Chapter 26

Acute Renal Failure and Chronic Kidney Disease

Renal failure is a condition in which the kidneys fail to remove metabolic end products from the blood and regulate the fluid, electrolyte, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, or urologic defects of nonrenal origin. Renal failure can occur as an acute or a chronic disorder. Acute renal failure is abrupt in onset and often is reversible if recognized early and treated appropriately. In contrast, chronic kidney disease is the end result of irreparable damage to the kidneys. It develops slowly, usually over the course of a number of years.

Acute Renal Failure

Acute renal failure (ARF), which is a common threat to seriously ill persons, represents a rapid decline in kidney function, resulting in an inability to maintain fluid and electrolyte balance and to excrete nitrogenous wastes.[1–6] Acute renal failure is also called *acute kidney injury*, because even small decrements in kidney function, changes that are insufficient to be recognized as renal failure, are associated with increased morbidity and mortality.[7,8] Despite advances in treatment methods, the mortality rate from ARF has not changed substantially since the 1960s.[1] This probably is because ARF is seen more often in older persons than before, and because it frequently is superimposed on other life-threatening conditions, such as trauma, shock, and sepsis.

The most common indicator of acute renal failure is *azotemia,* an accumulation of nitrogenous wastes (urea nitrogen, uric acid, and creatinine) in the blood and a decrease in the glomerular filtration rate (GFR). As a result, excretion of nitrogenous wastes is reduced and fluid and electrolyte balance cannot be maintained.

Types of Acute Renal Failure

Acute renal failure can be caused by several types of conditions, including a decrease in blood flow without

Acute Renal Failure

- Acute renal failure is caused by conditions that produce an acute shutdown in renal function.
- It can result from decreased blood flow to the kidney (prerenal failure), disorders that disrupt the structures in the kidney (intrinsic or intrarenal failure), or disorders that interfere with the elimination of urine from the kidney (postrenal failure).
- Acute renal failure, although it causes an accumulation of products normally cleared by the kidney, is a potentially reversible process if the factors causing the condition can be corrected.

ischemic injury; ischemic, toxic, or obstructive tubular injury; and obstruction of urinary tract outflow. The causes of ARF commonly are categorized as prerenal, intrinsic, and postrenal[1–6] (Fig. 26-1). Collectively, prerenal and intrinsic causes account for 80% to 95% of ARF cases.[3] Causes of renal failure within these categories are summarized in Chart 26-1.

Prerenal Failure

Prerenal failure, the most common form of ARF, is characterized by a marked decrease in renal blood flow. It is reversible if the cause of the decreased renal blood flow can be identified and corrected before kidney damage occurs.

Normally, the kidneys receive 22% of the cardiac output.[9] This large blood supply is required to remove metabolic wastes and regulate body fluids and electrolytes.

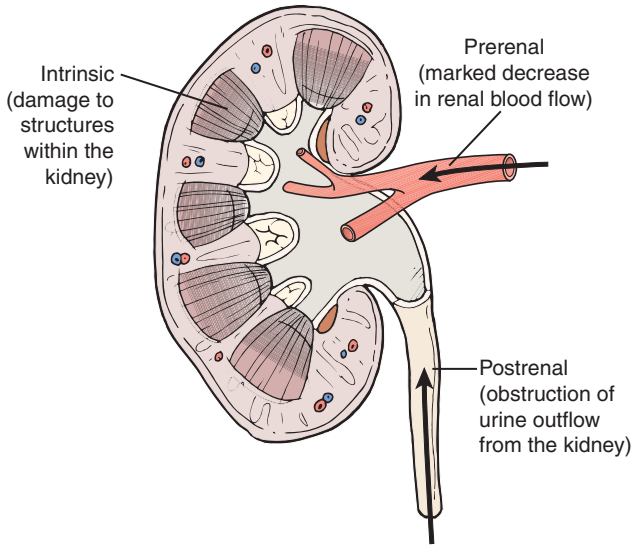

FIGURE 26-1. Types of acute renal failure.

CHART 26-1 Causes of Acute Renal Failure

Prerenal

Hypovolemia
- Hemorrhage
- Dehydration
- Excessive loss of gastrointestinal tract fluids
- Excessive loss of fluid due to burn injury

Decreased vascular filling
- Anaphylactic shock
- Septic shock

Heart failure and cardiogenic shock

Decreased renal perfusion due to sepsis, vasoactive mediators, drugs, diagnostic agents

Intrinsic or intrarenal

Acute tubular necrosis
- Prolonged renal ischemia
- Exposure to nephrotoxic drugs, heavy metals, and organic solvents
- Intratubular obstruction resulting from hemoglobinuria, myoglobinuria, myeloma light chains, or uric acid casts
- Acute renal disease (acute glomerulonephritis, pyelonephritis)

Postrenal

Bilateral ureteral obstruction

Bladder outlet obstruction

Fortunately, the normal kidney can tolerate relatively large reductions in blood flow before renal damage occurs. As renal blood flow falls, the GFR decreases, the amount of sodium and other substances that are filtered by the glomeruli is reduced, and the blood flow needed for the energy-dependent mechanisms that reabsorb these substances is reduced (see Chapter 24). As the GFR and urine output approach zero, oxygen consumption by the kidney approximates that required to keep renal tubular cells alive. When blood flow falls below this level, which is about 25% of normal, ischemic changes occur.[9] Because of their high metabolic rate, the tubular epithelial cells are most vulnerable to ischemic injury. Improperly treated, prolonged renal hypoperfusion can lead to ischemic tubular necrosis with significant morbidity and mortality.

Causes of prerenal failure include profound depletion of vascular volume (e.g., hemorrhage, loss of extracellular fluid volume), impaired perfusion due to heart failure and cardiogenic shock, and decreased vascular filling because of increased vascular capacity (e.g., anaphylaxis or sepsis). Elderly persons are particularly at risk because of their predisposition to hypovolemia and their high prevalence of renal vascular disorders.

Some vasoactive mediators, drugs, and diagnostic agents stimulate intense intrarenal vasoconstriction and can induce glomerular hypoperfusion and prerenal failure. Examples include endotoxins, radiocontrast agents such as those used for cardiac catheterization, cyclosporine (an immunosuppressant drug that is used to prevent transplant

rejection), amphotericin B (an antifungal agent), epinephrine, and high doses of dopamine.[3] Many of these agents also cause acute tubular necrosis (discussed later). In addition, several commonly used classes of drugs can impair renal adaptive mechanisms and can convert compensated renal hypoperfusion into prerenal failure. Angiotensin II is a potent renal vasoconstrictor that preferentially constricts the efferent arterioles of the kidney as a means of preserving the GFR in situations of arterial hypotension or volume depletion. The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the effects of angiotensin II on renal blood flow. They also reduce intraglomerular pressure and may have a renal protective effect in persons with hypertension or type 2 diabetes. However, when combined with diuretics, they may cause prerenal failure in persons with decreased blood flow due to large-vessel or small-vessel kidney disease. Prostaglandins have a vasodilatory effect on renal blood vessels. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce renal blood flow through inhibition of prostaglandin synthesis. In some persons with diminished renal perfusion, NSAIDs can precipitate prerenal failure.

Prerenal failure is manifested by a sharp decrease in urine output and a disproportionate elevation of blood urea nitrogen (BUN) in relation to serum creatinine levels. The kidney normally responds to a decrease in the GFR with a decrease in urine output. Thus, an early sign of prerenal failure is a sharp decrease in urine output. A low fractional excretion of sodium (<1%) suggests that oliguria is due to decreased renal perfusion and that the nephrons are responding appropriately by decreasing the excretion of filtered sodium in an attempt to preserve vascular volume. BUN levels also depend on the GFR. A low GFR allows more time for small particles such as urea to be reabsorbed into the blood. Creatinine, which is larger and nondiffusible, remains in the tubular fluid, and the total amount of creatinine that is filtered, although small, is excreted in the urine. Consequently, there also is a disproportionate elevation in the ratio of BUN to serum creatinine, from a normal value of 10:1 to a ratio greater than 20:1.[1]

Intrinsic Renal Failure

Intrinsic, or intrarenal, renal failure results from conditions that cause injury to structures within the kidney. The major causes of intrinsic failure are ischemia associated with prerenal failure, injury to the tubular structures of the nephron, and intratubular obstruction. Acute glomerulonephritis and acute pyelonephritis also are intrinsic causes of ARF. Injury to the tubular structures of the nephron (acute tubular necrosis) is the most common cause and often is ischemic or toxic in origin.

Acute Tubular Necrosis. Acute tubular necrosis (ATN) is characterized by the destruction of tubular epithelial cells with acute suppression of renal function (Fig. 26-2). ATN can be caused by a number of conditions, including acute tubular damage due to ischemia, sepsis, nephrotoxic effects of drugs, tubular obstruction, and toxins from a

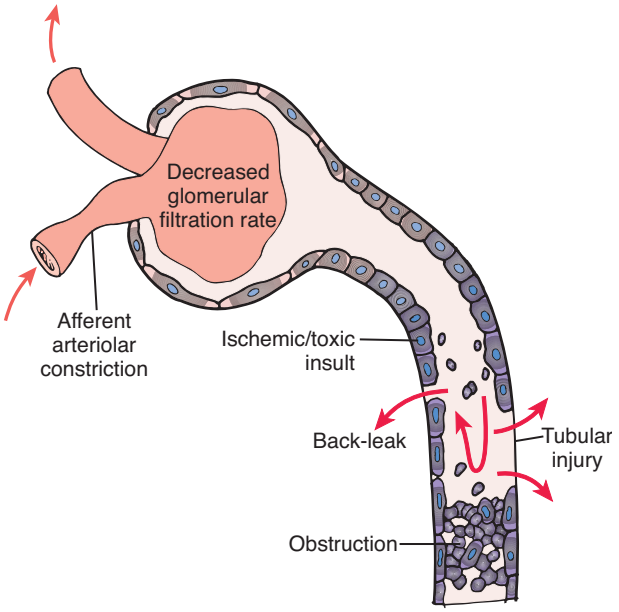

FIGURE 26-2. Pathogenesis of acute tubular necrosis (ATN). Sloughing and necrosis of tubular epithelial cells lead to obstruction and increased intraluminal pressure, which reduce glomerular filtration. Afferent arteriolar vasoconstriction caused in part by tubuloglomerular feedback mechanisms results in decreased glomerular capillary filtration pressure. Tubular injury and increased intraluminal pressure cause fluid to move from the tubular lumen into the interstitium (back-leak). (Modified from Rubin E., Farber J.L. [Eds.]. [1999]. *Pathology* [3rd ed., p. 901]. Philadelphia: Lippincott-Raven.)

massive infection.[3–5,10] Tubular epithelial cells are particularly sensitive to ischemia and also are vulnerable to toxins. The tubular injury that occurs in ATN frequently is reversible. The process depends on recovery of the injured cells, removal of the necrotic cells and intratubular casts, and regeneration of tubular cells to restore the normal continuity of the tubular epithelium.[5,11]

ATN occurs most frequently in persons who have major surgery, severe hypovolemia, or overwhelming sepsis, trauma, or burns.[3] Sepsis produces ischemia by provoking a combination of systemic vasodilation and intrarenal hypoperfusion. In addition, sepsis results in the generation of toxins that sensitize renal tubular cells to the damaging effects of ischemia. ATN complicating trauma and burns frequently is multifactorial in origin, resulting from the combined effects of hypovolemia, myoglobinuria, and other toxins released from damaged tissue. In contrast to prerenal failure, the GFR does not improve with the restoration of renal blood flow in ARF caused by ischemic ATN.

Nephrotoxic ATN complicates the administration of or exposure to many structurally diverse drugs and other nephrotoxic agents. These agents cause tubular injury by inducing varying combinations of renal vasoconstriction, direct tubular damage, or intratubular obstruction. The kidney is particularly vulnerable to nephrotoxic injury because of its rich blood supply and ability to concentrate toxins to high levels in the medullary portion of the

kidney. In addition, the kidney is an important site for metabolic processes that transform relatively harmless agents into toxic metabolites. Pharmacologic agents that are directly toxic to the renal tubule include antimicrobials such as aminoglycosides (e.g., gentamicin), cancer chemotherapeutic agents such as cisplatin and ifosfamide, and radiocontrast agents.[3,5] Several factors contribute to aminoglycoside nephrotoxicity, including a decrease in the GFR, preexisting renal disease, hypovolemia, and concurrent administration of other drugs that have a nephrotoxic effect. Cisplatin accumulates in proximal tubule cells, inducing mitochondrial injury and inhibition of adenosine triphosphatase (ATPase) activity and solute transport. Radiocontrast media–induced nephrotoxicity is thought to result from direct tubular toxicity and renal ischemia.[12] The risk for renal damage caused by radiocontrast media is greatest in elderly persons and those with preexisting kidney disease, volume depletion, diabetes mellitus, and recent exposure to other nephrotoxic agents.

The presence of multiple myeloma light chains, excess uric acid, myoglobin, or hemoglobin in the urine is the most frequent cause of ATN due to intratubular obstruction. Both myeloma cast nephropathy (Chapter 11) and acute urate nephropathy (Chapter 8) usually are seen in the setting of widespread malignancy or massive tumor destruction by therapeutic agents.[3] Hemoglobinuria results from blood transfusion reactions and other hemolytic crises. Skeletal and cardiac muscles contain myoglobin, which corresponds to hemoglobin in function, serving as an oxygen reservoir in the muscle fibers. Myoglobin normally is not found in the serum or urine. It has a low molecular weight; if it escapes into the circulation, it is rapidly filtered in the glomerulus. A life-threatening condition known as *rhabdomyolysis* occurs when increasing myoglobinuria levels cause myoglobin to precipitate in the renal tubules, leading to obstruction and damage to surrounding tubular cells. Myoglobinuria most commonly results from muscle trauma, but may result from extreme exertion, hyperthermia, sepsis, prolonged seizures, potassium or phosphate depletion, and alcoholism or drug abuse. Both myoglobin and hemoglobin discolor the urine, which may range from the color of tea to red, brown, or black.

The clinical course of ATN can be divided into three phases: the onset or initiating phase, the maintenance phase, and the recovery or reparative phase. The *onset* or *initiating phase,* which lasts hours or days, is the time from the onset of the precipitating event (e.g., ischemic phase of prerenal failure or toxin exposure) until tubular injury occurs.

The *maintenance phase* of ATN is characterized by a marked decrease in the GFR, causing sudden retention of endogenous metabolites, such as urea, potassium, sulfate, and creatinine, that normally are cleared by the kidneys. The urine output usually is lowest at this point. Fluid retention gives rise to edema, water intoxication, and pulmonary congestion. If the period of oliguria is prolonged, hypertension frequently develops and with it signs of uremia. When untreated, the neurologic manifestations of uremia progress from neuromuscular irritability to seizures, somnolence, coma, and death. Hyperkalemia usually is asymptomatic until the serum potassium level rises above 6 to 6.5 mEq/L (6 to 6.5 mmol/L), at which point characteristic electrocardiographic changes and symptoms of muscle weakness are seen.

Formerly, most patients with ATN were oliguric. During the past several decades, a nonoliguric form of ATN has become increasingly prevalent. Persons with nonoliguric failure have higher levels of glomerular filtration and excrete more nitrogenous waste, water, and electrolytes in their urine than persons with acute oliguric renal failure. Abnormalities in blood chemistry levels usually are milder and cause fewer complications. The decrease in oliguric ATN probably reflects new approaches to the treatment of poor cardiac performance and circulatory failure that focus on vigorous plasma volume expansion and the selective use of dopamine and other drugs to improve renal blood flow (see Chapter 20). Dopamine has renal vasodilator properties and inhibits sodium reabsorption in the proximal tubule, thereby decreasing the work demands of the nephron.

The *recovery phase* is the period during which repair of renal tissue takes place. Its onset usually is heralded by a gradual increase in urine output and a fall in serum creatinine, indicating that the nephrons have recovered to the point at which urine excretion is possible. Diuresis often occurs before renal function has fully returned to normal. Consequently, BUN and serum creatinine, potassium, and phosphate levels may remain elevated or continue to rise even though urine output is increased. In some cases, the diuresis may result from impaired nephron function and may cause excessive loss of water and electrolytes. Eventually, renal tubular function is restored with improvement in concentrating ability. At about the same time, the BUN and creatinine begin to return to normal. In some cases, mild to moderate kidney damage persists.

Postrenal Failure

Postrenal failure results from obstruction of urine outflow from the kidneys. The obstruction can occur in the ureter (i.e., calculi and strictures), bladder (i.e., tumors or neurogenic bladder), or urethra (i.e., prostatic hyperplasia). Prostatic hyperplasia is the most common underlying problem. Because both ureters must be occluded to produce renal failure, obstruction of the bladder rarely causes ARF unless one of the kidneys already is damaged or a person has only one kidney. The treatment of acute postrenal failure consists of treating the underlying cause of obstruction so that urine flow can be reestablished before permanent nephron damage occurs.

Diagnosis and Treatment

Given the high morbidity and mortality rates associated with ARF, attention should be focused on prevention and early diagnosis. This includes assessment measures to identify persons at risk for development of ARF, including those with preexisting renal insufficiency and diabetes. These persons are particularly at risk for development of

ARF due to nephrotoxic drugs (e.g., aminoglycosides and radiocontrast agents) or drugs such as the NSAIDs that alter intrarenal hemodynamics. Elderly persons are susceptible to all forms of ARF because of the effects of aging on renal reserve.

Careful observation of urine output is essential for persons at risk for development of ARF. Urine tests that measure urine osmolality, urinary sodium concentration, and fractional excretion of sodium help differentiate prerenal azotemia, in which the reabsorptive capacity of the tubular cells is maintained, from tubular necrosis, in which these functions are lost. One of the earliest manifestations of tubular damage is the inability to concentrate the urine. Further diagnostic information that can be obtained from the urinalysis includes evidence of proteinuria, hemoglobinuria, myoglobinuria, and casts or crystals in the urine. Blood tests for BUN and creatinine provide information regarding the ability to remove nitrogenous wastes from the blood. It also is important to exclude urinary obstruction.

A major concern in the treatment of ARF is identifying and correcting the cause (e.g., improving renal perfusion, discontinuing nephrotoxic drugs). Fluids are carefully regulated in an effort to maintain normal fluid volume and electrolyte concentrations. Adequate caloric intake is needed to prevent the breakdown of body proteins, which increases nitrogenous wastes.[5,8,10] Parenteral hyperalimentation may be used for this purpose. Because secondary infections are a major cause of death in persons with ARF, constant effort is needed to prevent and treat such infections.

Hemodialysis or continuous renal replacement therapy (CRRT) may be indicated when nitrogenous wastes and the water and electrolyte balance cannot be kept under control by other means.[5,10] Venovenous or arteriovenous CRRT has emerged as a method for treating ARF in patients too hemodynamically unstable to tolerate hemodialysis. An associated advantage of CRRT is the ability to administer nutritional support. The disadvantages are the need for prolonged anticoagulation therapy and continuous sophisticated monitoring.

In summary, acute renal failure (ARF) is an acute, potentially reversible suppression of kidney function. The disorder, which is a common threat to seriously ill persons in intensive care units, is characterized by a decrease in GFR, accumulation of nitrogenous wastes in the blood, and alterations in body fluids and electrolytes. ARF is classified as prerenal, intrinsic, and postrenal in origin. Prerenal failure is caused by decreased blood flow to the kidneys, intrinsic failure by disorders within the kidney itself, and postrenal failure by obstruction to urine output. Acute tubular necrosis, due to ischemia, sepsis, or nephrotoxic agents, is a common cause of acute intrarenal failure. Acute tabular necrosis (ATN) typically progresses through three phases: the initiation phase, during which tubular injury is induced; the maintenance phase, during which the GFR falls, nitrogenous wastes accumulate, and urine output decreases; and the recovery or reparative phase, during which the GFR, urine output, and blood levels of nitrogenous wastes return to normal.

Because of the high morbidity and mortality rates associated with ARF, identification of persons at risk is important to clinical decision making. Acute renal failure often is reversible, making early identification and correction of the underlying cause (e.g., improving renal perfusion, discontinuing nephrotoxic drugs) important. Treatment includes the judicious administration of fluids and hemodialysis or continuous renal replacement therapy.

Chronic Kidney Disease

Chronic kidney disease (CKD) is increasingly being recognized as a global health problem affecting people of all ages, races, and economic groups. The prevalence and incidence of the disease continues to rise, reflecting the growing elderly population and the increasing numbers of people with diabetes and hypertension. In the United States alone, 9.6% of noninstitutionalized adults are estimated to have CKD.[13] Statistics from Canada, Europe, Australia, and Asia confirm the high prevalence of CKD.[13,14]

Definition and Classification

Chronic kidney disease is a pathophysiologic process with multiple etiologies that results in the permanent loss of nephrons and a decline in function that frequently lead to kidney failure. Chronic kidney disease is commonly classified using the internationally accepted Kidney Disease Outcome Quality Initiative (KDOQI) staging system of the National Kidney Foundation (NKF).[15,16] The KDOQI definition and classification uses the GFR to classify CKD into five stages, beginning with kidney damage with normal or elevated GFR, progressing to CKD and, potentially, to kidney failure (Table 26-1). It is anticipated that early detection of kidney damage along with implementation of aggressive measures to decrease its progression can delay or prevent the onset of kidney failure.

GFR is used as it is much more sensitive than serum creatinine. Kidney damage that is present but undetected due to a normal GFR is classified as stage 1. Individuals with a mild decrease in GFR of 60 to 89 mL/minute/1.73 m^2 (corrected for body surface area) without kidney damage are classified as stage 2.[15] Decreased GFR without recognized markers of kidney damage can occur in infants and older adults and is usually considered to be "normal for age." Other causes of chronically decreased GFR without kidney damage in adults include removal of one kidney, extracellular fluid volume depletion, and systemic illnesses associated with reduced kidney perfusion, such as heart failure and cirrhosis.[15] Even at this stage, there is often a characteristic loss of renal reserve.

Chronic kidney disease, or stages 3 and 4 kidney disease, are defined as either kidney damage or a GFR of 30 to 59 mL/minute/1.73 m^2 for 3 months or longer.[15] CKD can result from a number of conditions that cause

TABLE 26-1 Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR, glomerular filtration rate.
Adapted from National Kidney Foundation. (2002). K/DOQI *clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification.* [Online.] Available: www.kidney.org/professionals/kdoqi/guidelines_ckd/toc/htm. Accessed April 16, 2009.

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

permanent loss of nephrons, including diabetes, hypertension, glomerulonephritis, systemic lupus erythematosus, and polycystic kidney disease.[15,17]

The KDOQI guidelines define stage 5 CKD or *kidney failure* "as either (1) a GFR of less than 15 mL/min/1.73 m², usually accompanied by most of the signs and symptoms of uremia, or (2) a need to start renal replacement therapy (dialysis or transplantation)."[15] These guidelines point out that kidney failure is not synonymous with end-stage renal disease (ESRD), which is an administrative term in the United States that indicates a person is being treated with dialysis and transplantation, a condition that qualifies persons to receive health care through the Medicare ESRD program.

Regardless of cause, CKD represents a loss of functioning kidney nephrons with progressive deterioration of glomerular filtration, tubular reabsorptive capacity, and endocrine functions of the kidneys. All forms of CKD are characterized by a reduction in the GFR, reflecting a corresponding reduction in the number of functional nephrons (Fig. 26-3).[17] The rate of nephron destruction differs from case to case, ranging from several months to many years. Typically, the signs and symptoms of CKD occur gradually and do not become evident until the disease is far advanced. This is because of the amazing compensatory ability of the kidneys. As

Chronic Kidney Disease

- Chronic kidney disease (CKD) represents the progressive decline in kidney function due to the permanent loss of nephrons.
- CKD can result from a number of conditions, including diabetes, hypertension, glomerulonephritis, and other kidney diseases.
- The glomerular filtration rate (GFR) is considered the best measure of kidney function.
- The National Kidney Foundation (NKF) Practice Guidelines divide CKD into five stages based on GFR, beginning with minimal loss of renal function (stage 1) and progressing to kidney failure (stage 5).
- The Practice Guidelines are intended to encourage the early diagnosis of CKD so that measures to delay or prevent its progression are instituted.

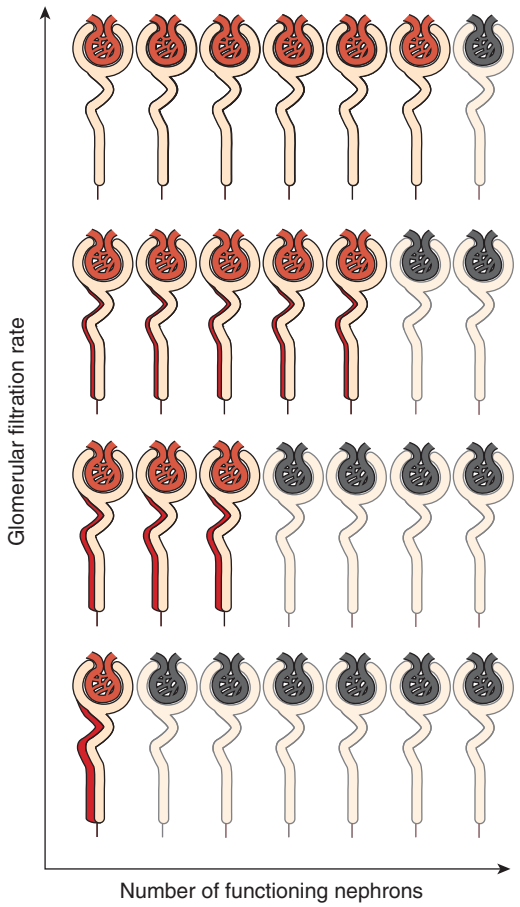

FIGURE 26-3. Relation of renal function and nephron mass. Each kidney contains about 1 million tiny nephrons. A proportional relation exists between the number of nephrons affected by a disease process and the resulting glomerular filtration rate.

kidney structures are destroyed, the remaining nephrons undergo structural and functional hypertrophy, each increasing its function as a means of compensating for those that have been lost. In the process, each of the remaining nephrons must filter more solute particles from the blood. It is only when the few remaining nephrons are destroyed that the manifestations of kidney failure become evident.

Glomerular Filtration Rate and Other Indicators of Renal Function

The GFR is considered the best measure of overall function of the kidney. The normal GFR, which varies with age, sex, and body size, is approximately 120 to 130 mL/minute/1.73 m^2 for normal young healthy adults.[15] A GFR below 60 mL/minute/1.73 m^2 represents a loss of one half or more of the level of normal adult kidney function.[18] In clinical practice, GFR is usually estimated using the serum creatinine concentration. Creatinine, a by-product of muscle metabolism, is freely filtered in the glomerulus and is not reabsorbed in the renal tubules. It is produced at a relatively constant rate by muscles in the body, and essentially all the creatinine that is filtered in the glomerulus is lost in the urine rather than being reabsorbed into the blood. Thus, serum creatinine can be used as an indirect method for assessing the GFR and the extent of kidney damage that has occurred in CKD.

Although the GFR can be obtained from measurements of creatinine clearance using timed (e.g., 24-hour) urine collection methods, the levels gathered are reportedly no more reliable than the estimated levels obtained by using serum creatinine levels.[15] Because GFR varies with age, sex, ethnicity, and body size, the Modification of Diet in Renal Diseases (MDRD) equation that takes these factors into account is often used for estimating the GFR based on serum creatinine levels[15,17,19] (available online at http://www.kidney.org/professionals/Kdoqi/gfr.cfm).

Proteinuria serves as a key adjunctive tool for measuring nephron injury and repair. Urine normally contains small amounts of protein. However, a persistent increase in protein excretion usually is a sign of kidney damage. The type of protein (e.g., low–molecular-weight globulins or albumin) depends on the type of kidney disease.[20] Increased excretion of low–molecular-weight globulins is a marker of tubulointerstitial disease, and excretion of albumin is a marker of CKD, resulting from hypertension or diabetes mellitus. For the diagnosis of CKD in adults and postpuberal children with diabetes, measurement of urinary albumin is preferred.[21] In most cases, urine dipstick tests are acceptable for detecting albuminuria. If the urine dipstick test is positive (1+ or greater), albuminuria is usually confirmed by quantitative measurement of the albumin-to-creatinine ratio in a spot (untimed) urine specimen.[20,21] Microalbuminuria, which is an early sign of diabetic kidney disease, refers to albumin excretion that is above the normal range but below the range normally detected by tests of total protein excretion in the urine. Populations at risk for CKD (i.e., those with diabetes mellitus, hypertension, or family history of kidney disease) should be screened for microalbuminuria, at least annually, as part of their health examination.[21]

Other markers of kidney disease include abnormalities in urine sediment (red and white blood cells) and abnormal findings on imaging studies.[16,17,20] Ultrasonography is particularly useful for detecting a number of kidney disorders, including urinary tract obstructions, infections, stones, and polycystic kidney disease. Other tests such as red blood cell indices, serum albumin levels, plasma electrolytes, and blood urea nitrogen are used to follow the progress of the disorder.

Clinical Manifestations

The manifestations of CKD include altered fluid, electrolyte, and acid-base balance; disorders of mineral metabolism and bone disease; anemia and coagulation disorders; cardiovascular complications; and disorders associated with an accumulation of nitrogenous wastes and impaired drug elimination[16,18,22] (Fig. 26-4). The underlying mechanisms for many of these manifestations are often interrelated. The point at which these disorders make their appearance and the severity of the manifestations are determined largely by coexisting disease conditions and the extent to which kidney function has been reduced. Many of them make their appearance before the GFR has reached the kidney failure stage.

Disorders of Fluid, Electrolyte, and Acid-Base Balance

The kidneys function in the regulation of extracellular fluid volume.[16] They do this by either eliminating or conserving sodium and water. CKD can produce dehydration or fluid overload, depending on the pathologic process of the kidney disease. In addition to volume regulation, the ability of the kidneys to concentrate the urine is diminished. An early symptom of kidney damage is *isosthenuria* or polyuria with urine that is almost isotonic with plasma (i.e., specific gravity of 1.008 to 1.012) and varies little from voiding to voiding.

As renal function declines further, the ability to regulate sodium excretion is reduced. The kidneys normally tolerate large variations in sodium intake while maintaining normal serum sodium levels. In CKD, they lose the ability to regulate sodium excretion. There is impaired ability to adjust to a sudden reduction in sodium intake and poor tolerance of an acute sodium overload. Volume depletion with an accompanying decrease in the GFR can occur with a restricted sodium intake or excess sodium loss caused by diarrhea or vomiting. Salt wasting is a common problem in advanced kidney failure because of impaired tubular reabsorption of sodium. Increasing sodium intake in persons with kidney failure often improves the GFR and whatever renal function remains. In patients with associated hypertension, the possibility of increasing blood pressure or producing congestive heart failure often excludes supplemental sodium intake.

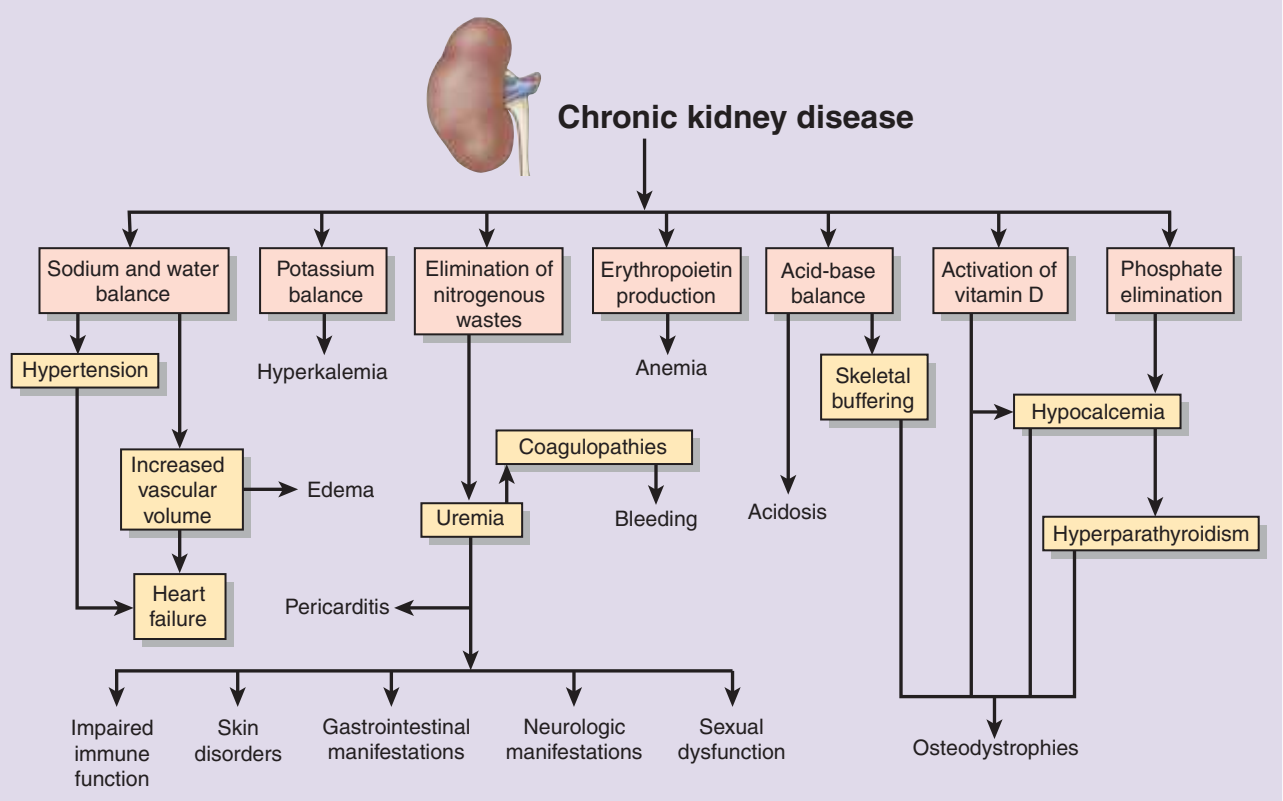

FIGURE 26-4. Mechanisms and manifestations of chronic kidney disease.

Approximately 90% of potassium excretion is through the kidneys. In CKD, potassium excretion by each nephron increases as the kidneys adapt to a decrease in the GFR. In addition, excretion in the gastrointestinal tract is increased. As a result, hyperkalemia usually does not develop until kidney function is severely compromised.[16] Because of this adaptive mechanism, it usually is not necessary to restrict potassium intake until the GFR has dropped below 5 to 10 mL/minute/1.73 m^2.[21] In persons with kidney failure, hyperkalemia often results from failure to follow dietary potassium restrictions; constipation; acute acidosis that causes the release of intracellular potassium into the extracellular fluid; trauma or infection that causes release of potassium from body tissues; or exposure to medications that contain potassium, prevent its entry into cells, or block its secretion in distal nephrons.

The kidneys also regulate the pH of the blood by eliminating hydrogen ions produced in metabolic processes and regenerating bicarbonate.[16] This is achieved through hydrogen ion secretion, sodium and bicarbonate reabsorption, and the production of ammonia, which acts as a buffer for titratable acids (see Chapter 8). With a decline in kidney function, these mechanisms become impaired and metabolic acidosis may occur when the person is challenged with an excessive acid load or loses excessive alkali, as in diarrhea. The acidosis that occurs in persons with kidney failure seems to stabilize as the disease progresses, probably as a result of the tremendous buffering capacity of bone. However, this buffering action is thought to increase bone resorption and contribute to the skeletal disorders that occur in persons with CKD.

Disorders of Calcium and Phosphorous Balance and Bone Disease

Abnormalities in calcium and phosphorous metabolism occur early in the course of CKD due to impaired phosphate elimination and vitamin D activation.[17,22–25] The regulation of serum phosphate levels requires a daily urinary excretion of an amount equal to that ingested in the diet. With deteriorating renal function, phosphate excretion is impaired, causing serum phosphate levels to rise. As a result, serum calcium levels, which are inversely regulated in relation to serum phosphate levels, fall. The drop in serum calcium, in turn, stimulates parathyroid hormone (PTH) release, with a resultant increase in calcium resorption from bone. Although serum calcium levels are maintained through increased PTH function, this adjustment is accomplished at the expense of the skeletal system and other body organs.

The kidneys regulate vitamin D activity by converting the inactive form of vitamin D (25[OH] vitamin D_3) to calcitriol (1,25[OH] vitamin D_3), the active form of vitamin D.[23–25] Reduced levels of 1,25[OH] vitamin D_3 impair the absorption of calcium from the intestine. Calcitriol also has a direct suppressive effect on PTH production; therefore, reduced levels of calcitriol produce an increase in PTH Levels. Most persons with CKD develop secondary hyperparathyroidism, the result of chronic

stimulation of the parathyroid glands. Vitamin D also regulates osteoblast differentiation, thereby affecting bone replacement.

The term *renal osteodystrophy* is used to describe the skeletal complications of CKD.[23–25] The skeletal changes that occur with CKD have been divided into two major types of disorders: high–bone-turnover and low–bone-turnover osteodystrophy. Some persons may have predominantly one type of bone disorder, whereas others may have a mixed type of bone disease. Inherent to both of these conditions is abnormal reabsorption and defective remodeling of bone (see Chapter 44). Mild forms of defective bone metabolism may be observed in early stages of CKD (stage 2), and they become more severe as kidney function deteriorates.

High–bone-turnover osteodystrophy, sometimes referred to as *osteitis fibrosa,* is characterized by increased bone resorption and formation, with bone resorption predominating. The disorder is associated with secondary hyperparathyroidism; altered vitamin D metabolism, along with resistance to the action of vitamin D; and impaired regulation of locally produced growth factors and inhibitors. There is an increase in both osteoblast and osteoclast numbers and activity. Although the osteoblasts produce excessive amounts of bone matrix, mineralization fails to keep pace, and there is a decrease in bone density and formation of porous and coarse-fibered bone. Cortical bone is affected more severely than cancellous bone. Bone marrow fibrosis is another component of osteitis fibrosa; it occurs in areas of increased bone cell activity. In advanced stages of the disorder, cysts may develop in the bone, a condition called *osteitis fibrosa cystica*.

Low–bone-turnover osteodystrophy is characterized by decreased numbers of osteoblasts and low or reduced numbers of osteoclasts, a low rate of bone turnover, and an accumulation of unmineralized bone matrix. There are two forms of low–bone-turnover osteodystrophy: osteomalacia and adynamic osteodystrophy. *Osteomalacia* is characterized by a slow rate of bone formation and defects in bone mineralization, which may be caused by vitamin D deficiency, excess aluminum deposition, or metabolic acidosis. Metabolic acidosis is thought to have a direct effect on both osteoblastic and osteoclastic activity, as well as on the mineralization process, by decreasing the availability of trivalent phosphate. Until the 1980s, the osteomalacia seen in CKD resulted mainly from aluminum intoxication. During the 1970s and 1980s, it was discovered that accumulation of aluminum from water used in dialysis and aluminum salts used as phosphate binders caused osteomalacia and adynamic bone disease. This discovery led to a change in the composition of dialysis solutions and the substitution of calcium carbonate for aluminum salts as phosphate binders. As a result, the prevalence of osteomalacia in persons with CKD has declined.

The second type of low–bone-turnover osteodystrophy, *adynamic osteodystrophy,* is characterized by a low number of osteoblasts, with the osteoclast number being normal or reduced. It is now recognized as being as common as high–bone-turnover osteodystrophy and is especially common among persons with diabetes. Adynamic bone disease is characterized by reduced bone volume and mineralization that may result, in part, from excessive suppression of PTH production with calcitriol.

Regardless of the cause of skeletal abnormalities in CKD, bone disease can lead to bone pain and muscle weakness. In the lower extremities, proximal muscle can give rise to gait abnormalities and make it difficult to get out of a chair or climb stairs. Spontaneous bone fractures can occur that are slow to heal. When the calcium–phosphate product (serum calcium [mg/dL] × serum phosphate [mg/dL]) rises above 60 to 70, metastatic calcifications are commonly seen in blood vessels, soft tissues, lungs, and myocardium.

Early treatment of hyperphosphatemia and hypocalcemia is important to prevent or slow the development of skeletal complications. Milk products and other foods high in phosphorus content are restricted in the diet. Phosphate-binding antacids (aluminum salts, calcium carbonate, or calcium acetate) may be prescribed to decrease absorption of phosphate from the gastrointestinal tract. Aluminum-containing antacids can contribute to the development of osteodystrophy, whereas calcium-containing phosphate binders can lead to hypercalcemia, thus worsening soft tissue calcification, especially in persons receiving vitamin D therapy. Phosphate-binding agents that do not contain calcium or aluminum (e.g., sevelamer, lanthanum) are now available.[23–25] Pharmacologic forms of activated vitamin D often are used to increase serum calcium levels and, at least partially, reverse the secondary hyperparathyroidism and osteitis fibrosis that occur with CKD. Secondary hyperparathyroidism may also be treated by activating the calcium-sensing receptor on the parathyroid gland (see Chapter 8). The calcimimetic agent cinacalcet, the first representative of a new class of drugs that act through the calcium-sensing receptor, has been approved for treatment of secondary hyperparathyroidism in CKD.[25] However, because adynamic bone disease is often a consequence of overzealous treatment of secondary hyperthyroidism, these agents require careful use.

Disorders of Hematologic Function

Anemia is a common complication of CKD. It tends to develop early in the course of the disease process, often interfering with quality of life.[26] Approximately 8 million people in the United States have stage 3 kidney disease (GFR of 30 to 60 mL/minute/1.73 m^2) and almost half of these persons are anemic.[27] Current KDOQI guidelines recommend monitoring of hemoglobin at least once a year in persons with CKD, with more frequent monitoring in the later stages when anemia treatment is necessary.

The anemia of CKD is due to several factors, including chronic blood loss, hemolysis, bone marrow suppression due to retained uremic factors, and decreased red cell production due to impaired production of erythropoietin and iron deficiency. The kidneys are the primary site for the production of the hormone *erythropoietin,* which controls red blood cell production.[26–28] In renal failure, erythropoietin production usually is insufficient to stimulate adequate red blood cell production by the bone marrow.

Among the causes of iron deficiency in persons with CKD are anorexia and dietary restrictions that limit intake and the blood loss that occurs during dialysis.

When untreated, anemia causes or contributes to weakness, fatigue, depression, insomnia, and decreased cognitive function. There also is an increasing concern regarding the physiologic effects of anemia on cardiovascular function.[28] The anemia of renal failure produces a decrease in blood viscosity and a compensatory increase in heart rate. The decreased blood viscosity also exacerbates peripheral vasodilation and contributes to decreased vascular resistance. Cardiac output increases in a compensatory fashion to maintain tissue perfusion. Anemia also limits myocardial oxygen supply, particularly in persons with coronary heart disease, predisposing to angina pectoris and other ischemic events.

A remarkable advance in the treatment of anemia in CKD was realized when recombinant human erythropoietin (rhEPO) became available.[16,26,27] The K/DOQI guidelines recommend maintaining a target hemoglobin level of at least 11 to 12 g/dL but find that evidence is insufficient to support routinely maintaining hemoglobin levels of 13 g/dL or greater. Because iron deficiency is common among persons with CKD, iron supplementation often is needed.[16,26] Iron can be given orally or intravenously. Intravenous iron is used for treatment of persons who are not able to maintain adequate iron status with oral iron. Although adverse reactions have been reported, intravenous preparations are generally safe and well tolerated.[27]

Bleeding disorders manifested by persons with CKD include epistaxis, menorrhagia, gastrointestinal bleeding, and bruising of the skin and subcutaneous tissues. Although platelet production often is normal in CKD, platelet function is impaired.[29] Coagulative function improves with dialysis but does not completely normalize, suggesting that uremia contributes to the problem. Persons with CKD also have greater susceptibility to thrombotic disorders, particularly if their underlying disease was characterized by a nephrotic presentation.

Disorders of Cardiovascular Function

Cardiovascular disease continues to be a major cause of death in persons with CKD. In fact, persons with CKD are more likely to die of cardiovascular disease than kidney failure.[30] Coexisting conditions that have been identified as contributing to the burden of cardiovascular disease include hypertension, diabetes mellitus, anemia, endothelial dysfunction, and vascular calcifications. Dyslipidemia is often an additional risk factor for cardiovascular disease in persons with CKD. The most common lipid abnormalities are hypertriglyceridemia, reduced high-density lipoprotein (HDL) levels, and increased concentrations of lipoprotein (a) (see Chapter 18).[31]

Hypertension commonly is an early manifestation of CKD. The mechanisms that produce hypertension in CKD are multifactorial; they include an increased vascular volume, elevation of peripheral vascular resistance, decreased levels of renal vasodilator prostaglandins, and increased activity of the renin-angiotensin-aldosterone system. Early identification and aggressive treatment of hypertension has been shown to slow the progression of renal impairment in many types of kidney disease.[16,22,30] Treatment involves salt and water restriction and the use of antihypertensive medications to control blood pressure. Many persons with CKD need to take several antihypertensive medications to control blood pressure (see Chapter 18).

The spectrum of cardiovascular disease due to CKD includes left ventricular hypertrophy, ischemic heart disease, and congestive heart failure.[16,22,32] People with CKD tend to have an increased prevalence of left ventricular dysfunction, with both depressed left ventricular ejection fraction, as in systolic dysfunction, and impaired ventricular filling, as in diastolic failure (see Chapter 19). Multiple factors lead to development of left ventricular dysfunction, including extracellular fluid overload, shunting of blood through an arteriovenous fistula for dialysis, and anemia. Anemia, in particular, has been correlated with the presence of left ventricular hypertrophy. These abnormalities, coupled with the hypertension that often is present, cause increased myocardial work and oxygen demand, with eventual development of heart failure.

Pericarditis occurs in approximately 20% of persons receiving chronic dialysis.[33] It can result from metabolic toxins associated with the uremic state or from dialysis. The manifestations of uremic pericarditis resemble those of viral pericarditis, with all its potential complications, including cardiac tamponade (see Chapter 19). The presenting signs include mild to severe chest pain with respiratory accentuation and a pericardial friction rub. Fever is variable in the absence of infection and is more common in dialysis than uremic pericarditis.

Disorders Associated with Accumulation of Nitrogenous Wastes

The accumulation of nitrogenous wastes in the blood, or *azotemia,* is often an early sign of kidney failure, occurring before other signs and symptoms become evident. Urea is one of the first nitrogenous wastes to accumulate in the blood, and the BUN level becomes increasingly elevated as CKD progresses. The normal concentration of urea in the blood is 8 to 20 mg/dL (2.9 to 7.1 mmol/L). In kidney failure, this level may rise to as high as 800 mg/dL (288 mmol/L).

Uremia, which literally means "urine in the blood," is the term used to describe the manifestations of kidney failure that are due to the accumulation of organic waste products in the blood.[34] Hypertension due to volume overload and anemia due to reduced production of erythropoietin were once regarded as signs of uremia; however, since their causes have been discovered, they are no longer considered as such.[34] The uremic state is characterized by signs and symptoms of altered neuromuscular function (e.g., fatigue, peripheral neuropathy, restless leg syndrome, sleep disturbances, uremic encephalopathy); gastrointestinal disturbances such as anorexia and nausea; white blood cell and immune dysfunction; amenorrhea and sexual dysfunction; and dermatologic manifestations such as pruritus. The onset of uremia in persons with CKD varies; some symptoms may be present to a lesser degree in persons with a GFR that is barely below 50% of normal.[34]

However, symptoms such as weakness and fatigue are often nonspecific and difficult to identify.

Neuromuscular Manifestations. Many persons with CKD have alterations in peripheral and central nervous system function.[17,22,35] Peripheral neuropathy, or involvement of the peripheral nerves, affects the lower limbs more frequently than the upper limbs. It is symmetric, affects both sensory and motor function, and is associated with atrophy and demyelination of nerve fibers, possibly due to uremic toxins. Restless leg syndrome is a manifestation of peripheral nerve involvement and can be seen in as many as two thirds of persons on dialysis. This syndrome is characterized by creeping, prickling, and itching sensations that typically are more intense at rest. Temporary relief is obtained by moving the legs. A burning sensation of the feet, which may be followed by muscle weakness and atrophy, is a manifestation of uremia.

The central nervous system disturbances in uremia are similar to those caused by other metabolic and toxic disorders. Sometimes referred to as *uremic encephalopathy,* the condition is poorly understood and may result, at least in part, from an excess of toxic organic acids that alter neural function. Electrolyte abnormalities, such as sodium shifts, also may contribute. The manifestations are more closely related to the progress of the uremic state than to the level of the metabolic end products. Reductions in alertness and awareness are the earliest and most significant indications of uremic encephalopathy. These often are followed by an inability to fix attention, loss of recent memory, and perceptual errors in identifying persons and objects. Delirium and coma occur late in the disease course; seizures are the preterminal event.

Disorders of motor function commonly accompany the neurologic manifestations of uremic encephalopathy. During the early stages, there often is difficulty in performing fine movements of the extremities; the gait becomes unsteady and clumsy with tremulousness of movement. Asterixis (dorsiflexion movements of the hands and feet) typically occurs as the disease progresses. It can be elicited by having the person hyperextend his or her arms at the elbow and wrist with the fingers spread apart. If asterixis is present, this position causes side-to-side flapping movements of the fingers.

Gastrointestinal Manifestations. Anorexia, nausea, and vomiting are common in persons with uremia, along with a metallic taste in the mouth that further depresses the appetite.[17,22] Early-morning nausea is common. Ulceration and bleeding of the gastrointestinal mucosa may develop, and hiccups are common. A possible cause of nausea and vomiting is the decomposition of urea by intestinal flora, resulting in a high concentration of ammonia. Nausea and vomiting often improve with restriction of dietary protein and after initiation of dialysis, and disappear after kidney transplantation.

Infection and Disorders of Immune Function. Infection is a common complication of CKD. Immunologic abnormalities decrease the efficiency of the immune response to infection.[22] All aspects of inflammation and immune function may be affected adversely by the high levels of urea and metabolic wastes, including a decreased granulocyte count, impaired humoral and cell-mediated immunity, and defective phagocyte function. The acute inflammatory response and delayed-type hypersensitivity response are impaired. Although persons with CKD have normal humoral responses to vaccines, a more aggressive immunization program may be needed. Skin and mucosal barriers to infection also may be defective. In persons who are maintained on dialysis, vascular access devices are common portals of entry for pathogens. Many persons with CKD fail to mount a fever with infection, making a diagnosis of infection more difficult.

Sexual Function. Alterations in sexual function and reproductive ability are common in CKD. The cause probably is multifactorial and may result from high levels of uremic toxins, neuropathy, altered endocrine function, psychological factors, and medications (e.g., antihypertensive drugs).

Impotence occurs in as many as 56% of male patients on dialysis.[36] Derangements of the pituitary and gonadal hormones, such as decreases in testosterone levels and increases in prolactin and luteinizing hormone levels, are common and cause erectile difficulties and decreased spermatocyte counts. Loss of libido may result from chronic anemia and decreased testosterone levels.

Impaired sexual function in women is manifested by abnormal levels of progesterone, luteinizing hormone, and prolactin. Hypofertility, menstrual abnormalities, decreased vaginal lubrication, and various orgasmic problems have been described. Amenorrhea is common among women who are on dialysis therapy.[17]

Skin Integrity. Skin disorders are common in persons with CKD.[17] The skin and mucous membranes often are dry, and subcutaneous bruising is common. Skin dryness is caused by a reduction in perspiration owing to the decreased size of sweat glands and the diminished activity of oil glands. Pruritus is common; it results from the high serum phosphate levels and the development of phosphate crystals that occur with hyperparathyroidism. Severe scratching and repeated needle sticks, especially with hemodialysis, break the skin integrity and increase the risk for infection. In the advanced stages of untreated kidney failure, urea crystals may precipitate on the skin as a result of the high urea concentration in body fluids. The fingernails may become thin and brittle, with a dark band just behind the leading edge of the nail followed by a white band. This appearance is known as *Terry nails*.

Disorders of Drug Elimination

The kidneys are responsible for the elimination of many drugs and their metabolites. CKD and its treatment can interfere with the absorption, distribution, and elimination of drugs.[37] The administration of large quantities of phosphate-binding antacids to control hyperphosphatemia and hypocalcemia in patients with advanced renal failure interferes with the absorption of some drugs. Many drugs are bound to plasma proteins, such as

albumin, for transport in the body; the unbound portion of the drug is available to act at the various receptor sites and is free to be metabolized. A decrease in plasma proteins, particularly albumin, that occurs in many persons with CKD results in less protein-bound drug and greater amounts of free drug.

In the process of metabolism, some drugs form intermediate metabolites that are toxic if not eliminated. Some pathways of drug metabolism, such as hydrolysis, are slowed with uremia. In persons with diabetes, for example, insulin requirements may be reduced as renal function deteriorates. Decreased elimination by the kidneys allows drugs or their metabolites to accumulate in the body and requires that drug dosages be adjusted accordingly. Some drugs contain unwanted nitrogen, sodium, potassium, and magnesium and must be avoided in patients with CKD. Penicillin, for example, contains potassium. Nitrofurantoin and ammonium chloride add to the body's nitrogen pool. Many antacids contain magnesium. Because of problems with drug dosing and elimination, persons with CKD should be cautioned against the use of over-the-counter remedies.

Management

Chronic kidney disease is treated by conservative management to prevent or slow the rate of nephron destruction and, when necessary, by renal replacement therapy with dialysis or transplantation.

Medical Management

Conservative treatment can often delay the progression of CKD.[17,38] It includes measures to retard deterioration of renal function and assist the body in managing the effects of impaired function. Urinary tract infections should be treated promptly and medication with renal damaging potential should be avoided. It should be noted that these strategies are complementary to the treatment of the original cause of the renal disorder, which is of the utmost importance and needs to be continually addressed.

Blood pressure control is important, as is control of blood glucose in persons with diabetes mellitus. Intensive glycemic control in persons with diabetes helps to prevent the development of microalbuminuria and retards the progression of diabetic nephropathy (see Chapter 33). In addition to reduction in cardiovascular risk, antihypertensive therapy in persons with CKD aims to slow the progression of nephron loss by lowering intraglomerular hypertension and hypertrophy.[17] Elevated blood pressure also increases proteinuria due to transmission of the elevated pressure to the glomeruli. This is the basis for the treatment guideline establishing 125/75 mm Hg as the target blood pressure for persons with CKD[15] (see Chapter 18). The ACE inhibitors and ARBs, which have a unique effect on the glomerular microcirculation (i.e., dilation of the efferent arteriole), are increasingly being used in the treatment of hypertension and proteinuria, particularly in persons with diabetes.[17]

It has become apparent that smoking has a negative impact on kidney function, and it is one of the most remedial risk factors for CKD.[39] The mechanisms of smoking-induced renal damage appear to include both acute hemodynamic effects (i.e., increased blood pressure, intraglomerular pressure, and urinary albumin excretion) and chronic effects (endothelial cell dysfunction).[39] Smoking is particularly nephrotoxic in elderly persons with hypertension and in those with diabetes. Importantly, the adverse effects of smoking appear to be independent of the underlying kidney disease.

Dialysis and Transplantation

Dialysis or renal replacement therapy is indicated when advanced uremia or serious electrolyte imbalances are present. The choice between dialysis and transplantation is dictated by age, related health problems, donor availability, and personal preference. Although transplantation often is the preferred treatment, dialysis plays a critical role as a treatment method for kidney failure. It is life sustaining for persons who are not candidates for transplantation or who are awaiting transplantation. There are two broad categories of dialysis: hemodialysis and peritoneal dialysis.

Hemodialysis. The basic principles of hemodialysis have remained unchanged over the years, although new technology has improved the efficiency and speed of dialysis.[40,41] A hemodialysis system, or artificial kidney, consists of three parts: a blood delivery system, a dialyzer, and a dialysis fluid delivery system. The dialyzer is usually a hollow cylinder composed of bundles of capillary tubes through which blood circulates, while the dialysate travels on the outside of the tubes.[40] The walls of the capillary tubes in the dialysis chamber are made up of a semipermeable membrane material that allows all molecules except blood cells and plasma proteins to move freely in both directions—from the blood into the dialyzing solution and from the dialyzing solution into the blood. The direction of flow is determined by the concentration of the substances contained in the two solutions. The waste products and excess electrolytes in the blood normally diffuse into the dialyzing solution. If there is a need to replace or add substances, such as bicarbonate, to the blood, these can be added to the dialyzing solution (Fig. 26-5).

During dialysis, blood moves from an artery through the tubing and blood chamber in the dialysis machine and then back into the body through a vein. Access to the vascular system is accomplished through an external arteriovenous shunt (i.e., tubing implanted into an artery and a vein) or, more commonly, through an internal arteriovenous fistula (i.e., anastomosis of a vein to an artery, usually in the forearm). Heparin is used to prevent clotting during the dialysis treatment; it can be administered continuously or intermittently. Problems that may occur during dialysis, depending on the rates of blood flow and solute removal, include hypotension, nausea, vomiting, muscle cramps, headache, chest pain, and disequilibrium syndrome. Most persons are dialyzed three times each

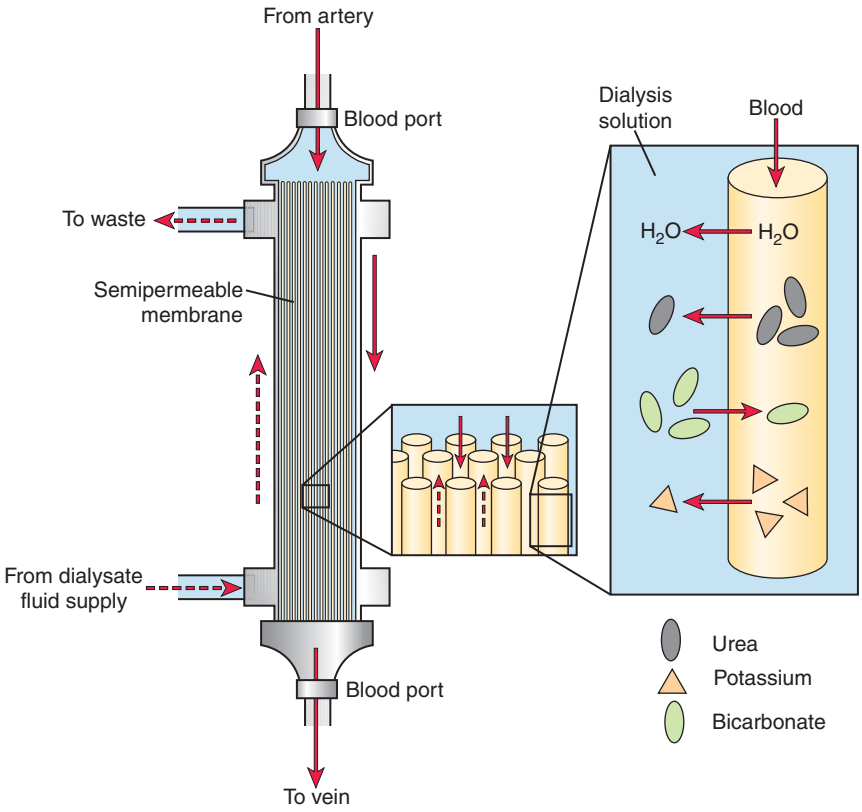

FIGURE 26-5. Schematic diagram of a hemodialysis system. The blood compartment and dialysis solution compartment are separated by a semipermeable membrane. This membrane is porous enough to allow all the constituents, except the plasma proteins and blood cells, to diffuse between the two compartments.

week for 3 to 4 hours. Many dialysis centers provide the option for patients to learn how to perform hemodialysis at home.

Peritoneal Dialysis. The same principles of diffusion, osmosis, and ultrafiltration that apply to hemodialysis apply to peritoneal dialysis.[40] The thin serous membrane of the peritoneal cavity serves as the dialyzing membrane. A Silastic catheter is surgically implanted in the peritoneal cavity below the umbilicus to provide access. The catheter is tunneled through subcutaneous tissue and exits on the side of the abdomen (Fig. 26-6). The dialysis process involves instilling a sterile dialyzing solution (usually 1 to 3 L) through the catheter over a period of approximately 10 minutes. The solution then is allowed to remain, or *dwell,* in the peritoneal cavity for a prescribed amount of time, during which the metabolic end products and extracellular fluid diffuse into the dialysis solution. At the end of the dwell time, the dialysis fluid is drained out of the peritoneal cavity by gravity into a sterile bag. The osmotic effects of glucose in the dialysis solution account for water removal.

Peritoneal dialysis can be performed at home or in a dialysis center and can be carried out by continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), or nocturnal intermittent peritoneal dialysis (NIPD)—all with variations in the number of exchanges and dwell times.[40] Individual preference, manual ability, lifestyle, knowledge of the procedure, and physiologic response to treatment are used to determine the type of dialysis that is used. The most common method is CAPD, a self-care procedure in which the person exchanges the dialysate four to six times a day. In CCPD, exchanges usually are performed at night, with the person connected to an automatic cycler. In the morning, the person, with the last exchange remaining in the abdomen, is disconnected from the cycler and goes about

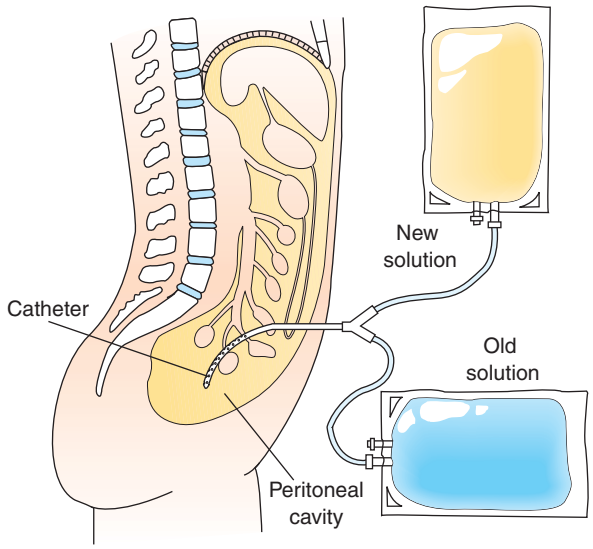

FIGURE 26-6. Peritoneal dialysis. A semipermeable membrane, richly supplied with small blood vessels, lines the peritoneal cavity. With dialysate dwelling in the peritoneal cavity, waste products diffuse from the network of blood vessels into the dialysate.

his or her usual activities. In NIPD, the person is given approximately 10 hours of automatic cycling each night, with the abdomen left dry during the day.

Potential problems with peritoneal dialysis include infection, catheter malfunction, dehydration caused by excessive fluid removal, hyperglycemia, and hernia. The most serious complication is infection, which can occur at the catheter exit site, in the subcutaneous tunnel, or in the peritoneal cavity (i.e., peritonitis).

Transplantation. Greatly improved success rates have made kidney transplantation the treatment of choice for many patients with CKD. The availability of donor organs continues to limit the number of transplantations performed each year. Donor organs are obtained from cadavers and living related donors (e.g., parent, sibling). Transplants from living unrelated donors (e.g., spouse) have been used in cases of suitable ABO blood type and tissue compatibility. The success of transplantation depends primarily on the degree of histocompatibility, adequate organ preservation, and immunologic management.[42] Maintenance immunosuppressive therapy plays an essential role in controlling T- and B-cell activation.

Dietary Management

A major component in the treatment of CKD is dietary management.[43] The goal of dietary treatment is to provide optimum nutrition while maintaining tolerable levels of metabolic wastes. The specific diet prescription depends on the type and severity of renal disease and on the dialysis modality. Because of the severe restrictions placed on food and fluid intake, these diets may be complicated and unappetizing. After kidney transplantation, some dietary restrictions still may be necessary, even when renal function is normal, to control the adverse effects from immunosuppressive medication.

Restriction of dietary proteins may decrease the progress of renal impairment in persons with advanced renal disease. Proteins are broken down to form nitrogenous wastes, and reducing the amount of protein in the diet lowers the BUN and reduces symptoms. Moreover, a high-protein diet is high in phosphates and inorganic acids. Considerable controversy exists over the degree of restriction needed. If the diet is too low in protein, protein malnutrition can occur, with a loss of strength, muscle mass, and body weight.

With CKD, adequate calories in the form of carbohydrates and fat are required to meet energy needs. This is particularly important when the protein content of the diet is severely restricted. If sufficient calories are not available, the limited protein in the diet goes into energy production, or body tissue itself is used for energy purposes.

Sodium and fluid restrictions depend on the kidneys' ability to excrete sodium and water and must be individually determined. Renal disease of glomerular origin is more likely to contribute to sodium retention, whereas tubular dysfunction causes salt wasting. Fluid intake in excess of what the kidneys can excrete causes circulatory overload, edema, and water intoxication. Thirst is a common problem among patients on hemodialysis, often resulting in large weight gains between treatments. Inadequate intake, on the other hand, causes volume depletion and hypotension and can cause further decreases in the already compromised GFR. It is common practice to allow a daily fluid intake of 500 to 800 mL, which is equal to insensible water loss plus a quantity equal to the 24-hour urine output.

When the GFR falls to extremely low levels in kidney failure or during hemodialysis therapy, dietary restriction of potassium becomes mandatory. Using salt substitutes that contain potassium or ingesting fruits, fruit juice, chocolate, potatoes, or other high-potassium foods can cause hyperkalemia. Most persons on CAPD do not need to limit potassium intake and often may even need to increase intake.

Persons with CKD are usually encouraged to limit their dietary phosphorus as a means of preventing secondary hyperparathyroidism, renal osteodystrophy, and metastatic calcification. Unfortunately, many processed and convenience foods contain considerable amounts of phosphorus additives. The most notable products using phosphorus additives are restructured meats (e.g., chicken nuggets, hot dogs), processed and spreadable cheeses, instant products (e.g., puddings, sauces), refrigerated bakery products, and beverages.[44] These phosphorus additives are highly absorbable. In a typical diet of grains, meats, and dairy products, only about 60% of phosphorus is absorbed, whereas phosphorus additives (e.g., polyphosphates, pyrophosphates) are almost 100% absorbed.[44] Identifying these newer phosphorus-containing foods is often challenging because manufacturers are no longer required to list the phosphorus content on food labels.

In summary, chronic kidney disease (CKD) results from the destructive effects of many forms of renal disease. Regardless of the cause, the consequences of nephron destruction in CKD are alterations in the filtration, reabsorption, and endocrine functions of the kidneys. Chronic disease is defined as either diagnosed kidney damage or a GFR of less than 60 mL/minute/1.73 m^2 for 3 months or more, and kidney failure as a GFR of less than 15 mL/minute/1.73 m^2, usually accompanied by most of the signs and symptoms of uremia or a need to start renal replacement therapy.

The manifestations of CKD reflect alterations in fluid, electrolyte, and acid-base balance; anemia and coagulopathies; cardiovascular complications; disorders of calcium and phosphate metabolism and skeletal disorders; and impaired elimination of drugs that are excreted by the kidney. It also results in an accumulation of nitrogenous wastes and signs and symptoms of the uremic state, such as neuromuscular disorders, gastrointestinal disturbances, immune disorders, sexual dysfunction, and discomforting skin changes.

The treatment measures for CKD can be divided into two types: conservative treatment measures and renal replacement therapy. Conservative treatment consists of measures to prevent or retard deterioration in remaining

renal function and assist the body in compensating for the existing impairment. Interventions that have been shown to retard the progression of CKD include blood pressure normalization and control of blood glucose in persons with diabetes. Recombinant human erythropoietin is used to treat the profound anemia that occurs in persons with CKD. Activated vitamin D can be used to increase calcium absorption and control secondary hyperparathyroidism. Renal replacement therapy (dialysis or kidney transplantation) is indicated when advanced uremia and serious electrolyte problems are present.

Chronic Kidney Disease in Children and Elderly Persons

Although the spectrum of CKD among children and elderly persons is similar to that of adults, several unique issues affecting these groups warrant further discussion.

Chronic Kidney Disease in Children

The true incidence of CKD in infants and children is unknown. Available data suggest that 1% to 2% of persons with CKD are in the pediatric age range.[45] The causes of CKD in children include congenital malformations, inherited disorders, acquired diseases, and metabolic syndromes. The underlying cause correlates closely with the age of the child.[46] In children younger than 5 years of age, CKD is commonly the result of congenital malformations, such as renal dysplasia or obstructive uropathy. After 5 years of age, acquired diseases (e.g., glomerulonephritis) and inherited disorders (e.g., familial juvenile nephronophthisis) predominate. CKD related to metabolic disorders, such as hyperoxaluria, and inherited disorders, such as polycystic kidney disease, may present throughout childhood.

The stages for progression of CKD in children are similar to those for adults: mild reduction of GFR to 60 to 89 mL/minute/1.73 m^2; moderate reduction of GFR to 30 to 59 mL/minute/1.73 m^2; severe reduction of GFR to 15 to 29 mL/minute/1.73 m^2; and kidney failure with a GFR of less than 15 mL/minute/1.73 m^2, or a need for renal replacement therapy.[47] Because the GFR is much lower in infancy and undergoes gradual changes in relation to body size during the first 2 years of age, these values apply only to children older than 2 years of age.[47]

The manifestations of CKD in children are quite varied and depend on the underlying disease condition. Features of CKD that are marked during childhood include severe growth impairment, developmental delay, delay in sexual maturation, bone abnormalities, and development of psychosocial problems. Critical growth periods occur during the first 2 years of life and during adolescence. Physical growth and cognitive development occur at a slower rate as consequences of CKD, especially among children with congenital kidney disease.[48] Puberty usually occurs at a later age in children with CKD, partly because of endocrine abnormalities. Renal osteodystrophies are more common and extensive in children than in adults. The most common condition seen in children is high–bone-turnover osteodystrophy caused by secondary hyperparathyroidism. Some hereditary renal diseases, such as medullary cystic disease, have patterns of skeletal involvement that further complicate the problems of renal osteodystrophy. Clinical manifestations of renal osteodystrophy include muscle weakness, bone pain, and fractures with minor trauma.[46] In growing children, rachitic bone changes, varus and valgus deformities of long bones, and slipped capital femoral epiphysis may be seen (see Chapter 43).

Factors related to impaired growth include deficient nutrition, anemia, renal osteodystrophy, chronic acidosis, and cases of nephrotic syndrome that require high-dose corticosteroid therapy. Nutrition is believed to be the most important determinant of growth during infancy. During childhood, growth hormone is important, and gonadotropic hormones become important during puberty. Parental heights provide a means of assessing growth potential (see Chapter 32). For many children, catch-up growth is important because a growth deficit frequently is established during the first months of life. Recombinant human growth hormone therapy has been used to improve growth in children with CKD.[49] Success of treatment depends on the level of bone maturation at the initiation of therapy.

All forms of renal replacement therapy can be safely and reliably used for children. Age is a defining factor in dialysis modality selection. The majority of North American children are treated with CCPD or NIPD, which leaves the child and family free of dialysis demands during waking hours, with the exchanges being performed automatically during sleep by the machine. Renal transplantation is considered the best alternative for children.[45,50] Early transplantation in young children is regarded as the best way to promote physical growth, improve cognitive function, and foster psychosocial development. Immunosuppressive therapy in children is similar to that used in adults. All of these immunosuppressive agents have side effects, including increased risk for infection. Corticosteroids, which have been the mainstay of chronic immunosuppressive therapy for decades, carry the risk for hypertension, orthopedic complications (especially aseptic necrosis), cataracts, and growth retardation.

Chronic Kidney Disease in Elderly Persons

Since the mid-1980s, there have been increasing numbers of elderly persons accepted to renal replacement therapy programs.[51,52] Data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that almost 75% of people 75 years of age or older have a GFR less than 90 mL/minute/1.73 m^2 and almost 25% may have a GFR less than 60 mL/minute/1.73 m^2.[51] However, the true prevalence or outcomes of CKD in the elderly have not been systematically studied. Also, the

presentation and course of CKD may be altered because of age-related changes in the kidneys and concurrent medical conditions.

Normal aging is associated with a decline in the GFR and subsequently with reduced homeostatic regulation under stressful conditions.[52] This reduction in GFR makes elderly persons more susceptible to the detrimental effects of nephrotoxic drugs, such as radiographic contrast compounds. The reduction in GFR related to aging is not accompanied by a parallel rise in the serum creatinine level because the serum creatinine level, which results from muscle metabolism, is significantly reduced in elderly persons because of diminished muscle mass and other age-related changes. The KDOQI guidelines suggest that the same criteria for establishing the presence of CKD in younger adults (i.e., GFR <60 mL/minute/1.73 m^2) should be used for the elderly. Evaluation of elderly persons with a GFR of 60 to 89 mL/minute/1.73 m^2 should include age-adjusted measurements of creatinine clearance, along with assessment of CKD risks, measurement of blood pressure, albumin-to-creatinine ratio in a "spot" urine specimen, and examination of the urine sediment for red and white blood cells.[51]

The prevalence of chronic disease affecting the cerebrovascular, cardiovascular, and skeletal systems is higher in this age group.[53] Because of concurrent disease, the presenting symptoms of kidney disease in elderly persons may be less typical than those observed in younger adults. For example, congestive heart failure and hypertension may be the dominant clinical features with the onset of acute glomerulonephritis, whereas oliguria and discolored urine more often are the first signs in younger adults. The course of CKD may be more complicated in older patients with numerous chronic diseases.

Treatment of the elderly with CKD is usually based on the severity of kidney function impairment and stratification of risk for progression to renal failure and cardiovascular disease.[52] Persons with low risk may require only modification of dosages of medications excreted by the kidney, monitoring of blood pressure, avoidance of drugs and procedures that increase the risk of ARF, and lifestyle modification to reduce the risk of cardiovascular disease.

Elderly persons with more severe impairment of kidney function may require renal replacement therapy. Treatment options for CKD in elderly patients include hemodialysis, peritoneal dialysis, transplantation, and acceptance of death from uremia. Neither hemodialysis nor peritoneal dialysis has proved to be superior in the elderly. The mode of renal replacement therapy should be individualized, taking into account underlying medical and psychosocial factors. Age alone should not preclude renal transplantation.[52,53] With increasing experience, many transplantation centers have increased the age for acceptance on transplant waiting lists. Reluctance to provide transplantation as an alternative may have been due, at least in part, to the scarcity of available organs and the view that younger persons are more likely to benefit for a longer time. The general reduction in T-lymphocyte function that occurs with aging has been suggested as a beneficial effect that increases transplant graft survival.

In summary, available data suggest that 1% to 2% of patients with CKD are in the pediatric age range. The causes of CKD include congenital malformations (e.g., renal dysplasia and obstructive uropathy), inherited disorders (e.g., polycystic kidney disease), acquired diseases (e.g., glomerulonephritis), and metabolic syndromes (e.g., hyperoxaluria). Problems associated with CKD in children include growth impairment, delay in sexual maturation, and more extensive bone abnormalities than in adults. Although all forms of renal replacement therapy can be safely and reliably used in children, CCPD, NIPD, or transplantation optimizes growth and development.

Since the mid-1980s, there have been increasing numbers of elderly persons accepted for renal replacement therapy programs. Normal aging is associated with a decline in the GFR, which makes elderly persons more susceptible to the detrimental effects of nephrotoxic drugs and other conditions that compromise renal function. Current guidelines for diagnosis of CKD and stratification of risk for progression to kidney failure are the same as for younger adults. Treatment options for chronic renal failure in elderly patients are also similar to those for younger adults.

REVIEW EXERCISES

1. A 55-year-old man with diabetes and coronary heart disease, who had undergone cardiac catheterization with the use of a radiocontrast agent 2 days ago, is admitted to the emergency department with a flulike syndrome including chills, nausea, vomiting, abdominal pain, fatigue, and pulmonary congestion. His serum creatinine is elevated, and he has protein in his urine. He is admitted to the intensive care unit with a tentative diagnosis of acute renal failure due to radiocontrast nephropathy.

A. Radiocontrast agents are thought to exert their effects through decreased renal perfusion and through direct toxic effects on renal tubular structures. Explain how each of these phenomena contributes to the development of acute renal failure.

B. Explain the elevated serum creatinine, proteinuria, and presence of pulmonary congestion.

2. A 35-year-old, 70-kg white man with diabetes mellitus is seen in the diabetic clinic for his 6-month check-up. His serum creatinine, which was slightly elevated at his last visit, is now 1.6 mg/dL.

A. Use the following website to estimate his GFR: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

B. Would he be classified as having chronic kidney disease? If so, what stage? What might be done to delay or prevent further deterioration of his kidney function?

3. Chronic kidney disease is accompanied by hyperphosphatemia, hypocalcemia, impaired activation of vitamin D, hyperparathyroidism, and skeletal complications.

A. Explain the impaired activation of vitamin D and its consequences on calcium and phosphate homeostasis, parathyroid function, and mineralization of bone in persons with CKD.

B. Explain the possible complications of the administration of activated forms of vitamin D on parathyroid function and calcium and phosphate homeostasis.

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