, called *necrotizing papillitis*, is characterized by necrosis of the renal papillae. It is particularly common in persons with diabetes and may also complicate acute pyelonephritis when there is significant urinary tract obstruction.

The onset of acute pyelonephritis typically is abrupt, with chills, fever, headache, back pain, tenderness over the costovertebral angle, and general malaise. It usually is accompanied by symptoms of bladder irritation, such as dysuria, frequency, and urgency. Pyuria occurs but is not diagnostic because it also occurs in lower UTIs. The development of necrotizing papillitis is associated with much poorer prognosis. These persons have evidence of overwhelming sepsis and, often, renal failure.

Acute pyelonephritis is treated with appropriate antimicrobial drugs. Unless obstruction or other complications occur, the symptoms usually disappear within several days. Hospitalization during initial treatment may be necessary. Depending on the cause, recurrent infections are possible.

*Chronic pyelonephritis* represents a progressive process. There is scarring and deformation of the renal calices and pelvis<sup>6</sup> (Fig. 23-10). The disorder appears to involve a bacterial infection superimposed on obstructive abnormalities or vesicoureteral reflux. Chronic obstructive pyelonephritis is associated with recurrent bouts of inflammation and scarring, which eventually lead to chronic pyelonephritis. Reflux, which is the most



■ **FIGURE 23-10** ■ Chronic pyelonephritis. Marked dilatation of calyces caused by inflammatory destruction of papillae, with atrophy and scarring of the overlying cortex. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 905]. Philadelphia: Lippincott Williams & Wilkins)

common cause of chronic pyelonephritis, results from superimposition of infection on congenital vesicoureteral reflux or intrarenal reflux. Reflux may be unilateral with involvement of a single kidney or bilateral leading to scarring and atrophy of both kidneys with the eventual development of chronic renal insufficiency.

Chronic pyelonephritis may cause many of the same symptoms as acute pyelonephritis, but its onset may be more insidious. Loss of tubular function and the ability to concentrate urine give rise to polyuria and nocturia, and mild proteinuria is common. Severe hypertension often is a contributing factor in the progress of the disease. Chronic pyelonephritis is a significant cause of renal failure. It is thought to be responsible for 11% to 20% of all cases of end-stage renal disease.<sup>5</sup>

### Drug-Related Nephropathies

Drug-related nephropathies involve functional or structural changes in the kidneys that occur after exposure to a drug. The kidneys are exposed to a high rate of delivery of any substance in the blood because of their large blood flow and high filtration pressure. The kidneys also are active in the metabolic transformation of drugs and therefore are exposed to a number of toxic metabolites. Some drugs and toxic substances damage the kidneys by causing a decrease in blood flow; others directly damage tubulointerstitial structures; and still others cause damage by producing hypersensitivity reactions.

The tolerance to drugs varies with age and depends on renal function, state of hydration, blood pressure, and the pH of the urine. Because of a decrease in physiologic function, elderly persons are particularly susceptible to kidney damage caused by drugs and toxins. The dangers of nephrotoxicity are increased

when two or more drugs capable of producing kidney damage are given at the same time.

Acute drug-related hypersensitivity reactions produce tubulointerstitial nephritis, with damage to the tubules and interstitium. This condition was observed initially in persons who were sensitive to the sulfonamide drugs; currently, it is observed most often with the use of methicillin and other synthetic antibiotics, and with the use of furosemide and the thiazide diuretics in persons sensitive to these drugs. The condition begins approximately 15 days (range, 2–40 days) after exposure to the drug.<sup>5,6</sup> At the onset, there is fever, eosinophilia, hematuria, mild proteinuria, and in approximately one fourth of cases, a rash. In approximately 50% of cases, signs and symptoms of acute renal failure develop. Withdrawal of the drug commonly is followed by complete recovery, but there may be permanent damage in some persons, usually in older persons. Drug nephritis may not be recognized in its early stage because it is uncommon.

Chronic analgesic nephritis, which is associated with analgesic abuse, causes interstitial nephritis with renal papillary necrosis. When first observed, it was attributed to phenacetin, a then-common ingredient of over-the-counter medications containing aspirin, phenacetin, and caffeine. Although phenacetin is no longer contained in these preparations, it has been suggested that other ingredients, such as aspirin and acetaminophen, also may contribute to the disorder. How much analgesic it takes to produce papillary necrosis is unknown.

Nonsteroidal anti-inflammatory drugs (NSAIDs) also have the potential for damaging renal structures, including medullary interstitial cells. Prostaglandins (particularly PGI<sub>2</sub> and PGE<sub>2</sub>) contribute to regulation of tubular blood flow.<sup>30</sup> The deleterious effects of NSAIDs on the kidney are thought to result from their ability to inhibit prostaglandin synthesis. Persons who are particularly at risk are the elderly because of age-related changes in renal function, persons who are dehydrated or have a decrease in blood volume, and persons with pre-existing kidney disease or renal insufficiency.

**In summary,** tubulointerstitial diseases affect the tubules and the surrounding interstitium of the kidneys. These disorders include pyelonephritis and the effects of drugs and toxins. Pyelonephritis, or infection of the kidney and kidney pelvis, can occur as an acute or a chronic condition. Acute pyelonephritis typically is caused by ascending bladder infections or infections that come from the bloodstream; it usually is successfully treated with appropriate antimicrobial drugs. Chronic pyelonephritis is a progressive disease that produces scarring and deformation of the renal calices and pelvis. Drug-induced impairment of tubulointerstitial structure and function usually is the result of direct toxic injury, decreased blood flow, or hypersensitivity reactions.

### NEOPLASMS

There are two major groups of renal neoplasms: embryonic kidney tumors (*i.e.*, Wilms' tumor), which occur during childhood, and renal cell carcinoma, which is the main kidney cancer in adults.

## Wilms' Tumor

Wilms' tumor (*i.e.*, nephroblastoma) is one of the most common primary neoplasms of young children. The median age at time of diagnosis of unilateral Wilms' tumor is approximately 3 years.<sup>31</sup> It is a mixed tumor, composed of epithelial and mesenchymal embryonic tissue elements.<sup>32</sup> An important feature of Wilms' tumor is its association with congenital anomalies, the most frequent being those affecting genitourinary structures.<sup>31</sup> Deletions involving at least two loci on chromosome 11 have been found in approximately 30% of children with Wilms' tumors. Some familial cases of Wilms' tumor are not associated with identifiable chromosomal deletions or mutations, suggesting a third locus may be involved.

Wilms' tumor usually is a solitary mass that occurs in any part of the kidney. It usually is sharply demarcated and variably encapsulated.<sup>6</sup> The tumors grow to a large size, distorting kidney structure. The tumors usually are staged using the Wilms' Tumor Study Group classification.<sup>31</sup> Stage I tumors are limited to the kidney and can be excised with the capsular surface intact. Stage II tumors extend into the kidney but can be excised. In stage III, extension of the tumor is confined to the abdomen, and in stage IV, hematogenous metastasis most commonly involves the lung. Bilateral kidney involvement occurs in 5% to 10% of cases.

The common presenting signs are a large asymptomatic abdominal mass and hypertension. Approximately 50% of children have abdominal pain, vomiting, or both.<sup>31</sup> Microscopic and gross hematuria are present in 10% to 25% of children. CT scans are used to confirm the diagnosis.

Treatment involves surgery, chemotherapy, and sometimes radiation therapy. Long-term survival rates have increased to approximately 90% with an aggressive treatment plan.<sup>31</sup>

## Renal Cell Carcinoma

Kidney cancer accounts for 2% of all adult cancer incidence and mortality in the United States.<sup>33</sup> The increased use of imaging procedures such as ultrasonography, CT scanning, and magnetic resonance imaging (MRI) has contributed significantly to earlier diagnosis and more accurate staging of kidney cancers.<sup>33</sup>

Renal cell carcinoma originates in the renal cortex and accounts for approximately 80% to 85% of kidney tumors, with transitional or squamous cell cancers of the renal pelvis accounting for most of the remaining cancers.<sup>34</sup> The cause of renal cell carcinoma remains unclear. It occurs most often in older persons in the sixth to seventh decade. Men are affected twice as frequently as women. Some of these tumors may occur as a result of chronic irritation associated with kidney stones. Epidemiologic evidence suggests a correlation between smoking and kidney cancer. Obesity also is a risk factor, particularly in women.<sup>34</sup> Additional risk factors include occupational exposure to petroleum products, heavy metals, and asbestos. The risk of renal cell carcinoma also is increased in persons with acquired cystic kidney disease associated with chronic renal insufficiency.<sup>34,35</sup> Most cases of renal cell carcinoma occur without a recognizable hereditary pattern. However, there are several rare forms of renal cell cancer that are characterized by an autosomal dominant pattern of inheritance, young age at onset (third and fourth decade), and bilateral or multifocal tumors.<sup>34,35</sup>

Kidney cancer is largely a silent disorder during its early stages, and symptoms usually denote advanced disease. Presenting features include hematuria, costovertebral pain, presence of a palpable flank mass, polycythemia, and fever. Hematuria, which occurs in 70% to 90% of cases, is the most reliable sign. However, it is intermittent and may be microscopic; as a result, the tumor may reach considerable size before it is detected. In approximately one third of cases, metastases are present at the time of diagnosis.

Kidney cancer is suspected when there are findings of hematuria and a renal mass. Ultrasonography, CT scanning, excretory urography, and renal angiography are used to confirm the diagnosis. MRI with intravenous gadolinium may be used when involvement of the inferior vena cava is suspected.

Surgery (radical nephrectomy with lymph node dissection) is the treatment of choice for all resectable tumors. Nephron-sparing surgery may be done when both kidneys are involved or when the contralateral kidney is threatened by an associated disease such as hypertension or diabetes mellitus. Single-agent and combination chemotherapy have been used with limited success. The prognosis depends on the stage of the cancer; the 5-year survival rate associated with stage I tumors is 65% to 85%; for stage IV tumors, it is 0% to 10%.<sup>34,35</sup>

**In summary**, there are two major groups of renal neoplasms: embryonic kidney tumors (*i.e.*, Wilms' tumor) that occur during childhood and adult renal cell carcinomas. Wilms' tumor is the most common malignant tumor of children. The most common presenting signs are a large abdominal mass and hypertension. Treatment is surgery, chemotherapy, and sometimes radiation therapy. The long-term survival rate for children with Wilms' tumor is approximately 90% with an aggressive plan of treatment.

Renal cell carcinoma accounts for 2% of all adult cancers. These tumors are characterized by a lack of early warning signs, diverse clinical manifestations, and resistance to chemotherapy and radiation therapy. Because of the lack of early warning signs, the tumors often are far advanced at the time of diagnosis. Diagnostic methods include ultrasonography and CT scans. The treatment of choice is surgical resection.

## REVIEW QUESTIONS

- Define the terms *agenesis*, *dysgenesis*, and *hypoplasia* as they refer to the development of the kidney.
- Describe the genetic basis for renal cystic disease, the pathology of the disorder, and its signs and symptoms.
- Describe the effects of urinary tract obstruction on renal structure and function.
- Cite three theories that are used to explain the formation of kidney stones.
- Explain the mechanisms of pain and infection that occur with kidney stones.
- Cite the organisms most responsible for UTIs and state why urinary catheters, obstruction, and reflux predispose to infections.

- List three physiologic mechanisms that protect against UTIs.
- Compare the manifestations of UTIs in different age groups, including infants, toddlers, adolescents, adults, and older adults.
- Use the terms *proliferation*, *sclerosis*, *membranous*, *diffuse*, *focal*, *segmental*, and *mesangial* to explain changes in glomerular structure that occur with glomerulonephritis.
- Relate the proteinuria, hematuria, pyuria, oliguria, edema, hypertension, and azotemia that occur with glomerulonephritis to changes in glomerular structure.
- Cite a definition of tubulointerstitial kidney disease.
- Explain the vulnerability of the kidneys to injury caused by drugs and toxins.
- Characterize Wilms' tumor in terms of age of onset, possible oncogenic origin, manifestations, and treatment.
- Cite the risk factors for renal cell carcinoma, describe the manifestations, and explain why the 5-year survival rate has been so low.



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