The kidneys are remarkable organs. Each is smaller than a person’s fist, but in a single day the two organs process approximately 1700 L of blood and combine its waste products into approximately 1.5 L of urine. As part of their function, the kidneys filter physiologically essential substances, such as sodium and potassium ions, from the blood and selectively reabsorb those substances that are needed to maintain the normal composition of internal body fluids. Substances that are not needed for this purpose or are in excess pass into the urine. In regulating the volume and composition of body fluids, the kidneys perform excretory and endocrine functions. The renin-angiotensin mechanism participates in the regulation of blood pressure and the maintenance of circulating blood volume, and erythropoietin stimulates red blood cell production.
KIDNEY STRUCTURE AND FUNCTION

Gross Structure and Location

The kidneys are paired, bean-shaped organs that lie outside the peritoneal cavity in the back of the upper abdomen, one on each side of the vertebral column at the level of the 12th thoracic to 3rd lumbar vertebrae (Fig. 22-1). The right kidney normally is situated lower than the left, presumably because of the position of the liver. In the adult, each kidney is approximately 10 to 12 cm long, 5 to 6 cm wide, and 2.5 cm deep and weighs approximately 113 to 170 g. The medial border of the kidney is indented by a deep fissure called the hilus. It is here that blood vessels and nerves enter and leave the kidney. The ureters, which connect the kidneys with the bladder, also enter the kidney at the hilus.

The kidney is a multilobular structure, composed of up to 18 lobes. Each lobule is composed of nephrons, which are the functional units of the kidney. Each nephron has a glomerulus that filters the blood and a system of tubular structures that selectively reabsorb material from the filtrate back into the blood and secrete materials from the blood into the filtrate as urine is being formed.

On longitudinal section, a kidney can be divided into an outer cortex and an inner medulla (Fig. 22-2). The cortex, which is reddish-brown, contains the glomeruli and convoluted tubules of the nephron and blood vessels. The medulla consists of light-colored, cone-shaped masses—the renal pyramids—that are divided by the columns of the cortex (i.e., columns of Bertin) that extend into the medulla. Each pyramid, topped by a region of cortex, forms a lobe of the kidney. The apexes of the pyramids form the papillae, which are perforated by the openings of the collecting ducts. The renal pelvis is a wide, funnel-shaped structure at the upper end of the ureter. It is made up of the calices or cuplike structures that drain the upper and lower halves of the kidney.

The kidney is ensheathed in a fibrous external capsule and surrounded by a mass of fatty connective tissue, especially at its ends and borders. The adipose tissue protects the kidney from mechanical blows and assists, together with the attached blood vessels and fascia, in holding the kidney in place. Although the kidneys are relatively well protected, they may be bruised by blows to the loin or by compression between the lower ribs and the ilium. Because the kidneys are outside the peritoneal cavity, injury and rupture do not produce the same threat of peritoneal involvement as rupture of organs such as the liver or spleen.

Each kidney is supplied by a single renal artery that arises on either side of the aorta. As the renal artery approaches the kidney, it divides into five segmental arteries that enter the hilus of the kidney. In the kidney, each segmental artery subdivides and branches several times. The smallest branches, the intralobular arteries, give rise to the afferent arterioles that supply the glomeruli (Fig. 22-3).

The Nephron

Each kidney is composed of more than 1 million tiny, closely packed functional units called nephrons. Each nephron consists of a glomerulus, where blood is filtered, and a tubular component. Here, water, electrolytes, and other substances needed to maintain the constancy of the internal environment are reabsorbed into the bloodstream while other unneeded materials are secreted into the tubular filtrate for elimination (see Fig. 22-4).

The Glomerulus

The glomerulus consists of a compact tuft of capillaries encased in a thin, double-walled capsule, called Bowman’s capsule. Blood flows into the glomerular capillaries from the afferent arteriole and flows out of the glomerular capillaries into the efferent arteriole, which leads into the peritubular capillaries. Fluid and particles from the blood are filtered through the capillary membrane into a fluid-filled space in Bowman’s capsule, called Bowman’s space. The portion of the blood that is filtered into the capsule space is called the filtrate. The mass of capillaries and its surrounding epithelial capsule are collectively referred to as the renal corpuscle (Fig. 22-5A). The glomerular capillary membrane is composed of three layers: the capillary endothelial layer, the basement membrane, and the single-celled capsular epithelial layer (see Fig. 22-5B). The endothelial layer lines the glomerulus and interfaces with blood as it moves through the capillary. This layer contains many small perforations, called fenestrations.

The epithelial layer that covers the glomerulus is continuous with the epithelium that lines Bowman’s capsule. The cells of the epithelial layer have unusual octopus-like structures that possess a large number of extensions, or foot processes (i.e., podocytes), which are embedded in the basement membrane. These foot processes form slit pores through which
probable that the epithelial cells are active in forming new basement membrane material throughout life. Alterations in the structure and function of the glomerular basement membrane are responsible for the leakage of proteins and blood cells into the filtrate that occurs in many forms of glomerular disease.

Another important component of the glomerulus is the mesangium. In some areas, the capillary endothelium and the basement membrane do not completely surround each capillary. Instead, the mesangial cells, which lie between the capillary tufts, provide support for the glomerulus in these areas (see Fig. 22-5B). The mesangial cells produce an intercellular substance similar to that of the basement membrane. This substance covers the endothelial cells where they are not covered by basement membrane. The mesangial cells possess (or can develop) phagocytic properties and remove macromolecular materials that enter the intercapillary spaces. Mesangial cells also exhibit contractile properties in response to neurohumoral substances and are thought to contribute to the regulation of blood flow through the glomerulus. In normal glomeruli, the mesangial area is narrow and contains only a small number of cells. Mesangial hyperplasia and increased mesangial matrix occur in a number of glomerular diseases.

Tubular Components of the Nephron

The nephron tubule is divided into four segments: a highly coiled segment called the proximal convoluted tubule, which drains Bowman’s capsule; a thin, looped structure called the loop of Henle; a distal coiled portion called the distal convoluted tubule; and the final segment called the collecting tubule, which joins with several tubules to collect the filtrate (Fig. 22-4). The filtrate passes through each of these segments before reaching the pelvis of the kidney.

Nephrons can be roughly grouped into two categories. Approximately 85% of the nephrons originate in the superficial part of the cortex and are called cortical nephrons. They have
short, thick loops of Henle that penetrate only a short distance into the medulla. The remaining 15% are called juxtamedullary nephrons. They originate deeper in the cortex and have longer and thinner loops of Henle that penetrate the entire length of the medulla. The juxtamedullary nephrons are largely concerned with urine concentration.

The proximal tubule is a highly coiled structure that dips toward the renal pelvis to become the descending limb of the loop of Henle. The ascending loop of Henle returns to the region of the renal corpuscle, where it becomes the distal tubule. The distal convoluted tubule, which begins at the juxtaglomerular complex, is divided into two segments: the diluting segment and the late distal tubule. The late distal tubule fuses with the collecting tubule. Like the distal tubule, the collecting duct is divided into two segments: the cortical collecting tubule and the inner medullary collecting tubule.

Throughout its course, the tubule is composed of a single layer of epithelial cells resting on a basement membrane. The structure of the epithelial cells varies with tubular function.
The cells of the proximal tubule have a fine villous structure that increases the surface area for reabsorption; they also are rich in mitochondria, which support active transport processes. The epithelial layer of the thin segment of the loop of Henle has few mitochondria, indicating minimal metabolic activity and passive reabsorptive function.

**Nephron Blood Supply**

The nephron is supplied by two capillary systems, the glomerulus and the peritubular capillary network (Fig. 22-4). The glomerulus is a unique, high-pressure capillary filtration system located between two arterioles—the afferent and the efferent arterioles—that selectively dilate or constrict to regulate glomerular capillary pressure and consequently their filtration. The peritubular capillary network is a low-pressure reabsorptive system that originates from the efferent arteriole. These capillaries surround all portions of the tubules, an arrangement that permits rapid movement of solutes and water between the fluid in the tubular lumen and the blood in the capillaries. The medullary nephrons are supplied with two types of capillaries: the peritubular capillaries, which are similar to those in the cortex, and the vasa recta, which are long, straight capillaries. The vasa recta accompany the long loops of Henle in the medullary portion of the kidney to assist in exchange of substances flowing in and out of that portion of the kidney and play an important role in concentrating the urine. The peritubular capillaries rejoin to form the venous channels by which blood leaves the kidneys and empties into the inferior vena cava.

Although nearly all the blood flow to the kidneys passes through the cortex, less than 10% is directed to the medulla and only approximately 1% goes to the papillae. Under conditions of decreased perfusion or increased sympathetic nervous system stimulation, blood flow is redistributed away from the cortex toward the medulla. This redistribution of blood flow decreases glomerular filtration while maintaining the urine concentrating ability of the peritubular capillaries, a factor that is important during conditions such as shock.

**Urine Formation**

Urine formation involves the filtration of blood by the glomerulus to form an ultrafiltrate of urine and the tubular reabsorption of electrolytes and nutrients needed to maintain the constancy of the internal environment while eliminating waste materials.

**Glomerular Filtration**

Urine formation begins with the filtration of essentially protein-free plasma through the glomerular capillaries into Bowman’s space. The movement of fluid through the glomerular capillaries is determined by the same factors (i.e., capillary filtration pressure, colloidal osmotic pressure, and capillary permeability) that affect fluid movement through other capillaries in the body (see Chapter 6). The glomerular filtrate has a chemical composition similar to plasma, but it contains almost no proteins because large molecules do not readily cross the glomerular wall. Approximately 125 mL of filtrate is formed each minute. This is called the glomerular filtration rate (GFR). This rate can vary from a few milliliters per minute to as high as 200 mL/minute.

The location of the glomerulus between two arterioles allows for maintenance of a high-pressure filtration system. The capillary filtration pressure (approximately 60 mm Hg) in the glomerulus is approximately two to three times higher than that of other capillary beds in the body. The filtration pressure and the GFR are regulated by the constriction and relaxation of the afferent and efferent arterioles. Constriction of the efferent arteriole increases resistance to outflow from the glomeruli and
increases the glomerular pressure and the GFR. Constriction of the afferent arteriole causes a reduction in the renal blood flow, glomerular filtration pressure, and GFR. The afferent and the efferent arterioles are innervated by the sympathetic nervous system and also are sensitive to vasoactive hormones, such as angiotensin II. During periods of strong sympathetic stimulation, such as occurs during shock, constriction of the afferent arteriole causes a marked decrease in renal blood flow and thus glomerular filtration pressure. Consequently, urine output can fall almost to zero.

**Tubular Reabsorption and Secretion**

From Bowman’s capsule, the glomerular filtrate moves into the tubular segments of the nephron. In its movement through the lumen of the tubular segments, the glomerular filtrate is changed considerably by the tubular transport of water and solutes. Tubular transport can result in reabsorption of substances from the tubular fluid into the blood or secretion of substances from the blood into the tubular fluid (Fig. 22-6). Segments of the renal tubule are adapted to reabsorb or secrete specific substances, using particular modes of transport.

The basic mechanisms of transport across the tubular epithelial cell membrane are similar to those of other cell membranes in the body and include active and passive transport mechanisms (see Chapter 1). Water and urea are passively absorbed along concentration gradients. Sodium, potassium, chloride, calcium, and phosphate ions, as well as urate, glucose, and amino acids are reabsorbed using primary or secondary active transport mechanisms to move across the tubular membrane. Some substances, such as hydrogen, potassium, and urate ions, are secreted into the tubular fluids. Under normal conditions, only approximately 1 mL of the 125 mL of glomerular filtrate that is formed each minute is excreted in the urine. The other 124 mL is reabsorbed in the tubules. This means that the average output of urine is approximately 60 mL/hour.

Renal tubular cells have two membrane surfaces through which substances must pass as they are reabsorbed from the tubular fluid. The side of the cell that is in contact with the tubular lumen and tubular filtrate is called the *luminal membrane*. The outside membrane that lies adjacent to the interstitial fluid and the peritubular capillaries is called the *basolateral membrane*. In most cases, substances move from the tubular filtrate into the tubular cell along a concentration gradient, but they require facilitated transport or carrier systems to move across the basolateral membrane into the interstitial fluid, where they are absorbed into the peritubular capillaries.

The bulk of energy used by the kidney is for active transport mechanisms that facilitate sodium reabsorption and cotransport of other electrolytes and substances such as glucose and amino acids (Fig. 22-7). Cotransport uses a carrier system in which two substances move in the same direction. The active transport of one substance such as sodium is coupled to the movement of a second substance such as glucose or an amino acid. A few substances, such as hydrogen, are secreted into the tubule using countertransport, in which the movement of one substance, such as sodium, enables the movement of a second substance in the opposite direction.
**Proximal Tubule.** Although tubular transport occurs throughout the renal tubule, most of it occurs in the proximal tubule. Approximately 65% of all reabsorptive and secretory processes that occur in the tubular system take place in the proximal tubule. There is almost complete reabsorption of nutritionally important substances, such as glucose, amino acids, lactate, and water-soluble vitamins. Electrolytes, such as sodium, potassium, chloride, and bicarbonate, are 65% to 80% reabsorbed. As these solutes move into the tubular cells, their concentration in the tubular lumen decreases, providing a concentration gradient for the osmotic reabsorption of water and urea. The proximal tubule is highly permeable to water, and the osmotic movement of water occurs so rapidly that the concentration difference of solutes on either side of the membrane seldom is more than a few milliosmoles.

Many substances, such as glucose, are freely filtered in the glomerulus and reabsorbed by energy-dependent cotransport carrier mechanisms. The maximum amount of substance that these transport systems can reabsorb per unit time is called the transport maximum. The transport maximum is related to the number of carrier proteins that are available for transport and usually is sufficient to ensure that all of a filtered substance such as glucose can be reabsorbed, rather than being eliminated in the urine. The plasma level at which the substance appears in the urine is called the renal threshold (Fig. 22-8). Under some circumstances, the amount of substance filtered in the glomerulus exceeds the transport maximum. For example, when the blood glucose level is elevated in uncontrolled diabetes mellitus, the amount that is filtered in the glomerulus often exceeds the transport maximum (approximately 320 mg/minute), and glucose spills into the urine.

**The Loop of Henle.** The loop of Henle is divided into three segments: the thin descending segment, the thin ascending segment, and thick ascending segment. The loop of Henle, taken as whole, always reabsorbs more sodium and chloride than water. This is in contrast to the proximal tubule, which reabsors sodium and water in equal proportions.

The thin descending limb is highly permeable to water and moderately permeable to urea, sodium, and other ions. As the urine filtrate moves down the descending limb, water moves out of the filtrate into the surrounding interstitium (Fig. 22-9). Thus, the osmolality of the filtrate reaches its highest point at the elbow of the loop of Henle. In contrast to the descending limb, the ascending limb of the loop of Henle is impermeable to water. In this segment, solutes are reabsorbed, but water cannot follow; as a result, the tubular filtrate becomes more and more dilute, often reaching an osmolality of 100 mOsm/kg of H$_2$O as it enters the distal convoluted tubule, compared with the 285 mOsm/kg of H$_2$O in plasma. This allows for excretion of free water from the body. For this reason, it is often called the diluting segment.

The thick segment of the loop of Henle begins in the ascending limb where the epithelial cells become thickened. The beginning of the thick ascending limb marks the border between the outer and inner medulla; thus, the thick ascending limb is found only in the cortex and outer medulla. As with the thin ascending limb, this segment is relatively impermeable to

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**FIGURE 22-9** Summary of movements of ions, urea, and water in the kidney during production of a maximally concentrated urine (1200 mOsm/kg H$_2$O). **Solid arrows** indicate active transport; **dashed arrows** indicate passive transport. The heavy outlining along the ascending limb of Henle’s loop indicates decreased water permeability in that tubule segment. Note the osmotic gradient in the medulla from the outer to the inner medulla. (Modified from Rhoades R.A., Tanner G.A. [1996]. Medical physiology [p. 441]. Boston: Little, Brown)
water. The epithelium of the thick segment has a Na⁺-K⁺-2Cl⁻-cotransport system that moves these ions out of the urine filtrate into the surrounding interstitium and peritubular capillaries (Fig. 22-10). Approximately 20% to 25% of the filtered load of sodium, potassium, and chloride is reabsorbed in the thick loop of Henle. This transport system is selectively blocked by diuretic agents known as loop diuretics. The Na⁺-K⁺-2Cl⁻-cotransport system also provides the electrochemical gradient needed for the passive reabsorption of the divalent magnesium and calcium ions. Thus, the inhibition of sodium transport in the thick loop of Henle by the loop diuretics causes an increase in the urinary excretion of these divalent ions in addition to sodium chloride.

In approximately one fifth of the juxtamedullary nephrons, the loops of Henle and special hairpin-shaped capillaries called the vasa recta descend into the medullary portion of the kidney. A countercurrent mechanism controls water and solute movement so that water is kept out of the area surrounding the tubule and sodium and urea are retained (see Fig. 22-9). The term countercurrent refers to a flow of fluids in opposite directions in adjacent structures. In this case, there is an exchange of solutes between the adjacent ascending and descending loops of Henle and between the ascending and descending sections of the vasa recta. Because of these exchange processes, a high concentration of osmotically active particles (approximately 1200 mOsm/kg of H₂O) collects in the interstitium of the kidney medulla. The presence of these osmotically active particles in the interstitium surrounding the medullary collecting tubules facilitates the antidiuretic hormone (ADH)-mediated reabsorption of water.

**Distal Convoluted Tubule.** Like the thick ascending loop of Henle, the distal convoluted tubule is relatively impermeable to water, and reabsorption of sodium chloride from this segment further dilutes the tubular fluid. Sodium reabsorption occurs through a sodium and chloride cotransport mechanism. Approximately 10% of filtered sodium chloride is reabsorbed in this section of the tubule. Unlike the thick ascending loop of Henle, neither calcium nor magnesium is passively absorbed in this segment of the tubule. Instead, calcium ions are actively reabsorbed in a process that is largely regulated by parathyroid hormone and possibly by vitamin D. The thiazide diuretics exert their action by inhibiting sodium chloride reabsorption in this segment of the renal tubules.

**Distal Tubule and Cortical Collecting Tubule.** The late distal tubule and the cortical collecting tubule constitute the site where aldosterone exerts its action on sodium and potassium reabsorption. Although responsible for only 2% to 5% of sodium chloride reabsorption, this site is largely responsible for determining the final sodium concentration of the urine. The late distal tubule with the cortical collecting tubule also is the major site for regulation of potassium excretion by the kidney. When the body is confronted with a potassium excess, as occurs with a diet high in potassium content, the amount of potassium secreted at this site may exceed the amount filtered in the glomerulus.

The mechanism for sodium reabsorption and potassium secretion by this section of the kidney is distinct from other tubular segments. This tubular segment is composed of two types of cells, the intercalated cells, where potassium is reabsorbed and hydrogen is secreted, and the principal cells, where aldosterone exerts its action. The secretion of hydrogen ions into the tubular fluid by the intercalated cells is accompanied by the reabsorption of bicarbonate ions. The intercalated cells can also reabsorb potassium ions. The principal cells reabsorb sodium and facilitate the movement of potassium into the urine filtrate. Under the influence of aldosterone, sodium moves from the urine filtrate into principal cells; from there it moves into the surrounding interstitial fluid and peritubular capillaries. Potassium moves from the peritubular capillaries into the principal cells and then into the urine filtrate.

**Medullary Collecting Duct.** The epithelium of the inner medullary collecting duct is well designed to resist extreme changes in the osmotic or pH characteristics of tubular fluid, and it is here that the urine becomes highly concentrated, highly diluted, highly alkaline, or highly acidic. During periods of water excess or dehydration, the kidneys play a major role in maintaining water balance.

ADH exerts its effect in the medullary collecting ducts. ADH maintains extracellular volume by returning water to the vascular compartment and leads to the production of a concentrated urine by removing water from the tubular filtrate. Osmoreceptors in the hypothalamus sense the increase in osmolality of extracellular fluids and stimulate the release of ADH from the posterior pituitary gland (see Chapter 6). The permeability of the collecting ducts to water is determined mainly by the concentration of ADH. In exerting its effect, ADH, also known as vasopressin, binds to vasopressin receptors on the blood side of the tubular cells. Binding of ADH to the vasopressin receptors leads to the opening of water channels on the luminal side of the tubular cells, producing a marked increase in water permeability. After the permeability of the collecting tubules has been established, water moves out of the tubular lumen and into the hyperosmotic interstitium of the medullary area, where it enters the peritubular capillaries for return to the vascular system. In the absence
of ADH, the water channels are closed, the tubular cells lose their water permeability, and a dilute urine is formed.

**Regulation of Renal Blood Flow**

In the adult, the kidneys are perfused with 1000 to 1300 mL of blood per minute, or 20% to 25% of the cardiac output. This large blood flow is mainly needed to ensure a sufficient GFR for the removal of waste products from the blood, rather than for the metabolic needs of the kidney. Feedback mechanisms intrinsic to the kidney normally keep blood flow and GFR constant despite changes in arterial blood pressure.

**Neural and Humoral Control Mechanisms**

The kidney is richly innervated by the sympathetic nervous system. Increased sympathetic activity causes constriction of the afferent and efferent arterioles and thus a decrease in renal blood flow. Intense sympathetic stimulation such as occurs in shock and trauma can produce marked decreases in renal blood flow and GFR, even to the extent of causing blood flow to cease altogether.

Several humoral substances, including angiotensin II, ADH, and endothelins, produce vasoconstriction of renal vessels. The endothelins are a group of peptides released from damaged endothelial cells in the kidney and other tissues. Although not thought to be important regulators of renal blood flow during everyday activities, endothelin I may play a role in reduction of blood flow in conditions such as postsischemic acute renal failure (see Chapter 24).

Other substances such as dopamine, nitric oxide, and prostaglandins (i.e., E₂ and I₂) produce vasodilation. Nitric oxide, a vasodilator produced by the vascular endothelium, appears to be important in preventing excessive vasoconstriction of renal blood vessels and allowing normal excretion of sodium and water. Prostaglandins are a group of mediators of cell function that are produced locally and exert their effects locally. Although prostaglandins do not appear to be of major importance in regulating renal blood flow and GFR under normal conditions, they may protect the kidneys against the vasoconstricting effects of sympathetic stimulation and angiotensin II. Salicylates and the nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis may cause reduction in renal blood flow and GFR under certain conditions.

**Autoregulation**

The constancy of renal blood flow is maintained by a process called autoregulation (see Chapter 14). Normally, autoregulation of blood flow is designed to maintain blood flow at a level consistent with the metabolic needs of the tissues. In the kidney, autoregulation of blood flow also must allow for precise regulation of water and solute secretion. For autoregulation to occur, the resistance to blood flow through the kidneys must be varied in direct proportion to the arterial pressure. The exact mechanisms responsible for the intrarenal regulation of blood flow are unclear. One of the proposed mechanisms is a direct effect on vascular smooth muscle that causes the blood vessels to relax when there is an increase in blood pressure, and to contract when there is a decrease in pressure. A second proposed mechanism is the feedback regulation exerted by the juxtaglomerular complex.
about the kidneys’ ability to remove metabolic wastes from the blood and maintain normal electrolyte and pH composition of the blood. As renal function declines, serum levels of substances such as urea, creatinine, phosphate, and potassium increase. The effect of renal failure on the concentration of serum electrolytes and metabolic end products is discussed in Chapter 24.

**Renal Clearance**
Renal clearance is the volume of plasma that is completely cleared each minute of any substance that finds its way into the urine. It is determined by the ability of the substance to be filtered in the glomeruli and the capacity of the renal tubules to reabsorb or secrete the substance. Every substance has its own clearance rate, the units of which are expressed as the volume of plasma that is cleared per unit time. It can be determined by measuring the amount of a substance that is excreted in the urine (i.e., urine concentration × urine flow rate in milliliters per minute) and dividing by its plasma concentration. Inulin, a large polysaccharide, is freely filtered in the glomeruli and neither reabsorbed nor secreted by the tubular cells. After intravenous injection, the amount that appears in the urine is equal to the amount that is filtered in the glomeruli (i.e., the clearance rate is equal to the GFR). Because of these properties, inulin can be used as a laboratory measure of the GFR.

Creatinine is a product of creatine metabolism in muscles; its formation and release are relatively constant and proportional to the amount of muscle mass present. Creatinine is freely filtered in the glomeruli, is not reabsorbed from the tubules into the blood, and is only minimally secreted into the tubules from the blood; therefore, its serum values depend closely on the GFR. Serum creatinine levels are often used as a measure of renal function. A normal serum creatinine level usually indicates normal renal function.

Some substances, such as urea, are freely filtered in the glomeruli, but the volume that is cleared from the plasma is less than the GFR, indicating that at least some of the substance is being reabsorbed. At normal plasma levels, glucose has a clearance of zero because it is reabsorbed in the tubules and none appears in the urine.

**Regulation of Sodium and Potassium Elimination**
Elimination of sodium and potassium is regulated by the GFR and by humoral agents that control reabsorption. Aldosterone functions in the regulation of sodium and potassium elimination. Atrial natriuretic peptide (ANP) contributes to the regulation of sodium elimination.

**Aldosterone.** Sodium reabsorption in the distal tubule and collecting duct is highly variable and depends on the presence of aldosterone, a hormone secreted by the adrenal gland. In the presence of aldosterone, almost all the sodium in the distal tubular fluid is reabsorbed, and the urine essentially becomes sodium free. In the absence of aldosterone, virtually no sodium is reabsorbed from the distal tubule. The remarkable ability of the distal tubular and collecting duct cells to alter sodium reabsorption in relation to changes in aldosterone allows the kidneys to excrete urine with sodium levels that range from a few tenths of a gram to 40 g per day. Like sodium, potassium is freely filtered in the glomerulus, but unlike sodium, potassium is reabsorbed from and secreted into the tubular fluid. The secretion of potassium into the tubular fluid occurs in the distal tubule and, like that of sodium, is regulated by aldosterone. Only approximately 70 mEq of potassium is delivered to the distal tubule each day, but the average person consumes this much and more potassium in the diet. Excess potassium that is not filtered in the glomerulus and delivered to the collecting tubule therefore must be secreted (i.e., transported from the blood) into the tubular fluid for elimination from the body. In the absence of aldosterone (as in Addison’s disease; see Chapter 31), potassium secretion becomes minimal. In these circumstances, potassium reabsorption exceeds secretion, and blood levels of potassium increase.

**Atrial Natriuretic Peptide.** Atrial natriuretic peptide, discovered in 1981, is a hormone believed to have an important role in salt and water excretion by the kidney. It is synthesized in muscle cells of the atria of the heart and released when the atria are stretched. The actions of ANP include vasodilation of the afferent and efferent arterioles, which results in an increase in renal blood flow and glomerular filtration rate. ANP also inhibits sodium reabsorption from the collecting tubules through its inhibition of aldosterone secretion and through direct action on the tubular cells. It also inhibits ADH release from the posterior pituitary gland, thereby increasing excretion of water by the kidneys. ANP also has vasodilator properties. Whether these effects are sufficient to produce long-term changes in blood pressure is uncertain.

**Regulation of pH**
The kidneys regulate body pH by conserving base bicarbonate (HCO₃⁻) and eliminating hydrogen ions (H⁺). Neither the blood buffer systems nor the respiratory control mechanisms for carbon dioxide elimination can eliminate H⁺ from the body. This is accomplished by the kidneys. The average North American diet results in the liberation of 40 to 80 mmol of H⁺ each day. Virtually all the H⁺ excreted in the urine is secreted into the tubular fluid by means of tubular secretory mechanisms. The lowest tubular fluid pH that can be achieved is 4.4 to 4.5. The ability of the kidneys to excrete H⁺ depends on buffers in the urine that combine with the H⁺. The three major urine buffers are HCO₃⁻, phosphate (HPO₄²⁻), and ammonia (NH₃). The HCO₃⁻ ions, which are present in the urine filtrate, combine with H⁺ ions that have been secreted into the tubular fluid; this results in the formation of carbon dioxide and water. The carbon dioxide is then absorbed into the tubular cells, and bicarbonate is regenerated. The HPO₄²⁻ ion is a metabolic end product that is filtered into the tubular fluid; it combines with a secreted H⁺ ion and is not reabsorbed. Ammonia is synthesized in tubular cells by deamination of the amino acid glutamine; it diffuses into the tubular fluid and combines with the H⁺ ion. An important aspect of this buffer system is that the deamination process increases when the body’s H⁺ ion concentration remains elevated for 1 to 2 days. These mechanisms for pH regulation are described more fully in Chapter 6.

**pH-Dependent Elimination of Organic Ions**
The proximal tubule actively secretes large amounts of different organic anions. Foreign anions (e.g., salicylates, penicillin) and endogenously produced anions (e.g., bile acids, uric acid) are actively secreted into the tubular fluid. Most of the anions
that are secreted use the same transport system, allowing the kidneys to rid the body of many different drugs and environmental agents. Because the same transport system is shared by different anions, there is competition for transport such that elevated levels of one substance tend to inhibit the secretion of other anions. The proximal tubules also possess an active transport system for organic cations that is analogous to that for organic ions.

**Uric Acid Elimination**

Uric acid is a product of purine metabolism (see Chapter 43). Excessively high blood levels (i.e., hyperuricemia) can cause gout, and excessive levels in the urine can cause kidney stones. Uric acid is freely filtered in the glomerulus and is reabsorbed and secreted into the proximal tubules. Uric acid is one of the anions that uses the previously described anion transport system in the proximal tubule. Tubular reabsorption normally exceeds secretion, and the net effect is removal of uric acid from the filtrate. Although the rate of reabsorption exceeds secretion, the secretory process is homeostatically controlled to maintain a constant plasma level. Many persons with elevated uric acid levels secrete less uric acid than do persons with normal uric acid levels.

Uric acid uses the same transport systems as other anions, such as aspirin, sulfinpyrazone, and probenecid. Small doses of aspirin compete with uric acid for secretion into the tubular fluid and reduce uric acid secretion, and large doses compete with uric acid for reabsorption and increase uric acid excretion in the urine. Because of its effect on uric acid secretion, aspirin is not recommended for treatment of gouty arthritis. Thiazide and loop diuretics (i.e., furosemide and ethacrynic acid) also can cause hyperuricemia and gouty arthritis, presumably through a decrease in extracellular fluid volume and enhanced uric acid reabsorption.

**Urea Elimination**

Urea is an end product of protein metabolism. The normal adult produces 25 to 30 g/day; the quantity rises when a high-protein diet is consumed, when there is excessive tissue breakdown, or in the presence of gastrointestinal bleeding. With gastrointestinal bleeding, the blood proteins are broken down to form ammonia in the intestine; the ammonia is then absorbed into the portal circulation and converted to urea by the liver before being released into the bloodstream. The kidneys, in their role as regulators of blood urea nitrogen (BUN) levels, filter urea in the glomeruli and then reabsorb it in the tubules. This enables maintenance of a normal BUN, which is in the range of 8 to 20 mg/dl. During periods of dehydration, the blood volume and GFR drop, and BUN levels increase. The renal tubules are permeable to urea, which means that the longer the tubular fluid remains in the kidneys, the greater is the reabsorption of urea into the blood. Only small amounts of urea are reabsorbed into the blood when the GFR is high, but relatively large amounts of urea are returned to the blood when the GFR is reduced.

**Drug Elimination**

Many drugs are eliminated in the urine. These drugs are selectively filtered in the glomerulus and reabsorbed or secreted into the tubular fluid. Only drugs that are not bound to plasma proteins are filtered in the glomerulus and therefore able to be eliminated by the kidneys.

Many drugs are weak acids or weak bases and are present in the renal tubular fluid partly as water-soluble ions and partly as nonionized lipid-soluble molecules. The nonionized lipid-soluble form of a drug diffuses more readily through the lipid membrane of the tubule and then back into the bloodstream. The water-soluble ionized form remains in the urine filtrate. The ratio of ionized to nonionized drug depends on the pH of the urine. For example, aspirin is highly ionized in alkaline urine and in this form is rapidly excreted in the urine. Aspirin is largely nonionized in acid urine and is reabsorbed, rather than excreted. Alkaline or acid diuresis may be used to increase elimination of drugs in the urine, particularly in situations of drug overdose.

**Endocrine Functions of the Kidney**

In addition to their function in regulating body fluids and electrolytes, the kidneys function as an endocrine organ in that they produce chemical mediators that travel through the blood to distant sites where they exert their actions. The kidneys participate in control of blood pressure by way of the renin-angiotensin mechanism, in calcium metabolism by activating vitamin D, and in regulating red blood cell production through the synthesis of erythropoietin.

**The Renin-Angiotensin-Aldosterone Mechanism**

The renin-angiotensin-aldosterone mechanism plays an important part in the short-term and long-term regulation of blood pressure (see Chapter 16). Renin is synthesized and stored in the juxaglomerular cells of the kidney. This enzyme is released in response to a decrease in renal blood flow or a change in the composition of the distal tubular fluid, or as the result of sympathetic nervous system stimulation. Renin itself has no direct effect on blood pressure. Rather, it acts enzymatically to convert a circulating plasma protein called angiotensinogen to angiotensin I. Angiotensin I, which has few vasoconstrictor properties, leaves the kidneys and enters the circulation; as it is circulated through the lungs, angiotensin-converting enzyme catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor, and it acts directly on the kidneys to decrease salt and water...
excretion. Both mechanisms have relatively short periods of action. Angiotensin II also stimulates aldosterone secretion by the adrenal gland. Aldosterone acts on the distal tubule to increase sodium reabsorption and exerts a longer-term effect on the maintenance of blood pressure. Renin also functions by means of angiotensin II to produce constriction of the efferent arteriole as a means of preventing a serious decrease in glomerular filtration pressure.

**Erythropoietin**
Erythropoietin is a polypeptide hormone that regulates the differentiation of red blood cells in the bone marrow (see Chapter 13). Between 89% and 95% of erythropoietin is formed in the kidneys. The synthesis of erythropoietin is stimulated by tissue hypoxia, which may be brought about by anemia, residence at high altitudes, or impaired oxygenation of tissues caused by cardiac or pulmonary disease. Persons with end-stage kidney disease often are anemic because of an inability of the kidneys to produce erythropoietin. This anemia usually is managed by the administration of epoetin-alfa, a synthetic form of erythropoietin produced through DNA technology, to stimulate erythropoiesis.

**Vitamin D**
Activation of vitamin D occurs in the kidneys. Vitamin D increases calcium absorption from the gastrointestinal tract and helps to regulate calcium deposition in bone. It also has a weak stimulatory effect on renal calcium absorption. Although vitamin D is not synthesized and released from an endocrine gland, it often is considered as a hormone because of its pathway of molecular activation and mechanism of action.

It exists in several forms: natural vitamin D (cholecalciferol), which results from ultraviolet irradiation of the skin, and synthetic vitamin D (ergocalciferol), which is derived from irradiation of ergosterol. The active form of vitamin D is 1,25-dihydroxycholecalciferol. Cholecalciferol and ergocalciferol must undergo chemical transformation to become active: first to 25-hydroxycholecalciferol in the liver and then to 1,25-dihydroxycholecalciferol in the kidneys. Persons with end-stage renal disease are unable to transform vitamin D to its active form and must rely on pharmacologic preparations of the active vitamin (calcitriol) for maintaining mineralization of their bones.

In summary, the kidneys perform excretory and endocrine functions. In the process of excreting wastes, the kidneys filter the blood and then selectively reabsorb those materials that are needed to maintain a stable internal environment. The kidneys rid the body of metabolic wastes, regulate fluid volume, regulate the concentration of electrolytes, assist in maintaining acid-base balance, aid in the regulation of blood pressure through the renin-angiotensin-aldosterone mechanism and control of extracellular fluid volume, regulate red blood cell production through erythropoietin, and aid in calcium metabolism by activating vitamin D.

The kidneys selectively eliminate water, waste products, excess electrolytes, and other substances that are not needed to maintain the constancy of the internal environment. Renal clearance is the volume of plasma that is completely cleared each minute of any substance that finds its way into the urine.

It is determined by the ability of the substance to be filtered in the glomeruli and the capacity of the renal tubules to reabsorb or secrete the substance. The GFR is the amount of filtrate that is formed each minute as blood moves through the glomeruli. It is regulated by the arterial blood pressure and renal blood flow in the normally functioning kidney. The juxtaglomerular complex is thought to represent a feedback control system that links changes in the GFR with renal blood flow.

In addition to their function in regulating body fluids and electrolytes, the kidneys function as an endocrine organ in that they produce chemical mediators that travel through the blood to distant sites where they exert their actions. The kidneys participate in control of blood pressure by way of the renin-angiotensin mechanism, in calcium metabolism by activating vitamin D, and in regulating red blood cell production through the synthesis of erythropoietin.

**Tests of Renal Function**

The functions of the kidney are to filter the blood and selectively reabsorb those substances that are needed to maintain the constancy of body fluids and excrete metabolic wastes. Laboratory tests of the urine and blood can provide valuable information about kidney pathology and the adequacy of renal function.

**Urine Tests**

Urine is a clear, amber-colored fluid that is approximately 95% water and 5% dissolved solids. The kidneys normally produce approximately 1.5 L of urine each day. Normal urine contains metabolic wastes and few or no plasma proteins, blood cells, or glucose molecules.

Urine tests can be performed on a single urine specimen or on a 24-hour urine specimen. First-voided morning specimens are useful for qualitative protein and specific gravity testing. A freshly voided specimen is most reliable. Urine specimens that have been left standing may contain lysed red blood cells, disintegrating casts, and rapidly multiplying bacteria.

Casts are molds of the distal nephron lumen. A gel-like substance called Tamm-Horsfall mucoprotein, which is formed in the tubular epithelium, is the major protein constituent of urinary casts. Casts composed of this gel but devoid of cells are called hyaline casts. These casts develop when the protein concentration of the urine is high (as in nephrotic syndrome), urine osmolality is high, and urine pH is low. The inclusion of granules or cells in the matrix of the protein gel leads to the formation of various other types of casts.

Because of the glomerular capillary filtration barrier, less than 150 mg of protein is excreted in the urine during 24 hours in a healthy person. Qualitative and quantitative tests to determine urinary protein content are important tools to assess the extent of glomerular disease. pH-sensitive reagent strips are used to test for the presence of proteins, whereas immunoassay methods are used to test for microalbuminuria (30 to 300 mg albumin/24 hours).
The specific gravity (or osmolality) of urine varies with its concentration of solutes. Urine specific gravity provides a valuable index of the hydration status and functional ability of the kidneys. Healthy kidneys can produce a concentrated urine with a specific gravity of 1.030 to 1.040. During periods of marked hydration, the specific gravity can approach 1.000. With the loss of nephrons and diminished renal function, there is a loss of renal concentrating ability, and the urine specific gravity may fall to levels of 1.006 to 1.010 (usual range is 1.010 to 1.025 with normal fluid intake). These low levels are particularly significant if they occur during periods that follow a decrease in water intake (e.g., during the first urine specimen on arising in the morning). The ability to concentrate urine also depends on the availability of and renal response to ADH. The urine specific gravity is decreased when ADH levels are decreased, such as in diabetes insipidus, and it is increased when ADH levels are inappropriately elevated, such as in the syndrome of inappropriate ADH.

**Glomerular Filtration Rate**

The GFR provides a gauge of renal function. It can be measured clinically by collecting timed samples of blood and urine. Creatinine, a product of creatine metabolism by the muscle, is filtered by the kidneys but not reabsorbed in the renal tubule. Creatinine levels in the blood and urine can be used to measure GFR. The clearance rate for creatinine is the amount that is completely cleared by the kidneys in 1 minute. The formula is expressed as $C = \frac{UV}{P}$, in which $C$ is the clearance rate (mL/minute), $U$ is the urine concentration (mg/dL), $V$ is the urine volume excreted (mL/minute or 24 hours), and $P$ is plasma concentration (mg/dL).

Normal creatinine clearance is 115 to 125 mL/minute. This value is corrected for body surface area, which reflects the muscle mass where creatinine metabolism takes place. The test may be done on a 24-hour basis, with blood being drawn when the urine collection is completed. In another method, two 1-hour urine specimens are collected, and a blood sample is drawn in between.

**Blood Tests**

Blood tests can provide valuable information about the kidneys’ ability to remove metabolic wastes from the blood and maintain normal electrolyte and pH composition of the blood. Normal blood values are listed in Table 22-1. Serum levels of potassium, phosphate, BUN, and creatinine increase in renal failure. Serum pH, calcium, and bicarbonate levels decrease in renal failure. The effect of renal failure on the concentration of serum electrolytes and metabolic end products is discussed in Chapter 24.

**Serum Creatinine**

Serum creatinine levels reflect the glomerular filtration rate. Because these measurements are easily obtained and relatively inexpensive, they often are used as a screening measure of renal function. Creatinine is a product of creatine metabolism in muscles; its formation and release are relatively constant and proportional to the amount of muscle mass present. Creatinine is freely filtered in the glomeruli, is not reabsorbed from the tubules into the blood, and is only minimally secreted into the tubules from the blood; therefore, its blood values depend closely on the GFR.

The normal creatinine value is approximately 0.6 mg/dL of blood for a woman with a small frame, approximately 1.0 mg/dL of blood for a normal adult man, and approximately 1.2 mg/dL of blood for a muscular man. There is an age-related decline in creatinine clearance in many elderly persons because muscle mass and the GFR decline with age (see Chapter 24). A normal serum creatinine level usually indicates normal renal function. In addition to its use in calculating the GFR, the serum creatinine level is used in estimating the functional capacity of the kidneys (Fig. 22-12). If the serum creatinine value doubles, the GFR—and renal function—probably has fallen to one half of its normal state. A rise in the serum creatinine level to three times its normal value suggests that there is a 75% loss of renal function, and with creatinine values of 10 mg/dL or more, it can be assumed that approximately 90% of renal function has been lost.

**Blood Urea Nitrogen**

Urea is formed in the liver as a by-product of protein metabolism and is eliminated entirely by the kidneys. Therefore,

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**TABLE 22-1 Normal Blood Chemistry Levels**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Normal Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea nitrogen</td>
<td>8.0–20.0 mg/dL (2.9–7.1 mmol/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6–1.2 mg/dL (50–100 µmol/L)</td>
</tr>
<tr>
<td>Sodium</td>
<td>135–145 mEq/L (135–148 mmol/L)</td>
</tr>
<tr>
<td>Chloride</td>
<td>98–106 mEq/L (98–106 mmol/L)</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–5 mEq/L (3.5–5 mmol/L)</td>
</tr>
<tr>
<td>Carbon dioxide (CO₂ content)</td>
<td>24–29 mEq/L (24–29 mmol/L)</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5–10.5 mg/dL (2.1–2.6 mmol/L)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.5–4.5 mg/dL (0.77–1.45 mmol/L)</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>1.4–7.4 mg/dL (0.154–0.42 mmol/L)</td>
</tr>
<tr>
<td>pH</td>
<td>7.35–7.45</td>
</tr>
</tbody>
</table>

*Values may vary among laboratories, depending on the method of analysis used.

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**FIGURE 22-12** Relation between the percentage of renal function and serum creatinine levels.
BUN is related to the GFR but, unlike creatinine, also is influenced by protein intake, gastrointestinal bleeding, and hydration status. Increased protein intake and gastrointestinal bleeding increase urea by means of protein metabolism. In gastrointestinal bleeding, the blood is broken down by the intestinal flora, and the nitrogenous waste is absorbed into the portal vein and transported to the liver, where it is converted to urea. During dehydration, elevated BUN levels result from increased concentration. Approximately two thirds of renal function must be lost before a significant rise in the BUN level occurs.

The BUN is less specific for renal insufficiency than creatinine, but the \textit{BUN–creatinine ratio} may provide useful diagnostic information. The ratio normally is approximately 10:1. Ratios greater than 15:1 represent prerenal conditions, such as congestive heart failure and upper gastrointestinal tract bleeding, that produce an increase in BUN but not in creatinine. A ratio of less than 10:1 occurs in persons with liver disease and in those who receive a low-protein diet or chronic dialysis because BUN is more readily dialyzable than creatinine.

\textbf{In summary,} urinalysis and blood tests that measure levels of by-products of metabolism and electrolytes provide information about renal function. Serum creatinine reflects the glomerular filtration rate and can be used as an estimate of renal function. Measurements of BUN, which is formed in liver as a by-product of protein metabolism and eliminated almost entirely by the kidney, are also a measure of renal function.

**REVIEW QUESTIONS**

- Describe the location and gross structure of the kidney and explain why kidney injury does not produce peritonitis.
- Explain the structure and function of the capillary structures of the nephron (glomerulus and peritubular capillaries) and the tubular components of the nephron in terms of filtering and reabsorbing nutrients, eliminating waste products, and maintaining the acid-base and electrolyte composition of the extracellular fluid.

**Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.**

**BIBLIOGRAPHY**


