Color enhanced scanning electron micrograph of podocytes wrapped around the glomerular capillaries.

CHAPTER

26

Urinary System

The kidneys make up the body's main purification system. They remove waste products, many of which are toxic, from the blood. The kidneys also help control the composition of blood and blood volume. Approximately one-third of one kidney is all that's needed to maintain homeostasis. Even after extensive damage, the kidneys can still perform their life-sustaining function. If the kidneys are damaged further, however, death results unless specialized medical treatment is administered.

The **urinary system** consists of two kidneys; a single, midline urinary bladder; two ureters, which carry urine from the kidneys to the urinary bladder; and a single urethra, which carries urine from the bladder to the outside of the body (figure 26.1*a*).

This chapter explains the *functions of the urinary system* (947), *kidney anatomy and histology* (947), *anatomy and histology of the ureters and urinary bladder* (953), *urine production* (954), *regulation of urine concentration and volume* (970), *clearance and tubular maximum* (973), and *urine movement* (974). We conclude the chapter with a look at the *effects of aging on the kidneys* (976).

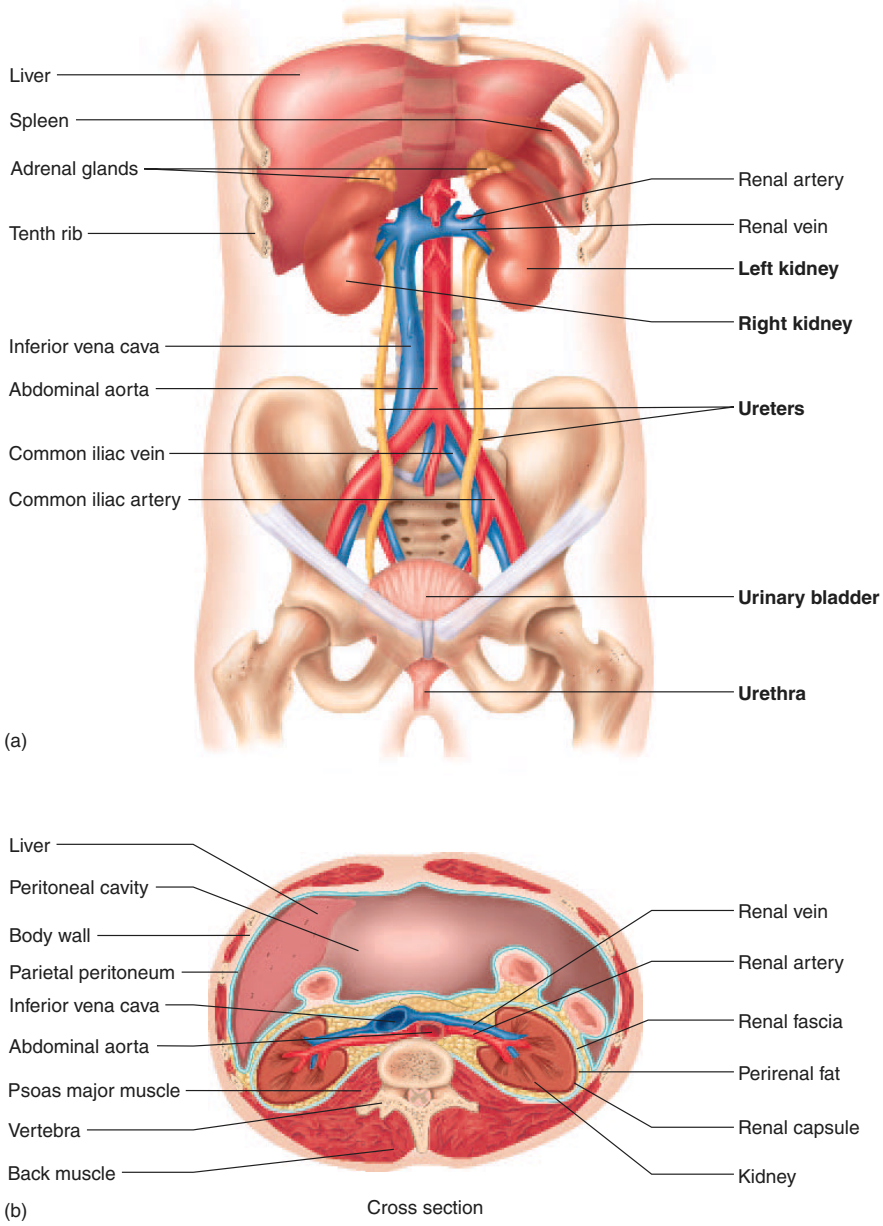


Figure 26.1 Anatomy of the Urinary System

The urinary system consists of two kidneys, two ureters, a single urinary bladder, and a single urethra. (*a*) The kidneys are located in the abdominal cavity, with the right kidney just below the liver and the left kidney below the spleen. The ureters extend from the kidneys to the urinary bladder within the pelvic cavity. An adrenal gland is located at the superior pole of each kidney. (*b*) The kidneys are located behind the parietal peritoneum. Surrounding each kidney is the perirenal fat. The renal arteries extend from the abdominal aorta to each kidney, and the renal veins extend from the kidneys to the inferior vena cava.

Functions of the Urinary System

Objective

- ***List and explain the major functions performed by the kidneys.***

The kidneys are the major excretory organs of the body. The skin, liver, lungs, and intestines eliminate some waste products, but if the kidneys fail to function, these other excretory organs cannot adequately compensate. The following functions are performed by the kidneys:

1. *Filtering of blood.* Proteins and blood cells are retained in the blood, while a large volume of filtrate is produced. Most of the filtrate volume is reabsorbed back into the blood along with useful molecules and ions. A small volume of water, metabolic wastes, toxic molecules, and excess ions remain in the filtrate. Additional waste products are secreted into the filtrate and the result is the formation of urine.
2. *Regulation of blood volume.* The kidneys play a major role in controlling the extracellular fluid volume in the body by producing either a large volume of dilute urine or a small volume of concentrated urine.
3. *Regulation of the concentration of solutes in the blood.* The kidneys help regulate the concentration of the major ions such as Na^+, Cl^-, K^+, Ca^{2+}, and HPO_4^{-2}.
4. *Regulation of the pH of the extracellular fluid.* The kidneys secrete variable amounts of H^+ to help regulate the extracellular fluid pH.
5. *Regulation of red blood cell synthesis.* The kidneys secrete a hormone, erythropoietin, which regulates the synthesis of red blood cells in bone marrow (see chapter 19).
6. *Vitamin D synthesis.* The kidneys play an important role in controlling blood levels of Ca^{2+} by regulating the synthesis of vitamin D (see chapter 6).

1. List the functions performed by the kidneys, and briefly explain each.

Kidney Anatomy and Histology

Objectives

- ***Describe the location, size, shape, and internal anatomy of the kidneys.***
- ***Describe the structure of the nephron and the orientation of its parts within the kidney.***
- ***List the components of the filtration membrane.***
- ***Describe the course of blood flow through the kidney.***

Location and External Anatomy of the Kidneys

The **kidneys** are bean-shaped and about the size of a tightly clenched fist. They lie behind the peritoneum on the posterior abdominal wall on either side of the vertebral column near the lateral borders of the psoas major muscles (figure 26.1). The kidneys extend from the level of the last thoracic (T_{12}) to the third lumbar (L3) vertebrae and the rib cage partially protects them. The liver is superior to the right kidney, causing the right kidney to be slightly lower than the left. Each kidney measures about 11 cm long, 5 cm wide, and 3 cm thick and weighs about 130 g. The **renal capsule,** a layer of fibrous connective tissue, surrounds each kidney. **Perirenal fat,** a dense layer of adipose tissue, in turn, engulfs the renal capsule. This perirenal fat acts as a shock absorber cushioning the kidneys against mechanical shock. A thin layer of loose connective tissue, the **renal fascia,** anchors the kidneys and surrounding adipose tissue to the abdominal wall.

The **hilum** (hī′lŭm) is a small area that lies on the medial side of each kidney, where the renal artery and nerves enter and the renal vein and ureter exit the kidneys. The hilum opens into the **renal sinus,** a cavity that contains fat and connective tissue (figure 26.2).

Internal Anatomy and Histology of the Kidneys

A frontal section of the kidney reveals that the kidney is divided into an outer **cortex** and an inner **medulla,** which surrounds the renal sinus (see figure 26.2). **Renal pyramids** are cone-shaped structures that make up the medulla. **Medullary rays** extend from the renal pyramids into the cortex. **Renal columns** consist of the same tissue as the cortex that projects between the renal pyramids. The bases of the pyramids form the boundary between the cortex and the medulla. The tips of the pyramids, the **renal papillae,** point toward the renal sinus. **Minor calyces** (kal′i-sēz; cup of flower) are funnel-shaped chambers into which the renal papillae extend.

The minor calyces of several pyramids merge to form larger funnels, the **major calyces.** Each kidney contains 8–20 minor calyces and 2 or 3 major calyces. The major calyces converge to form an enlarged chamber called the **renal pelvis,** which is surrounded by the renal sinus. The renal pelvis narrows into a small-diameter tube, the **ureter,** which exits the kidney at the hilum and connects to the urinary bladder. Urine formed within the kidney flows from the renal papillae into the minor calyces. From the minor calyces, urine flows into the major calyces, collects in the renal pelvis, and then leaves the kidney through the ureter.

The **nephron** (nef′ron) is the histological and functional unit of the kidney (figure 26.3). Each nephron is a tubelike structure with an enlarged terminal end called Bowman's capsule, a proximal tubule, a loop of Henle (nephronic loop), and a distal tubule. The distal tubule empties into a collecting duct, which carries urine from the cortex of the kidney toward the renal papilla. Near the tip of the renal papilla, several collecting ducts merge into a larger-diameter tubule called a **papillary duct** which empties into a minor calyx. The renal corpuscles, proximal tubules, and distal tubules are located in the renal cortex, but the collecting tubules, parts of the loops of Henle, and the papillary ducts are in the renal medulla.

There are approximately 1.3 million nephrons in each kidney. Most nephrons measure 50–55 mm in length. Nephrons whose renal corpuscles lie near the medulla are called

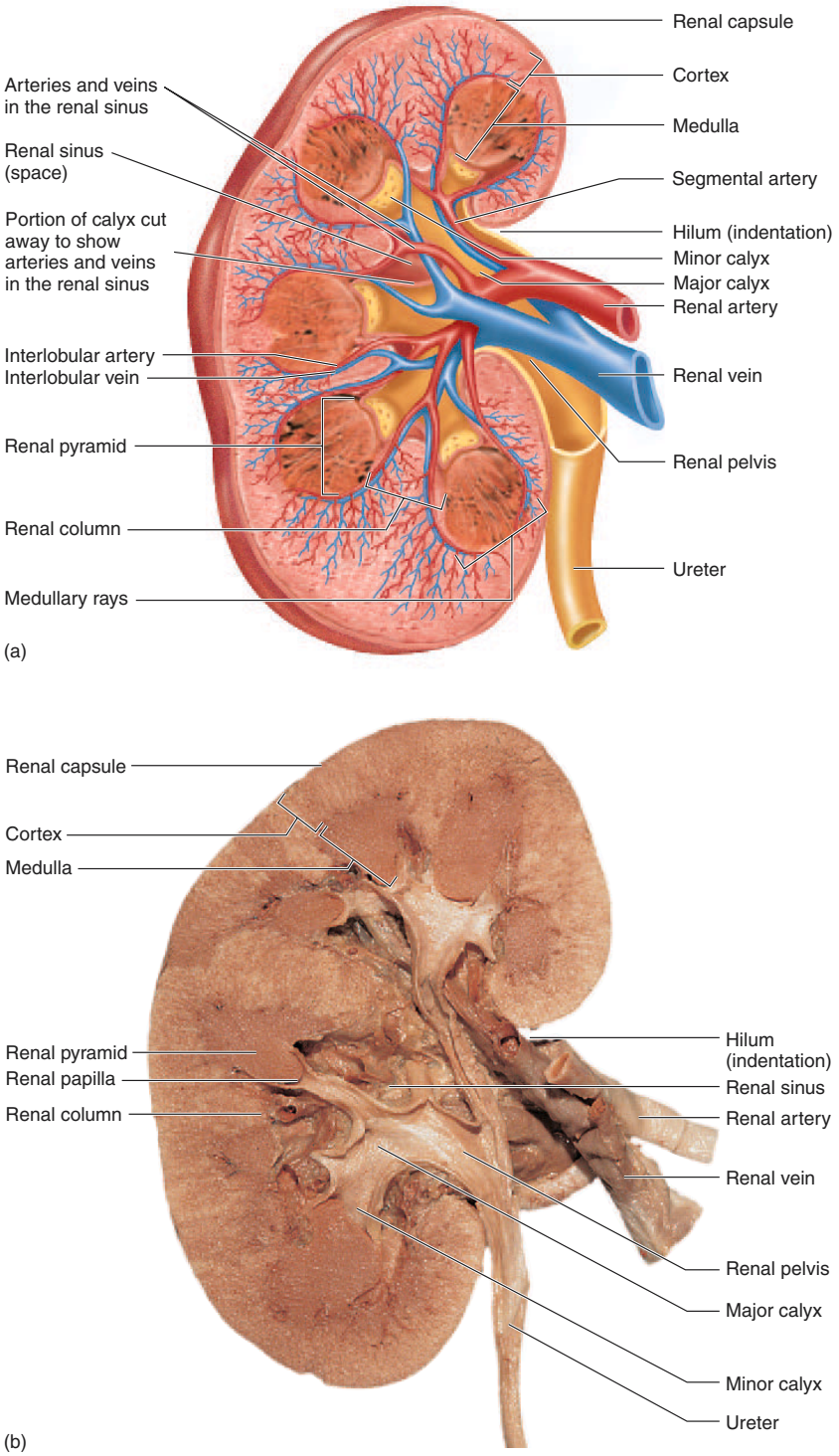
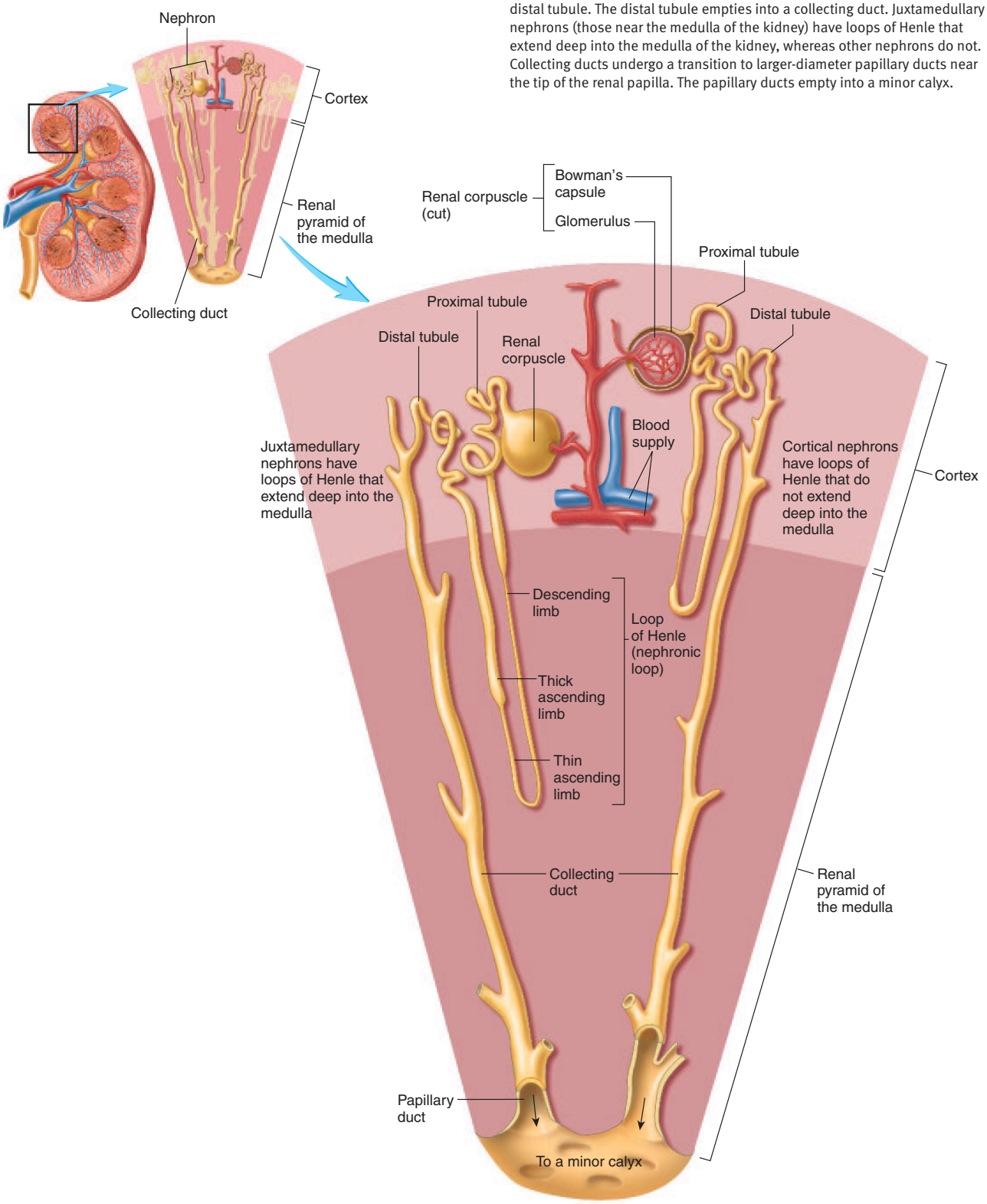


Figure 26.2 Longitudinal Section of the Kidney and Ureter

(*a*) The cortex forms the outer part of the kidney, and the medulla forms the inner part. A central cavity called the renal sinus contains the renal pelvis. The renal columns of the kidney project from the cortex into the medulla and separate the pyramids. (*b*) Photograph of a longitudinal section of a human kidney and ureter.

Figure 26.3 Functional Unit of the Kidney—the Nephron

A nephron consists of a renal corpuscle, proximal tubule, loop of Henle, and distal tubule. The distal tubule empties into a collecting duct. Juxtamedullary nephrons (those near the medulla of the kidney) have loops of Henle that extend deep into the medulla of the kidney, whereas other nephrons do not. Collecting ducts undergo a transition to larger-diameter papillary ducts near the tip of the renal papilla. The papillary ducts empty into a minor calyx.



juxtamedullary (juks′ta-med′ŭ-lār-ē; *juxta* is Latin, meaning next to) **nephrons.** They have long loops of Henle, which extend deep into the medulla. Only about 15% of the nephrons are juxtamedullary nephrons. The remainder of the nephrons are called **cortical nephrons,** and their loops of Henle do not extend deep into the medulla (see figure 26.3).

Each **renal corpuscle** consists of the enlarged end of a nephron, called **Bowman's capsule** (glomerular capsule), and a network of capillaries, called the **glomerulus** (glō-măr′ū-lŭs) (figure 26.4*a* and *b*). The wall of Bowman's capsule is indented to form a double-walled chamber. The glomerulus, which looks like a wad of yarn, fills the indentation. Fluid flows from the glomerulus into Bowman's capsule, and then into the proximal tubule, which carries fluid away from Bowman's capsule.

Bowman's capsule has an outer layer, called the **parietal layer,** and an inner layer, called the **visceral layer** (see figure 26.4*b*). The parietal layer is constructed of simple squamous epithelium that becomes cube-shaped at the beginning of the proximal tubule. The **visceral layer** is constructed of specialized **podocyte cells,** which wrap around the glomerular capillaries.

Numerous windowlike openings, called **fenestrae** (fenes′trē), are in the endothelial cells of the glomerular capillaries. Gaps, called **filtration slits,** are between cell processes of the podocytes that make up the visceral layer of Bowman's capsule. A basement membrane lies sandwiched between the endothelial cells of the glomerular capillaries and the podocytes of Bowman's capsule. Together the capillary endothelium, the basement membrane, and the podocytes of Bowman's capsule form the kidney's **filtration membrane** (figure 26.4*c* and *d*). Urine formation begins when fluid from the glomerular capillaries moves across the filtration membrane into the lumen, or space, inside Bowman's capsule.

An **afferent** (af′er-ent) **arteriole** supplies blood to the glomerulus and an **efferent** (ef′er-ent) **arteriole** drains it. A layer of smooth muscle lines both the afferent and efferent arterioles. At the point where the afferent arteriole enters the renal corpuscle, the smooth muscle cells form a cufflike arrangement around the arteriole. These cells are called **juxtaglomerular cells.** Lying between the afferent and efferent arterioles adjacent to the renal corpuscle is part of the distal tubule of the nephron. Specialized tubule cells in this section are collectively called the **macula** (mak′ū-lă) **densa.** The juxtaglomerular cells of the afferent arteriole and the macula densa cells intimately contact each other. Coupled together, they are called the **juxtaglomerular apparatus** (see figure 26.4*b*).

The **proximal tubule,** also called the **proximal convoluted tubule,** measures approximately 14 mm long and 60 µm in diameter. Simple cuboidal epithelium makes up its wall. The cells rest on a basement membrane, which forms the outer surface of the tubule. Many microvilli project from the luminal surface of the cells (figure 26.5*a* and *b*).

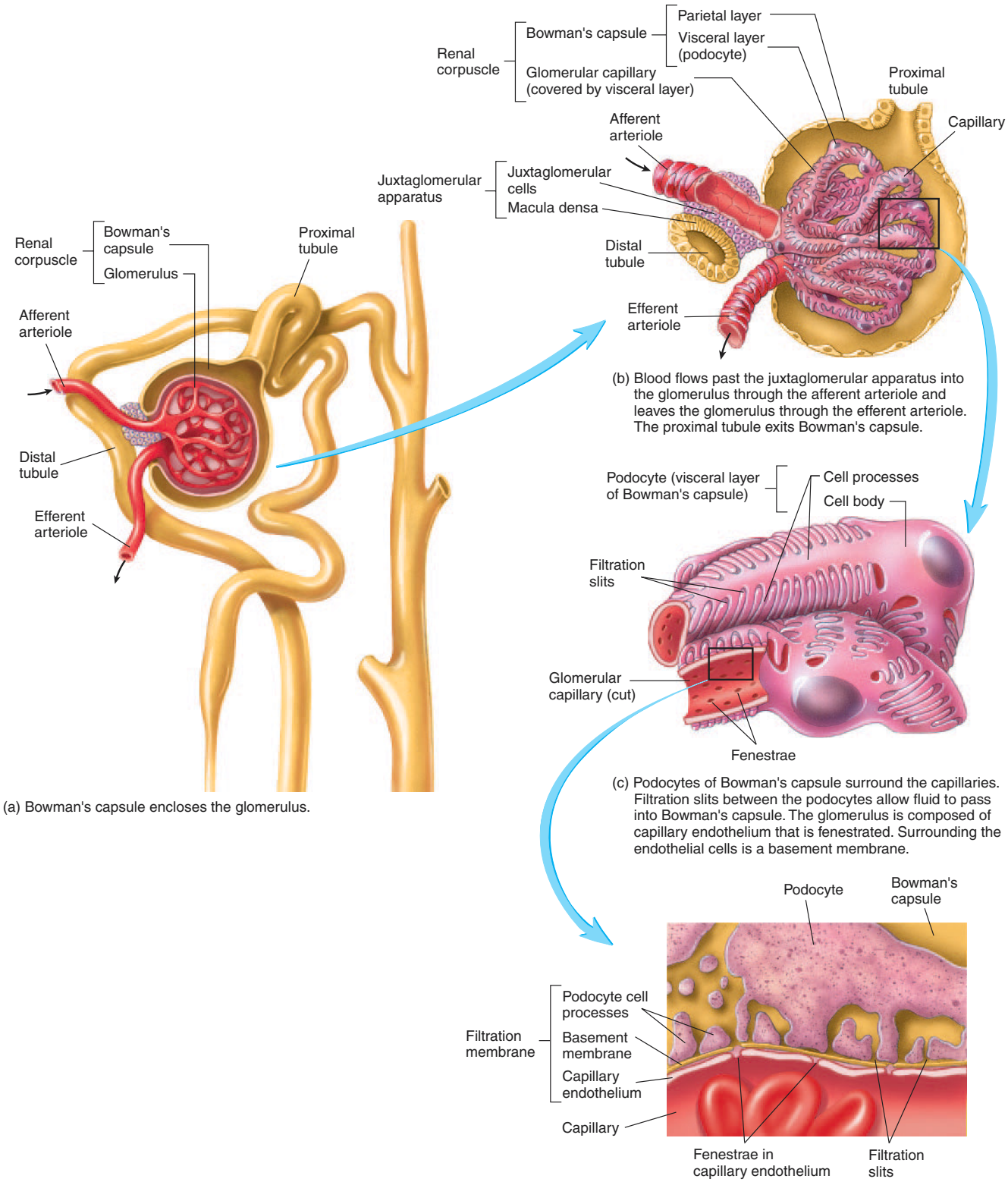
The **loops of Henle** (nephronic loops) are continuations of the proximal tubules. Each loop has two limbs, one **descending** and one **ascending.** The first part of the descending limb is similar in structure to the proximal tubules. The loops of Henle that extend into the medulla become very thin near the end of the loop (see figure 26.5*a* and *c*). The lumen in the thin part narrows, and an abrupt transition occurs from simple cuboidal epithelium to simple squamous epithelium. Like the descending limb, the first part of the ascending limb is thin and is made of simple squamous epithelium. Soon, however, it becomes thicker, and simple cuboidal epithelium replaces the simple squamous epithelium. The thick part of the loop returns toward the renal corpuscle and ends by giving rise to the distal tubule near the macula densa.

The **distal tubules,** also called the **distal convoluted tubules,** are not as long as the proximal tubules. The epithelium is simple cuboidal, but the cells are smaller than the epithelial cells in the proximal tubules and do not possess a large number of microvilli (figure 26.5*a* and *d*). The distal tubules of many nephrons connect to the **collecting ducts,** which are composed of simple cuboidal epithelium. The collecting ducts, which are larger in diameter than other segments of the nephron, form much of the medullary rays and extend through the medulla toward the tips of the renal pyramids.

Arteries and Veins of the Kidneys

A **renal artery** branches off the abdominal aorta and enters the renal sinus of each kidney (figure 26.6*a*). **Segmental arteries** diverge from the renal artery to form **interlobar arteries,** which ascend within the renal columns toward the renal cortex. Branches from the interlobar arteries diverge near the base of each pyramid and arch over the bases of the pyramids to form the **arcuate** (ar′kū-āt) **arteries. Interlobular arteries** project from the arcuate arteries into the cortex, and afferent arterioles are derived from the interlobular arteries or their branches. The afferent arterioles supply blood to the glomerular capillaries of the renal corpuscles. Efferent arterioles arise from the glomerular capillaries and carry blood away from the glomeruli. After each efferent arteriole exits the glomerulus, it gives rise to a plexus of capillaries called the **peritubular capillaries** around the proximal and distal tubules. Specialized parts of the peritubular capillaries, called **vasa recta** (vā′să rek′tă), course into the medulla along with the loops of Henle (figure 26.6*b*) and then back toward the cortex. The peritubular capillaries drain into **interlobular veins,** which in turn drain into the **arcuate veins.** The arcuate veins empty into the **interlobar veins,** which drain into the **renal vein.** The renal vein exits the kidney and connects to the inferior vena cava.

2. *What structures surround the kidney?*
3. *Name the two layers of the kidney. What are the renal columns and renal pyramids?*
4. *Describe the relationship between the calyces, the renal pelvis, and the ureter.*
5. *What is the functional unit of the kidney? Name its parts.*
6. *Describe the parts of the filtration membrane. What is its function?*
7. *What is the juxtaglomerular apparatus?*
8. *Describe the type of epithelium found in the nephron and the collecting duct.*
9. *Describe the blood supply for the kidney.*



(a) Bowman's capsule encloses the glomerulus.

(b) Blood flows past the juxtaglomerular apparatus into the glomerulus through the afferent arteriole and leaves the glomerulus through the efferent arteriole. The proximal tubule exits Bowman's capsule.

(c) Podocytes of Bowman's capsule surround the capillaries. Filtration slits between the podocytes allow fluid to pass into Bowman's capsule. The glomerulus is composed of capillary endothelium that is fenestrated. Surrounding the endothelial cells is a basement membrane.

(d) Capillary endothelial cells, the basement membrane, and podocytes make up the filtration membrane of the kidney.

Figure 26.4 Renal Corpuscle

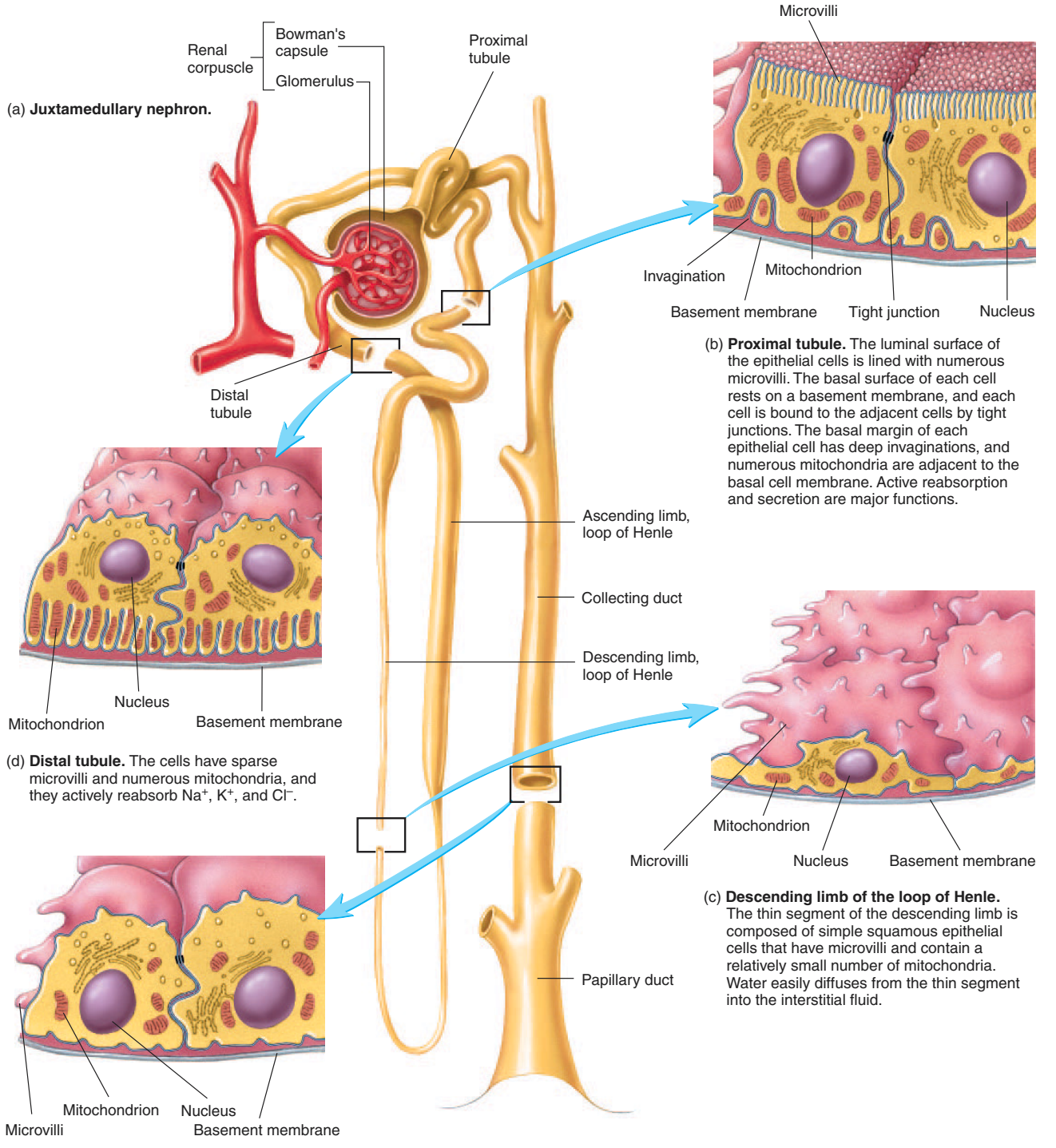


Figure 26.5 Histology of the Nephron

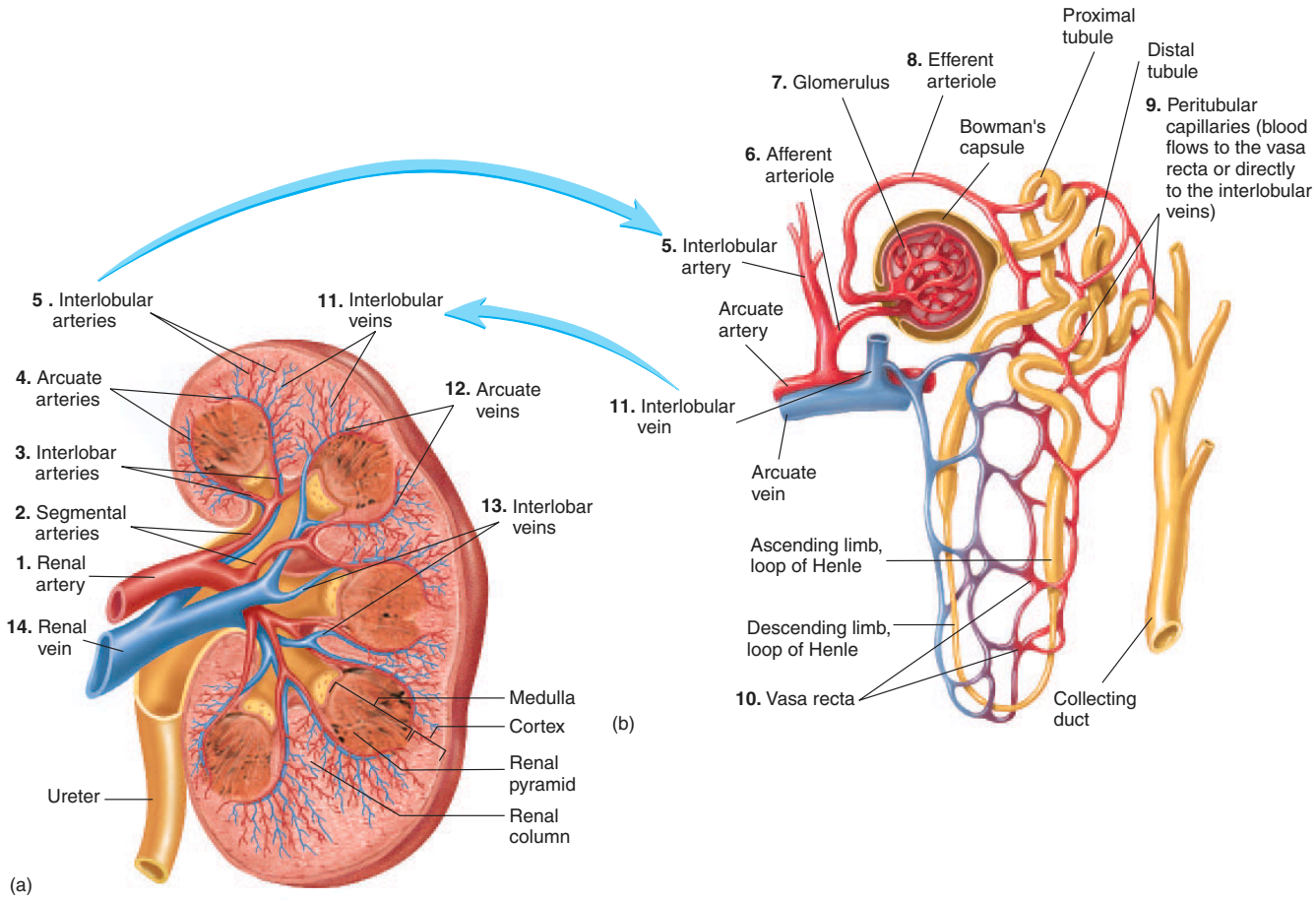


Figure 26.6 Blood Flow Through the Kidney

(*a*) Blood flow through the larger arteries and veins of the kidney. (*b*) Blood flow through the arteries, capillaries, and veins that provide circulation to the nephrons.

Anatomy and Histology of the Ureters and Urinary Bladder

Objective

- ***Describe the anatomy and histology of the ureters and urinary bladder.***

The **ureters** are tubes through which urine flows from the kidneys to the urinary bladder. The ureters extend inferiorly and medially from the renal pelvis at the renal hilum of each kidney to reach the urinary bladder (see figures 26.1 and 26.7), which stores urine. The **urinary bladder** is a hollow muscular container that lies in the pelvic cavity just posterior to the symphysis pubis. The ureters enter on its posterolateral surface. In the male, the urinary bladder is just anterior to the rectum, and in the female, it's just anterior to the vagina and inferior and anterior to the uterus. Its volume increases and decreases depending on how much or how little urine is stored in it at any given time.

The urethra, which transports urine to the outside of the body, exits the urinary bladder inferiorly and anteriorly (figure 26.7*a*). The triangular area of its wall between the two ureters posteriorly and the urethra anteriorly is called the **trigone** (trī′gōn). This region differs histologically from the rest of the urinary bladder wall and expands minimally during filling.

Transitional epithelium lines both the ureters and the urinary bladder. The rest of the walls of these structures consists of a lamina propria, a muscular coat, and a fibrous adventitia (figure 26.7*b* and *c*). The wall of the urinary bladder is much thicker than the wall of a ureter. This thickness is caused by layers, composed primarily of smooth muscle, that are external to the epithelium. The epithelium itself ranges from four or five cells thick when the urinary bladder is empty to two or three cells thick when it is distended. Transitional epithelium is specialized so that the cells slide past one another, and the number of cell layers decreases as the volume of the urinary bladder increases. The epithelium of the urethra is stratified or pseudostratified columnar epithelium.

Where the urethra exits the urinary bladder, elastic connective tissue and smooth muscle keep urine from flowing out of the urinary bladder until pressure in the urinary bladder is great enough to force urine to flow from it. The elastic tissue and smooth muscle forms an **internal urinary sphincter** in males, which contracts to keep semen from entering the urinary bladder during

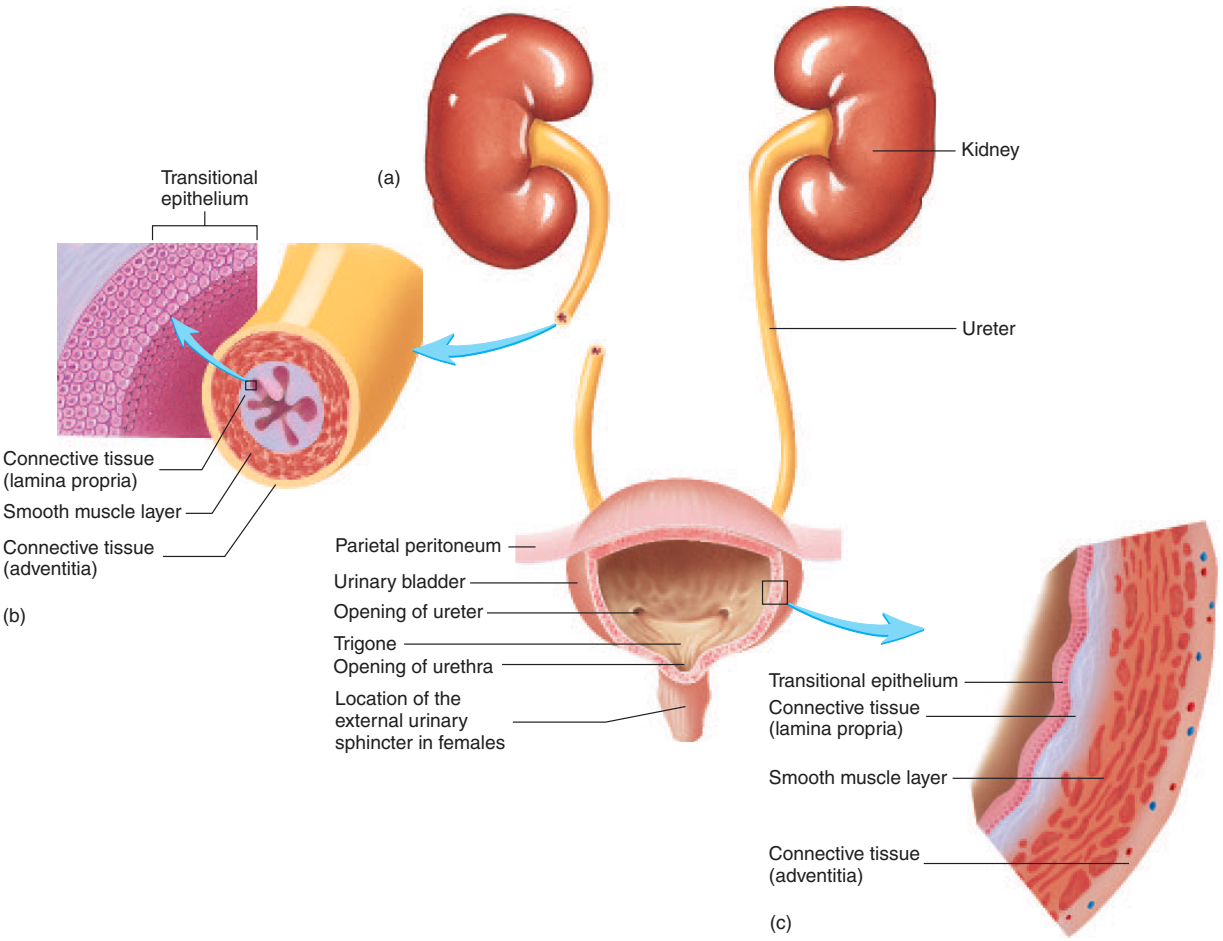


Figure 26.7 Ureters and Urinary Bladder

(*a*) Ureters extend from the pelvis of the kidney to the urinary bladder. (*b*) The walls of the ureters and the urinary bladder are lined with transitional epithelium, which is surrounded by a connective tissue layer (lamina propria), smooth muscle layers, and a fibrous adventitia. (*c*) Section through the wall of the urinary bladder.

sexual intercourse (see chapter 28). The **external urinary sphincter** is skeletal muscle that surrounds the urethra as the urethra extends through the pelvic floor. It acts like a valve that controls the flow of urine through the urethra.

In the male, the urethra extends to the end of the penis, where it opens to the outside (see chapter 28). The urethra is much shorter in females than in males, and it opens into the vestibule anterior to the vaginal opening.

10. *What are the functions of the ureters, urethra, and urinary bladder? Describe their structure, including the epithelial lining of their inner surfaces. What is the trigone?*

P R E D I C T 1

Cystitis (sis-tī′tis) is inflammation of the urinary bladder. It typically results from infections that often occur when bacteria from outside the body enter the bladder. Are males or females more prone to cystitis? Explain.

Urine Production

Objectives

- *List and describe the three major processes involved in the production of urine.*
- *Define the terms renal blood flow rate, renal plasma flow rate, and glomerular filtration rate.*
- *Describe the structure of the filtration barrier and the composition of the filtrate.*
- *List the factors that influence filtration pressure and the rate of filtrate formation.*

Nephrons are called the **functional units of the kidney** because they are the smallest structural components capable of producing urine. Filtration, reabsorption, and secretion are the three major processes critical to the formation of urine (figure 26.8). **Filtration** is movement of fluid across the filtration membrane as a

result of a pressure difference. The fluid entering the nephron is called the **filtrate. Reabsorption** is the movement of substances from the filtrate back into the blood. In general, most of the water and useful solutes are reabsorbed, while waste products, excess solutes, and a small amount of water are not (table 26.1). **Secretion** is the active transport of solutes into the nephron. Urine produced by the nephrons consists of solutes and water filtered and solutes secreted into the nephron minus the solutes and water that are reabsorbed.

Filtration

The part of the total cardiac output that passes through the kidneys is called the **renal fraction.** Table 26.2 presents the calculation of renal blood flow rate and other kidney flow rates. The renal fraction varies from 12%–30% of the cardiac output in healthy resting adults, but it averages 21%. This means the average **renal blood flow rate** is 1176 mL/min. The plasma that flows through the kidneys each minute, called the **renal plasma flow rate,** is equal to the renal blood flow rate multiplied by the portion of the blood that is made up of plasma, which is approximately 55% (1176 mL/min × 0.55 = 646.8 mL plasma/min, or approximately 650 mL plasma/min).

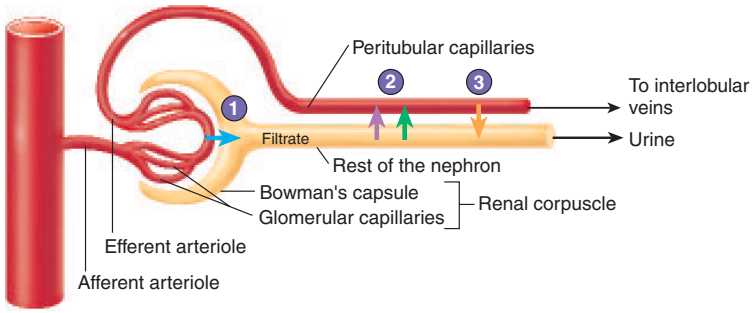
The part of the plasma flowing through the kidney that is filtered through the filtration membranes into the lumen of Bowman's capsules to become filtrate is called the **filtration fraction.** The filtration fraction averages 19% of the plasma flowing through the kidney (650 mL plasma/min × 0.19 = 123.5 mL plasma/min). Thus, approximately 125 mL of filtrate is produced each minute. The amount of filtrate produced each minute is called the **glomerular filtration rate (GFR),** which is equivalent to approximately 180 L of filtrate produced daily. Because only 1–2 L of urine is produced each day by a healthy person, it's obvious that not all of the filtrate becomes urine. Approximately 99% of the filtrate volume is reabsorbed as it passes through the nephron, and less than 1% becomes urine.

P R E D I C T 2

If the filtration fraction increases from 19% to 22% and if 99.2% of the filtrate is reabsorbed, how much urine is produced in a normal person with a cardiac output of 5600 mL/min? (*Hint:* See table 26.2.)

Urine formation results from the following three processes:

1. **Filtration** — Filtration (*blue arrow*) is the movement of materials across the filtration membrane into the lumen of Bowman's capsule to form filtrate.
2. **Reabsorption** — Solutes are reabsorbed (*purple arrow*) across the wall of the nephron by transport processes, such as active transport and cotransport. Water is reabsorbed (*green arrow*) across the wall of the nephron by osmosis.
3. **Secretion** — Solutes are secreted (*orange arrow*) across the wall of the nephron into the filtrate.



Process Figure 26.8 Urine Formation

Table 26.1 Concentrations of Major Solutes

Substance	Plasma	Filtrate	Net Movement of Solute*	Urine	Urine Concentration Plasma Concentration
Water (L)	180	180	178.6	1.4	—
Organic molecules (mg/100mL)					
Protein	3900–5000	6–11	−100.0	0†	0
Glucose	100	100	−100.0	0	0
Urea	26	26	−11.4	1820	70
Uric acid	3	3	−2.7	42	14
Creatinine	1.1	1.1	0.5	196	140
Ions (mEq/L)					
Na^+	142	142	−141.0	128	0.9
K^+	5	5	−4.5	60	12.0
Cl^-	103	103	−101.9	134	1.3
HCO_3^-	28	28	−27.9	14	0.5

*In many cases, solute moves into and out of the nephron. Numbers indicate net movement. Negative numbers are net movement out of the filtrate, and positive numbers are net movement into the filtrate.
†Trace amounts of protein can be found in the urine. A value of zero is assumed here.

Table 26.2 Calculation of Renal Flow Rates

Substance	Amount per Minute (mL)	Calculation
Renal blood flow	1176	Amount of blood flowing through the kidneys per minute; equals cardiac output (5600 mL blood/min) times the percent (21%; renal fraction) of cardiac output that enters the kidneys. 5600 mL blood/min × 0.21 = 1176 mL blood/min
Renal plasma flow	650	Amount of plasma flowing through the kidneys per minute; equals renal blood flow times percent of the blood that is plasma. Because the hematocrit is the percent of the blood that consists of formed elements, the percent of the blood that is plasma is 100 minus the hematocrit. Assuming a hematocrit of 45, the percent of the blood that is plasma is 55% (100 − 45). Renal plasma flow is therefore 55% of renal blood flow. 1176 mL blood/min × 0.55 ≈ 650 mL plasma/min
Glomerular filtration rate (GFR)	125	Amount of plasma (filtrate) that enters Bowman's capsule per minute; equals renal plasma flow times the percent (19%; filtration fraction) of the plasma that enters the renal capsule. 650 mL plasma/min × 0.19 ≈ 125 mL filtrate/min
Urine	1	Nonreabsorbed filtrate that leaves the kidneys per minute; equals glomerular filtration rate times the percent (0.8%) of the filtrate that is not reabsorbed into the blood. 125 mL filtrate/min × 0.008 = 1 mL urine/min Milliliters of urine per minute can be converted to liters of urine per day by multiplying by 1.44. 1 mL urine/min × 1.44 = 1.4 L/day

Filtration Barrier

The filtration membrane is a **filtration barrier,** which prevents the entry of blood cells and proteins into the lumen of Bowman's capsule but allows other blood components to enter. The filtration membrane is many times more permeable than a typical capillary. Water and solutes of a small molecular diameter readily pass from the glomerular capillaries through the filtration membrane into Bowman's capsule, but larger molecules do not. The fenestrae of the glomerular capillary, the basement membrane, and the podocyte cells (see figure 26.4*d*) prevent molecules larger than 7 nm in diameter or with a molecular mass of 40,000 daltons from passing through. Most plasma proteins are slightly larger than 7 nm in diameter and are retained in the glomerular capillaries. Albumin, which has a diameter just slightly less than 7 nm, enters the filtrate in small amounts so that the filtrate contains about 0.03% protein. Protein hormones are also small enough to pass through the filtration barrier. Proteins that do pass through the filtration membrane are actively reabsorbed by endocytosis and metabolized by the cells in the proximal tubule. Consequently, little protein is found in the urine of healthy people.

P R E D I C T 3

Hemoglobin has a smaller diameter than albumin, but very little hemoglobin passes from the blood into the filtrate. Explain why. Under what circumstances would large amounts of hemoglobin enter the filtrate?

Hematuria and Glomerulonephritis

Hematuria (hē-mă-too′rē-ă, hem-ă-too′rē-ă) occurs when red blood cells are found in the urine. The source of red blood cells in the urine can be from outside the kidney or from the kidney. Conditions outside the kidney that result in hematuria include kidney stones or tumors in the renal pelvis, ureter, urinary bladder, prostate, or urethra. Infections of the urinary tract, resulting in inflammation of the urinary bladder (cystitis), of the prostate gland (prostatitis, pros-tă-tī′tis), and of the urethra (urethritis, ū-rē-thrī′tis) can also cause hematuria. Conditions inside the kidney include those that affect the filtration membrane or other areas of the kidney. Inflammation of the glomeruli, called **glomerulonephritis** (glō-mār′ū-lō-nef-rī′tis), can increase the permeability of the filtration membrane and allow blood cells to cross. Other areas of the kidney can be a source of blood in response to inflammation of the nephrons due to infections, tumors in the kidney tissue, and infarcted areas of the kidney, where an artery is blocked, resulting in necrosis of part of the kidney tissue.

Filtration Pressure

The formation of filtrate depends on a pressure gradient, called the **filtration pressure,** which forces fluid from the glomerular capillary across the filtration membrane into the lumen of Bowman's capsule. The filtration pressure results from the sum of the forces that move fluid out of the glomerular capillary into the lumen of Bowman's capsule and those that move fluid out of the lumen of Bowman's capsule into the glomerular capillary (figure 26.9). The **glomerular capillary pressure (GCP),** the blood pressure inside the capillary, moves fluid out of the capillary into Bowman's capsule. The glomerular capillary pressure averages approximately 45 mm Hg, which is much higher than that in most capillaries. Opposing the movement of fluid into the lumen of Bowman's capsule is the **capsule pressure (CP),** which is approximately 10 mm Hg, caused by the pressure of filtrate already inside Bowman's capsule. The **colloid osmotic pressure (COP)** within the glomerular capillary exists because plasma proteins do not pass through the filtration membrane. Instead, they remain within the glomerular capillary and produce an osmotic force of about 28 mm Hg that favors fluid movement to the glomerular capillary from Bowman's capsule. The filtration pressure is therefore approximately 7 mm Hg.

Filtration capillary pressure (7 mm Hg)	=	Glomerular pressure (45 mm Hg)	−	Capsule pressure (10 mm Hg)	−	Colloid osmotic pressure (28 mm Hg)

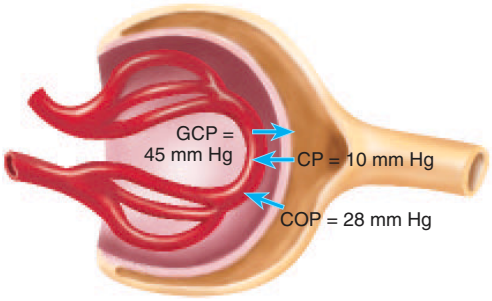
The high glomerular capillary pressure results from a low resistance to blood flow in the afferent arterioles and glomerular capillaries and from a higher resistance to blood flow in the efferent arterioles. As the diameter of a vessel decreases, resistance to flow through the vessel increases (see chapter 21), and pressure upstream from the point of decreased vessel diameter is higher than the pressure downstream from the point of decreased diameter. For example, in the extreme case of a completely closed vessel, pressure is higher upstream from the constriction and it falls to zero downstream from the constriction. The efferent arterioles have a small diameter, and the blood pressure is higher within the glomerular capillaries because of the low resistance to blood flow in the afferent arterioles and glomerular capillaries and because of the higher resistance to blood flow in the efferent arterioles. Also, the pressure is lower in the peritubular capillaries which are downstream from the efferent arterioles. Consequently, filtrate is forced across the filtration membrane into the lumen of Bowman's capsule. The low pressure in the peritubular capillaries allows fluid to move into them from the interstitial fluid.

The smooth muscle cells in the walls of the afferent and efferent arterioles can alter the vessel diameter and the glomerular filtration pressure. For example, dilation of the afferent arterioles or constriction of the efferent arterioles increases glomerular capillary pressure, increasing filtration pressure and glomerular filtration.

11. *Name the three general processes involved in the production of urine.*
12. *Define the terms renal blood flow, renal plasma flow, and glomerular filtration rate. How do they affect urine production?*
13. *Describe the filtration barrier. What substances do not pass through it?*
14. *What is filtration pressure? How does glomerular capillary pressure affect filtration pressure and the amount of urine produced?*
15. *How do systemic blood pressure and afferent arteriole diameter affect glomerular capillary pressure?*

P R E D I C T 4

Karl was pouring gasoline from a small can into his lawnmower when it ignited. He experienced third-degree burns on his chest, neck, arms, and hands. In the hospital emergency room, his blood pressure was found to be in the low normal range, his heart rate was very high, and his pulse was weak. His skin appeared very pale. There was a delay of a couple of hours from the time of the accident until an I.V. was started. For several hours after the accident he produced almost no urine. Explain that response.



Filtration pressure = GCP – COP – CP

45 mm Hg GCP (glomerular capillary pressure)
–28 mm Hg COP (colloid osmotic pressure)
–10 mm Hg CP (capsule pressure)

7 mm Hg filtration pressure

Figure 26.9 Filtration Pressure

Filtration pressure across the filtration membrane is equal to the glomerular capillary pressure (GCP) minus the colloid osmotic pressure (COP) in the glomerular capillary minus the pressure in Bowman's capsule (CP).

Tubular Reabsorption

Objectives

- *Explain how tubular reabsorption in the proximal tubule is accomplished and how it influences filtrate composition.*
- *Describe the permeability characteristics of the descending limb of the loop of Henle, and discuss how the movement of substances across its wall influences the composition of the filtrate.*
- *Describe the permeability and transport characteristics of the ascending limb of the loop of Henle, and explain how they influence filtrate composition.*
- *Describe permeability and transport characteristics of the distal tubule and collecting duct, and explain how they influence filtrate composition.*
- *Describe tubular secretion, and give examples of substances secreted into the lumen of the nephron.*

The filtrate leaves the lumen of Bowman's capsule and flows through the proximal tubule, the loop of Henle, and the distal tubule and then into the collecting ducts. As it passes through these structures, many of the substances in the filtrate undergo **tubular reabsorption.** Tubular reabsorption results from processes, such as diffusion, facilitated diffusion, active transport, cotransport, and osmosis. Inorganic salts, organic molecules, and about 99% of the filtrate volume leave the nephron and enter the interstitial fluid. These substances then enter the low-pressure peritubular capillaries and flow through the renal veins to enter the general circulation (see figure 26.8).

Solutes reabsorbed from the lumen of the nephron to the interstitial fluid include amino acids, glucose, and fructose, as well as Na^+, K^+, Ca^{2+}, HCO_3^-, and Cl^-. A more complete list is provided in table 26.3 for each part of the nephron.

Water follows the solutes that are reabsorbed across the wall of the nephron. As the solutes in the nephron are reabsorbed, water follows the solutes by the process of osmosis. The transport processes and the permeability characteristics of each portion of the nephron are responsible for reabsorption of the filtrate. The small volume of the filtrate (approximately 1% of the filtrate volume) that forms urine contains a relatively high concentration of urea, uric acid, creatinine, K^+, and other substances that are toxic in high concentrations. Regulation of solute reabsorption and the permeability characteristics of portions of the nephron allow for the production of a small volume of very concentrated urine or a large volume of very dilute urine. The mechanisms in the wall of the nephron responsible for reabsorption are described in the following section. Mechanisms that regulate urine concentration are described in a later section of this chapter ("Urine Concentration Mechanism," p. 963).

Reabsorption in the Proximal Tubule

Most reabsorbed substances must pass through the cells that make up the wall of the nephrons. These cells have an **apical surface,** which makes up the inside surface of the nephron, a **basal surface,** which forms the outer wall of the nephron, and **lateral surfaces,** which are bound to the lateral surfaces of other cells of the nephron. Reabsorption of most solute molecules from the proximal tubule is linked to the primary active transport of Na^+ across the **basal membrane** of the nephron epithelial cells from the cytoplasm into the interstitial fluid, thereby creating a low concentration of Na^+ inside the cells (figure 26.10). At the basal cell membrane, ATP provides the energy required to move Na^+ out of the cell in exchange for K^+ by countertransport. Because the concentration of Na^+ in the lumen of the tubule is high, a large concentration gradient is present from the lumen of the nephron to the intracellular fluid of the cells lining the nephron. This concentration gradient for Na^+ is the source of energy for the cotransport of many solute molecules from the lumen of the nephron into the nephron cells.

Table 26.3 Reabsorption of Major Solutes from the Nephron

Apical Membrane	Basal Membrane
Proximal Nephron	
Substances cotransported with Na^+	Active transport
	Na^+ (exchanged for K^+)
K^+	Facilitated diffusion
Cl^-	K^+
Ca^{2+}	Cl^-
Mg^{2+}	Ca^{2+}
HCO_3^-	HCO_3^-
PO_4^{3-}	PO_4^{3-}
Amino acids	Amino acids
Glucose	Glucose
Fructose	Fructose
Galactose	Galactose
Lactate	Lactate
Succinate	Succinate
Citrate	Citrate
Diffusion between nephron cells	
K^+	
Ca^{2+}	
Mg^{2+}	
Thick Ascending Limb of the Loop of Henle	
Substances cotransported with Na^+	Active transport
	Na^+ (exchanged for K^+)
K^+	Facilitated diffusion
Cl^-	K^+
	Cl^-
Diffusion between nephron cells	
K^+	
Ca^{2+}	
Mg^{2+}	
Distal Nephron and Collecting Duct	
Substances cotransported with Na^+	Active transport
	Na^+ (exchanged for K^+)
Cl^-	Facilitated diffusion
K^+	K^+
	Cl^-

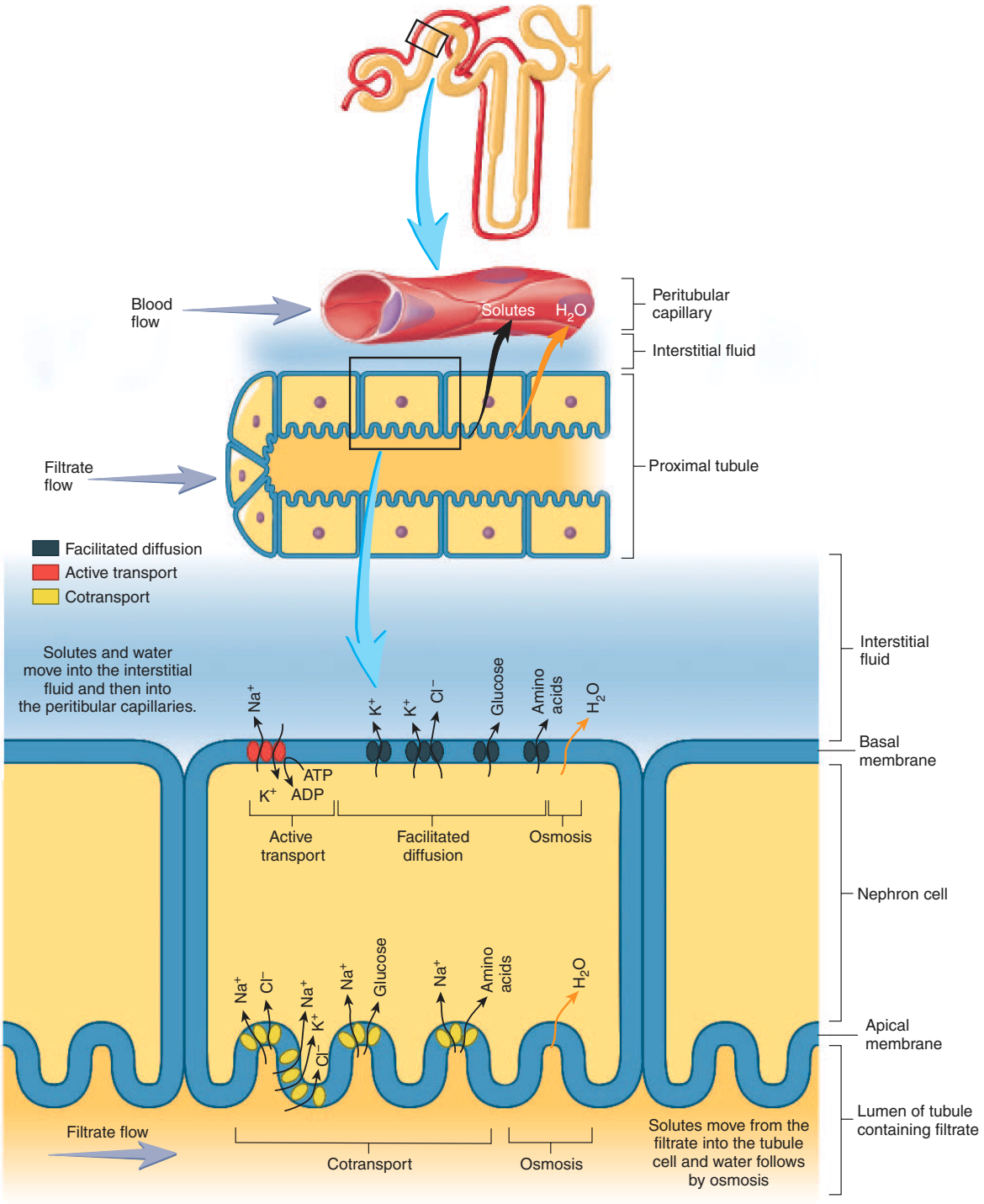


Figure 26.10 Reabsorption of Solutes in the Proximal Nephron

Cotransport of molecules and ions across the epithelial lining of the nephron depends on the active transport of sodium ions, in exchange for potassium ions, across the basal membrane. Cotransport is the process by which carrier proteins move molecules or ions with Na^+ across the apical membrane. The Na^+ concentration gradient provides the energy for cotransport. Amino acids, glucose, K^+, Cl^-, and most other solutes are transported into the cells of the nephron with Na^+. Water enters and leaves the cell by osmosis. Glucose, amino acids, Na^+, Cl^-, and many other solutes leave the cells across the apical membrane by facilitated diffusion.

Carrier molecules that transport amino acids, glucose, and other solutes are located within the apical membrane, which separates the lumen of the nephron from the cytoplasm of epithelial cells. Each of these carrier molecules binds specifically to one of the substances to be transported and to Na^+. The concentration gradient for Na^+ provides the source of energy that moves both the Na^+ and the other molecules or ions bound to the carrier molecule from the lumen into the cell of the nephron. Once the cotransported molecules are inside the cell, they cross the basal membrane of the cell by facilitated diffusion.

Some solutes also diffuse between the cells from the lumen of the nephron into the interstitial fluid. The concentration of these solutes increases as other solutes are cotransported and water moves by osmosis from the lumen into interstitial fluid. As the concentration gradient for these solutes increases above the concentration in the interstitial fluid, they diffuse between the epithelial cells. Some K^+, Ca^{2+}, and Mg^{2+} diffuse between the cells of the proximal tubule wall from the lumen of the tubule to the interstitial fluid. Reabsorption of these solutes by diffusion occurs even though these same ions are also reabsorbed by cotransport processes.

Reabsorption of solutes in the proximal tubule is extensive, and the tubule is permeable to water. As solute molecules are transported from the nephron to the interstitial fluid, water moves by osmosis in the same direction. By the time the filtrate has reached the end of the proximal tubule, its volume has been reduced by approximately 65%. The concentration of the filtrate in the proximal tubule remains about the same as that of the interstitial fluid (300 mOsm/kg) because the wall of the nephron is permeable to water.

Reabsorption in the Loop of Henle

The loop of Henle descends into the medulla of the kidney, where the concentration of solutes in the interstitial fluid is very high. The thin segment of the loop of Henle (figure 26.11) is highly permeable to water and moderately permeable to urea, sodium, and most other ions. It's adapted to allow passive movement of solutes through its wall, although water passes through much more rapidly than solutes. As the filtrate passes through the thin segment of the loop of Henle, water moves out of the nephron by osmosis. Some solutes move into the nephron. By the time the filtrate has reached the end of the thin segment of the loop of Henle, the volume of the filtrate has been reduced by another 15%, and the concentration of the filtrate is equal to the high concentration of the interstitial fluid (1200 mOsm/L).

Both the thin and thick portions of the ascending limb of the loop of Henle are impermeable to water. Therefore, no additional water diffuses from the nephron as it passes through this limb. The ascending limb of the loop of Henle is surrounded by interstitial fluid that becomes less concentrated toward the cortex. As the filtrate flows through the thin segment of the limb, solutes diffuse into the interstitial fluid, making the filtrate less concentrated. Water cannot follow the solutes because the thin segment is not permeable to water. The thick segment is not permeable to either water or solutes. Solutes such as Na^+, K^+, and Cl^-, however, are transported from the thick segment of the ascending limb of the loop of Henle into the interstitial fluid. Cotransport is responsible for the movement of K^+ and Cl^- with Na^+ across the apical membrane of the ascending limb of the loop of Henle (figure 26.12).

Once inside the cells of the ascending limb, Cl^- and K^+ cross the basal cell membrane into the interstitial fluid from a higher concentration inside the cells to a lower concentration outside the cells by facilitated diffusion. The concentration gradient for Na^+ is created by the active transport of the Na^+ out of the cell in exchange for K^+ across the basal membrane (see figure 26.12).

Because the ascending limb of the loop of Henle is impermeable to water and because ions are transported out of the ascending limb, the concentration of solutes in the nephron is reduced to about 100 mOsm/kg by the time the fluid reaches the distal tubule. In contrast, the concentration of the interstitial fluid in the cortex is about 300 mOsm/kg. Thus the filtrate entering the distal tubule is much more dilute than the interstitial fluid surrounding it.

Osmoles, Osmolality, and Osmosis

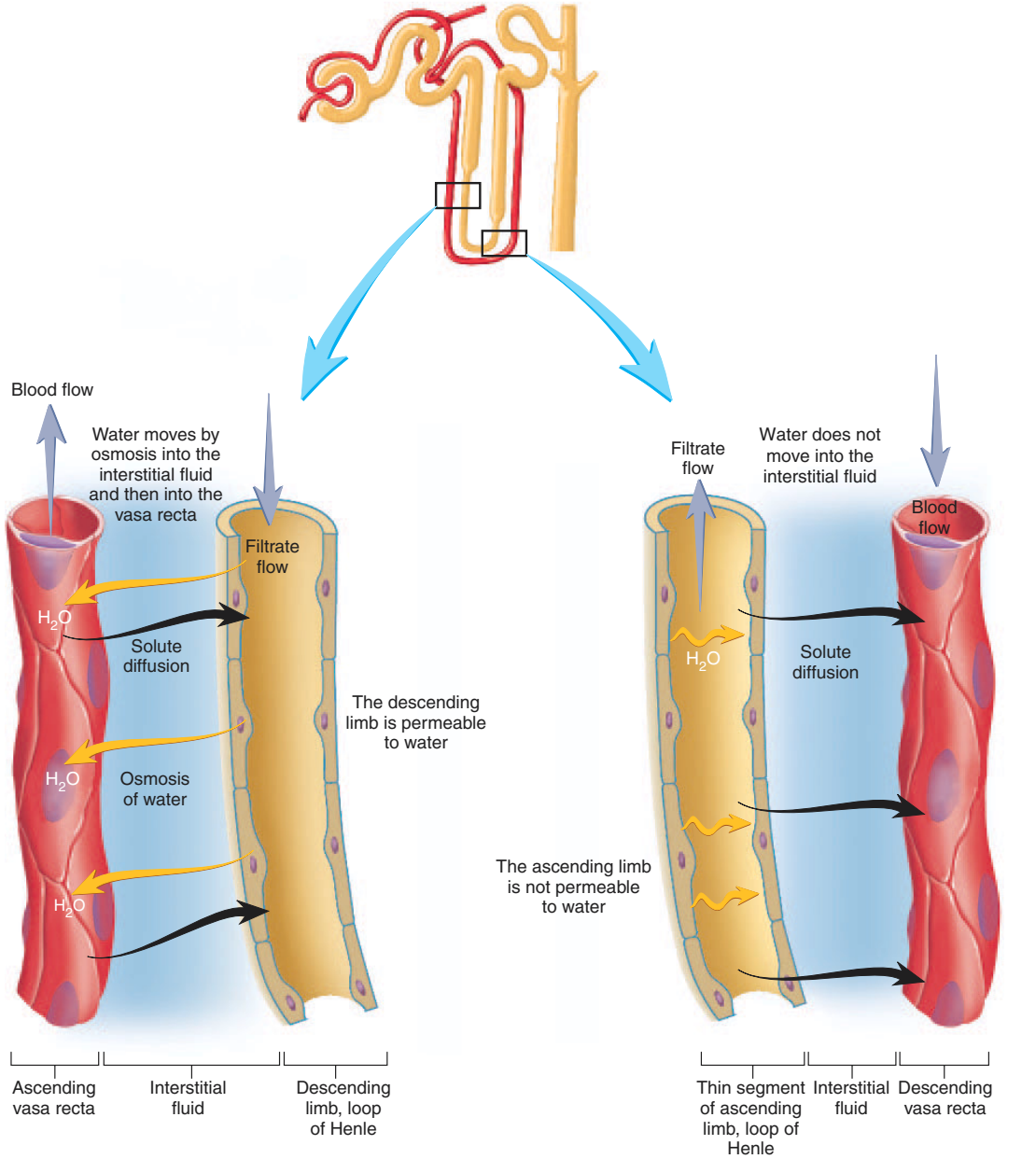
An **osmole** is a measure of the number of particles in a solution. One osmole is the molecular mass, in grams, of a solute times the number of ions or particles into which it dissociates in solution. A milliosmole (mOsm) is 1/1000 of an osmole. The osmolality of a solution is the number of osmoles in a kilogram of solution. Water moves by osmosis from a solution with a lower osmolality to a solution with a higher osmolality. Thus water moves by osmosis from a solution of 100 mOsm/kg toward a solution of 300 mOsm/kg (see appendix C).

Reabsorption in the Distal Tubule and Collecting Duct

Cl^- is transported across the apical membrane of the distal tubules and collecting ducts with Na^+. The concentration gradient for Na^+ is a result of the active transport of Na^+ across the basal cell membrane. In addition, the collecting ducts extend from the cortex of the kidney, where the concentration of the interstitial fluid is approximately 300 mOsm/kg, through the medulla of the kidney, where the concentration of the interstitial fluid is very high. Water moves by osmosis into the more concentrated interstitial fluid when the distal tubule and collecting duct are permeable to water. Consequently, a small volume of very concentrated urine is produced. Water does not move by osmosis into the interstitial fluid when the distal tubule and collecting duct are not permeable to water. Consequently, a large volume of dilute urine is produced. The production of dilute or concentrated urine is under hormonal control, which is described in the upcoming section "Urine Concentration Mechanism," p. 963.

Changes in the Concentration of Solutes in the Nephron

Urea enters the glomerular filtrate and is in the same concentration there as in the plasma. As the volume of filtrate decreases in the nephron, the concentration of urea increases because renal tubules

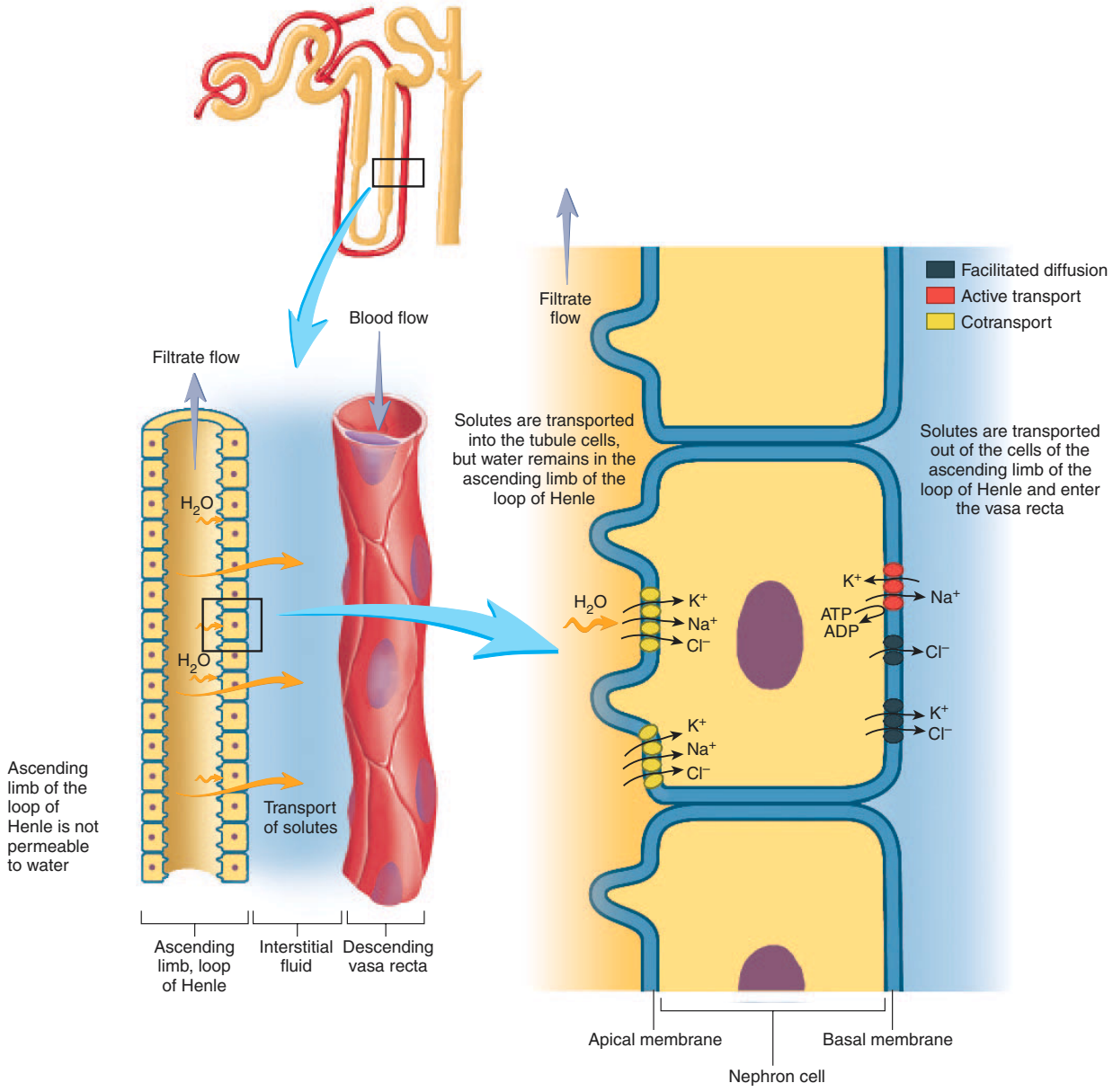


(a) The wall of the descending limb of the loop of Henle is permeable to water and, to a lesser extent, to solutes. The interstitial fluid in the medulla of the kidney and blood in the vasa recta have a high solute concentration (high osmolality). Water therefore moves by osmosis from the tubule into the interstitial fluid and into the vasa recta. To a lesser extent, solutes diffuse from the vasa recta and interstitial fluid into the tubule.

(b) The thin segment of the ascending limb of the loop of Henle is not permeable to water, but is permeable to solutes. The solutes diffuse out of the tubule and into the more dilute interstitial fluid as the ascending limb projects toward the cortex. The solutes diffuse into the descending vasa recta.

Figure 26.11 Reabsorption in the Thin Segment of the Descending and Ascending Limb of the Loop of Henle

are not as permeable to urea as they are to water. Only 40%–60% of the urea is passively reabsorbed in the nephron, although about 99% of the water is reabsorbed. In addition to urea, urate ions, creatinine, sulfates, phosphates, and nitrates are reabsorbed but not to the same extent as water. They therefore become more concentrated in the filtrate as the volume of the filtrate becomes smaller. These substances are toxic if they accumulate in the body, so their accumulation in the filtrate and elimination in urine help maintain homeostasis.



The wall of the ascending limb of the loop of Henle is not permeable to water. Na^+ move across the wall of the basal membrane by active transport, establishing a concentration gradient for Na^+. K^+ and Cl^- are cotransported with Na^+ across the apical membrane and ions pass by facilitated diffusion across the basal cell membrane of the tubule cells.

Figure 26.12 Reabsorption in the Thick Segment of the Ascending Limb of the Loop of Henle

Conjugation and Excretion

Some drugs, environmental pollutants, and other foreign substances that gain access to the circulatory system are reabsorbed from the nephron. These substances are usually lipid-soluble, nonpolar compounds. They enter the glomerular filtrate and are reabsorbed passively by a process similar to that by which urea is reabsorbed. Because these substances are passively reabsorbed within the nephron, they are not rapidly excreted. The liver cells attach other molecules to them by a process called **conjugation** (kon-jŭ-gā′shŭn), which converts them to more water-soluble molecules. These more water-soluble substances enter the filtrate but do not pass as readily through the wall of the nephron, are not reabsorbed from the renal tubules, and consequently are more rapidly excreted in the urine. One of the important functions of the liver is to convert nonpolar toxic substances to more water-soluble forms, thus increasing the rate at which they are excreted in the urine.

Tubular Secretion

Tubular secretion involves the movement of some substances, such as by-products of metabolism that become toxic in high concentrations and drugs or molecules not normally produced by the body, into the nephron (table 26.4). As with tubular reabsorption, tubular secretion can be either active or passive. Ammonia is synthesized in the epithelial cells of the nephron and diffuses into the lumen of the nephron. H^+, K^+, penicillin, and ***para*-aminohippuric acid** (par′ă-a-mē′nō-hi-pūr′ik; *p*-aminohippuric acid; **PAH**), among others, are actively secreted by either active transport or countertransport processes into the nephron.

For example, a countertransport process moves H^+ from cells of the nephron into the nephron's lumen. H^+ bind to carrier molecules on the inside of the plasma membrane, and Na^+ bind to the carrier molecules on the outside of the plasma membrane. As Na^+ move into the cell, H^+ move out of the cell (figure 26.13). The secreted H^+ are produced as a result of carbon dioxide and water reacting to form H^+ and HCO_3^-. The countertransport molecules secrete H^+ into the nephron's lumen, and Na^+ enter the nephron cell. Na^+ and HCO_3^- are cotransported across the basal membrane of the cell and enter the peritubular capillaries. H^+ are secreted into the proximal and distal tubules, and K^+ are actively secreted in the distal tubule (see chapter 27). Penicillin and *p*-aminohippuric acid are examples of substances not normally produced by the body that are actively secreted into the proximal tubules.

16. *What happens to most of the filtrate that enters the nephron?*
17. *On what side of the nephron tubule cell does active transport take place during reabsorption and secretion of materials?*
18. *Describe how cotransport works in the nephron.*
19. *Name the substances that are moved by active and passive transport. In what part of the nephron does this movement take place?*
20. *Where does tubular secretion take place? What substances are secreted? Are these substances secreted by active or passive transport?*

Urine Concentration Mechanism

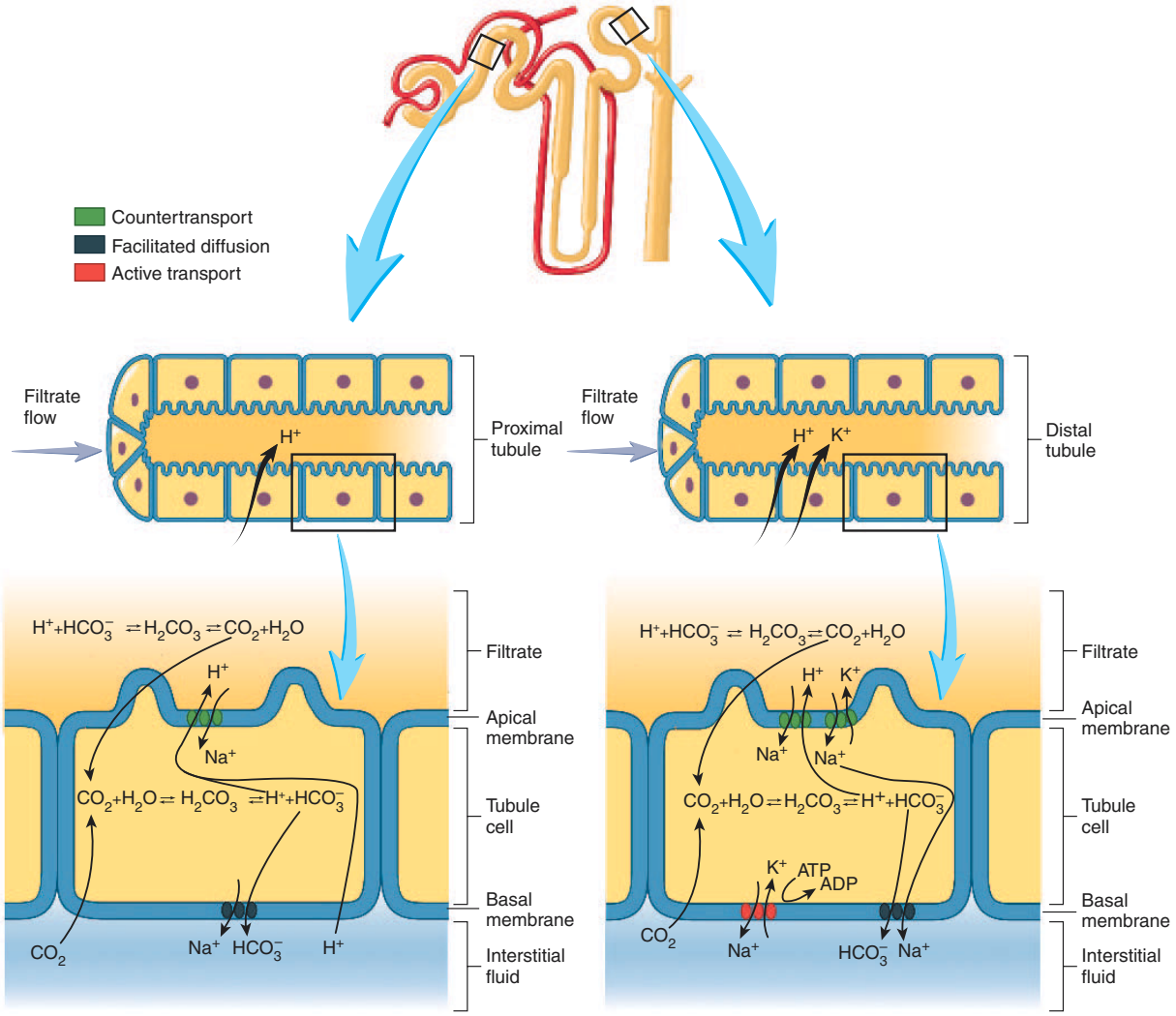
Objectives

- *Describe the role of the distal tubule and collecting ducts in producing concentrated urine.*
- *Describe how the loops of Henle, the vasa recta, and urea maintain the medullary concentration gradient.*

When a large volume of water is consumed, it's necessary to eliminate the excess without losing large amounts of electrolytes or other substances essential for the maintenance of homeostasis. The response of the kidneys is to produce a large volume of dilute urine. On the other hand, when drinking water is not available, producing a large volume of dilute urine would lead to rapid dehydration. When water intake is restricted, the kidneys produce a small volume of concentrated urine that contains sufficient waste products to prevent their accumulation in the circulatory system. The kidneys are able to produce urine with concentrations that vary between 65 and 1200 mOsm/kg while maintaining an extracellular fluid osmolality very close to 300 mOsm/kg. The maintenance of a high concentration of solutes in the medulla, the countercurrent functions of the loops of Henle, and the mechanism that controls the permeability of the distal nephron to water are essential for the kidneys to control the volume and concentration of the urine they produce.

Table 26.4 Secretion of Substances into the Nephron

Transport Process	Substance Transported
Proximal Convoluted Tubule	
Active transport	H^+
	Hydroxybenzoates
	para-aminohippuric acid
	Neurotransmitters Dopamine Acetylcholine Epinephrine
	Bile pigments
	Uric acid
	Drugs and toxins Penicillin Atropine Morphine Saccharin
Passive transport	Ammonia
Distal Convoluted Tubule	
Active transport	K^+
Passive transport	K^+ H^+



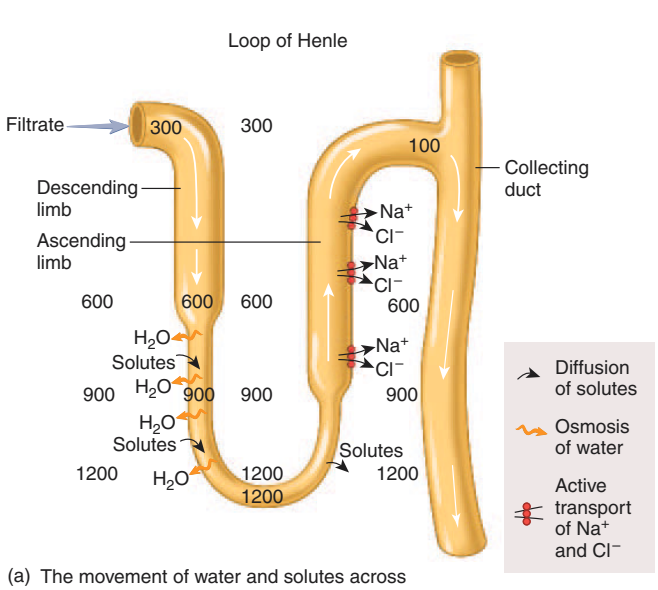
(a) H^+ are secreted into the filtrate by a countertransport mechanism in the proximal tubule, in which H^+ are exchanged for Na^+. The H^+ are derived from two sources. They diffuse from the peritubular capillaries into the interstitial fluid and then into the tubule, or they are derived from the reaction between carbon dioxide and water in the cell. Na^+ and HCO_3^- are cotransported across the basal membrane into the interstitial fluid and then diffuse into the peritubular capillaries.

(b) H^+ and K^+ are secreted into the filtrate by countertransport mechanisms in the distal tubule. Na^+ and K^+ are moved by active transport across the basal membrane of the tubule cell. Na^+ and HCO_3^- are cotransported across the basal membrane into the interstitial fluid and then diffuse into the peritubular capillaries.

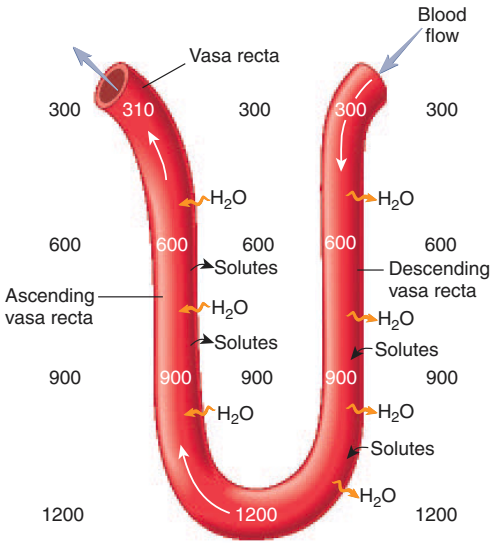
Figure 26.13 Secretion of Hydrogen and Potassium Ions into the Nephron

Medullary Concentration Gradient

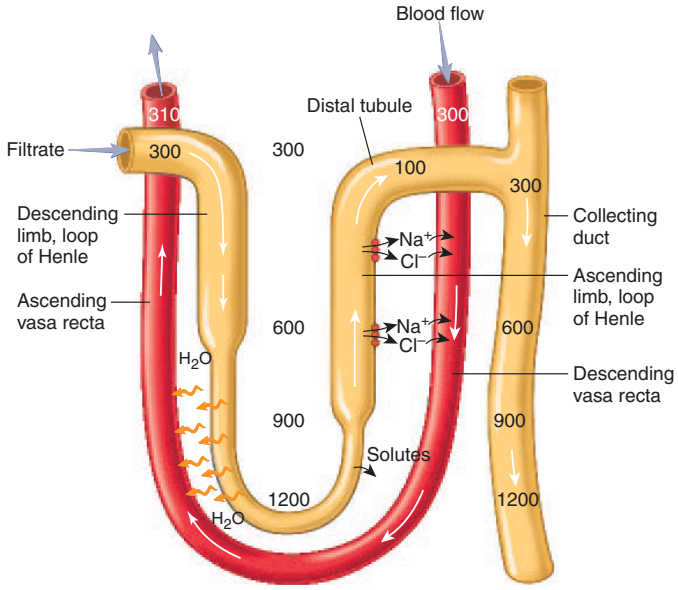
The ability of the kidney to concentrate urine depends on maintaining a high concentration of solutes in the medulla. The interstitial fluid concentration is about 300 mOsm/kg in the cortical region of the kidney. Solutes become progressively more concentrated in the medulla until they reach 1200 mOsm/kg near the tips of the renal pyramids (figure 26.14). Maintenance of the high solute concentration in the kidney medulla depends on the functions of the loops of Henle, the vasa recta, and on the distribution of urea. The major mechanisms that create and maintain the high solute concentration in the renal medulla are:



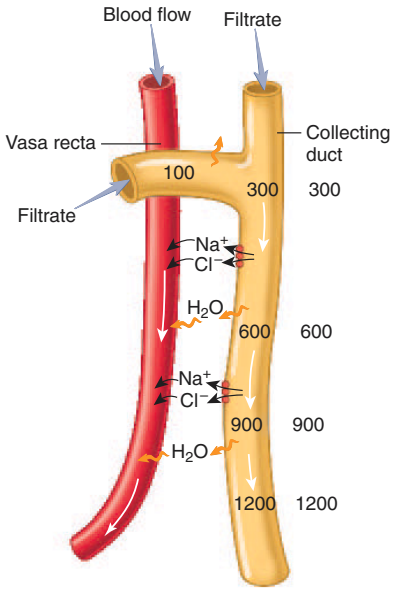
(a) The movement of water and solutes across the wall of the loop of Henle.



(b) The movement of water and solutes across the wall of the vasa recta.



(c) The loop of Henle and the vasa recta function together. Water moves out of the descending limb of the loop of Henle and enters the vasa recta. Solutes diffuse out of the ascending thin segment of the loop of Henle and enter the vasa recta, but water does not. Solutes transported out of the thick segment of the ascending limb of the loop of Henle enter the vasa recta. Excess water and solutes are carried away from the medulla without reducing the high concentration of solutes. The concentration of the filtrate is reduced to 100 mOsm/kg by the time it reaches the distal tubule.



(d) Water and solutes move out of the collecting duct into the vasa recta.

Figure 26.14 Filtrate Concentration and the Medullary Concentration Gradient

The loop of Henle and the vasa recta function together to maintain a high concentration of solutes in the medulla of the kidney. See the text for a description of water and solute movements for each part of this figure.

Clinical Focus Kidney Dialysis

The artificial kidney (renal dialysis machine) is a machine used to treat patients suffering from renal failure. The use of this machine often allows people with severe acute renal failure to recover without developing the side effects of renal failure, and the machine can substitute for the kidneys for long periods in people suffering from chronic renal failure.

Renal dialysis allows blood to flow though tubes made of a selectively permeable membrane. On the outside of the dialysis tubes is a fluid that contains the same concentration of solutes as the plasma, except for the metabolic waste products. As a consequence, a diffusion gradient exists for the metabolic waste products from the blood to the dialysis fluid. The dialysis membrane has pores that are too small to allow plasma proteins to pass through them. For smaller solutes the dialysis fluid contains the same beneficial solutes as the plasma, so the net movement of these substances is zero. In contrast, the dialysis fluid contains no metabolic waste products, so metabolic waste products diffuse rapidly from the blood into the dialysis fluid.

Blood usually is taken from an artery, passed through tubes of the dialysis machine, and then returned to a vein. The rate of blood flow is normally several hundred milliliters per minute, and the total surface area of exchange in the machine is close to 10,000–20,000 cm^2 (figure A).

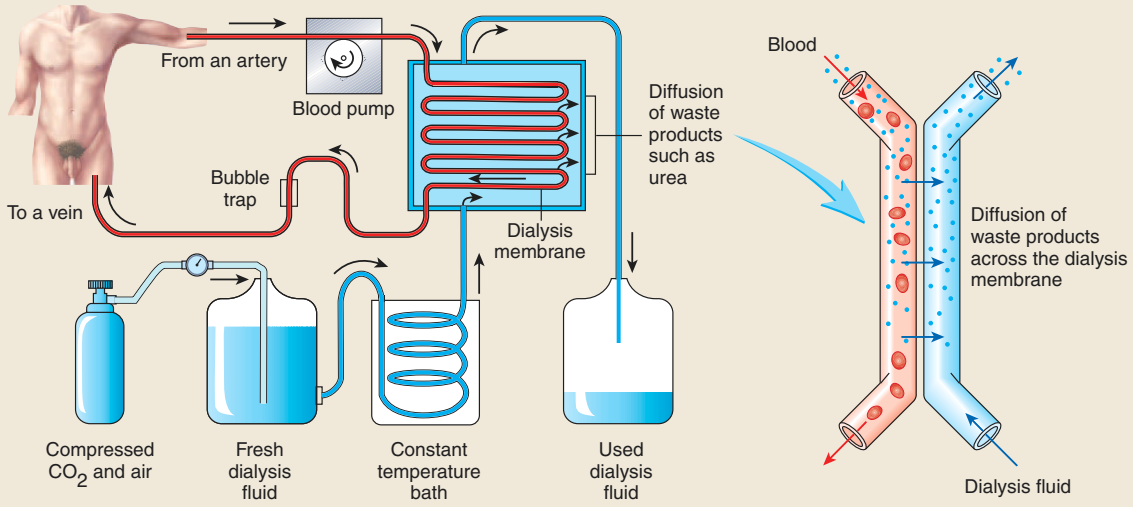


Figure A Kidney Dialysis

During kidney dialysis blood flows through a system of tubes composed of a selectively permeable membrane. Dialysis fluid, the composition of which is similar to that of blood, except that the concentration of waste products is very low, flows in the opposite direction on the outside of the dialysis tubes. Consequently, waste products such as urea diffuse from the blood into the dialysis fluid. Other substances such as sodium, potassium, and glucose do not rapidly diffuse from the blood into the dialysis fluid because there is no concentration gradient for these substances between the blood and the dialysis fluid.

1. The active transport of Na^+ and the cotransport of ions such as K^+ and Cl^- and other ions out of the thick portion of the ascending limb of the loop of Henle into the interstitial fluid of the medulla.
2. Diffusion of smaller amounts of water than solutes from the loops of Henle into the interstitial fluid.
3. The vasa recta supply blood to the medulla of the kidney and remove water and solutes that enter the medulla without destroying the high concentration of solutes in the interstitial fluid of the medulla.
4. Active transport of ions from the collecting ducts into the interstitial fluid of the medulla.
5. The passive diffusion of urea from the collecting ducts into the interstitial fluid of the medulla.

The roles of each of these mechanisms in the maintenance of the high concentration of solutes in the medulla of the kidney are described in the following sections:

1. *Loops of Henle.* The walls of the descending limbs of the loops of Henle are permeable to water. As filtrate flows into the medulla of the kidney through the descending limbs, water diffuses out of the nephrons into the more concentrated interstitial fluid. The walls of the ascending limbs of the loops of Henle are impermeable to water. Solutes diffuse out of the thin segment of the ascending limb as it passes through progressively less concentrated interstitial fluid on its way back to the cortex of the kidney. Na^+, K^+, and Cl^- are actively transported out of the thick

segment of the ascending limb into the interstitial fluid. Thus, water enters the interstitial fluid from the descending limbs and solutes enter the interstitial fluid from the ascending limbs of the loops of Henle (figure 26.14*a*).

2. *The vasa recta.* The vasa recta are countercurrent systems that remove excess water and solutes from the medulla of the kidney without changing the high concentration of solutes in the medullary interstitial fluid. The vasa recta also supply blood to the medulla of the kidney. **Countercurrent** (kown′ter-ker′ent) **systems** consist of parallel tubes in which fluid flows, but in opposite directions, and heat or substances such as water or solutes diffuse from tubes carrying fluid in one direction to tubes carrying fluid in the opposite direction so that the fluid in both sets of tubes has nearly the same composition. The vasa recta are a countercurrent system because blood flows through them to the kidney medulla and, after the vessels turn near the tip of the renal pyramid, the blood is carried in the opposite direction. The walls of the vasa recta are permeable to water and to solutes. As blood flows toward the medulla, water moves out of the vasa recta, and some solutes diffuse into them. As blood flows back toward the cortex, water moves into the vasa recta, and some solutes diffuse out of them (figure 26.14*b*). The rates of diffusion are such that slightly more water and slightly more solute are carried from the medulla by the vasa recta than enter it. Thus, the composition of the blood at both ends of the vasa recta is nearly the same, with the volume and osmolality being slightly greater as the blood once again reaches the cortex.

   The loops of Henle and the vasa recta are in parallel with one another, and their functions are closely related. The water and solutes that leave the loops of Henle enter the vasa recta. The vasa recta carry away the water and solutes without diminishing the high concentration of solutes in the medulla of the kidney (figure 26.14*c*). Water passes by osmosis from the collecting ducts and solutes, such as Na^+ and Cl^- are actively transported out of the collecting ducts and pass into the interstitial fluid of the medulla of the kidney (figure 26.14*d*). The water and solutes that leave the collecting ducts also enter the vasa recta and are carried away from the medulla.

   The loops of Henle and vasa recta function together to maintain a high concentration of solutes in the interstitial fluids of the medulla and to carry away the water and solutes that enter the medulla from the loops of Henle and collecting ducts.

3. *Urea.* **Urea** (ū-rē′ă) molecules are responsible for a substantial part of the high osmolality in the medulla of the kidney (figure 26.15). The walls of the descending limbs of the loops of Henle are permeable to urea, and urea diffuses into the descending limbs from the interstitial fluid. The ascending limbs of the loops of Henle and the distal tubules are impermeable to urea. The collecting ducts are permeable to urea, however, and some urea diffuses out of the collecting ducts into the interstitial fluid of the medulla. Thus, urea flows in a cycle from the interstitial fluid into the descending limbs of the loops of Henle, through the ascending limbs, through the distal tubules, and into the collecting ducts. Urea then diffuses from the collecting ducts back into the interstitial fluid of the medulla. Consequently, a high urea concentration is maintained in the medulla of the kidney.

Summary of Changes in Filtrate Volume and Concentration

In the average person, about 180 L of filtrate enter the proximal tubules daily. Glucose, amino acids, Na^+, Ca^{2+}, K^+, Cl^-, and other substances (see table 26.3) are actively transported, and water moves by osmosis from the lumens of the proximal tubules into the interstitial fluid. The excess solutes and water then enter the peritubular capillaries. Consequently, approximately 65% of the filtrate is reabsorbed as water, and solutes move from the proximal tubules into the interstitial fluid. The osmolality of both the interstitial fluid and the filtrate is maintained at about 300 mOsm/L.

The filtrate then passes into the descending limbs of the loops of Henle, which are highly permeable to water and solutes. As the descending limbs penetrate deep into the medulla of the kidney, the surrounding interstitial fluid has a progressively greater osmolality. Water diffuses out of the nephrons as solutes slowly diffuse into them. By the time the filtrate reaches the deepest part of the loops of Henle, its volume has been reduced by an additional 15% of the original volume

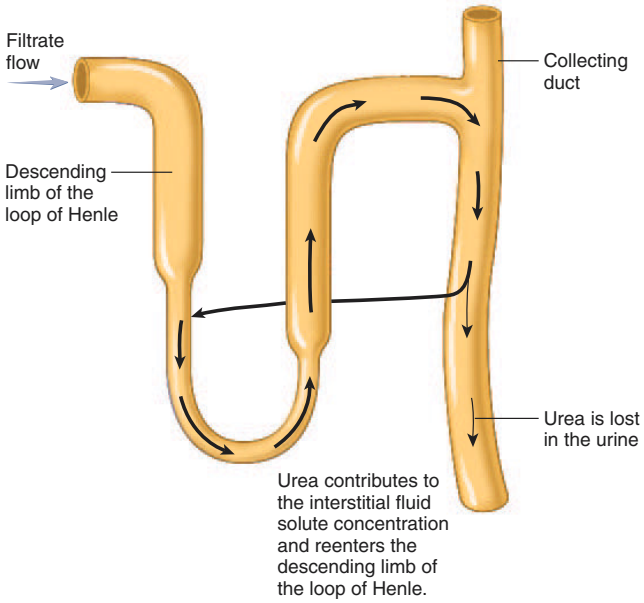
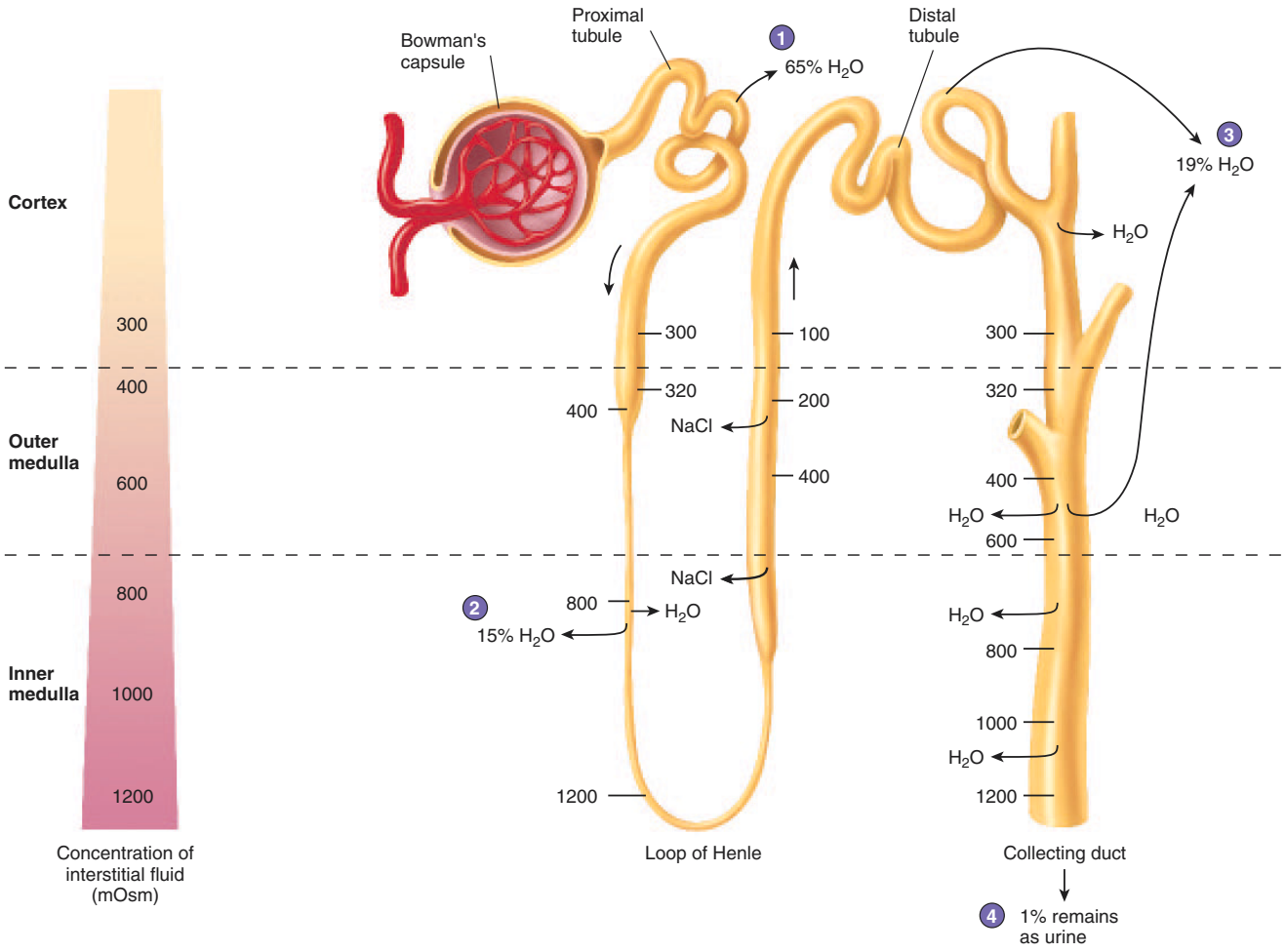


Figure 26.15 **The Medullary Concentration Gradient and Urea Cycling**

The concentration of urea in the medulla of the kidney is high and contributes to the overall high concentration of solutes there. The wall of the collecting duct is permeable to urea. Urea diffuses out of the collecting duct into the interstitial fluid of the medulla. The wall of the descending limb of the loop of Henle is also permeable to urea. Urea diffuses from the interstitial fluid into the descending limb. Thus a cycle is produced in which urea flows into the descending limb, through the ascending limb, through the distal nephron, through the collecting duct, out of the collecting duct, and back into the descending limb.



1. Approximately 180 L of filtrate enters the nephrons each day; of that volume 65% is reabsorbed in the proximal tubule. In the proximal tubule, solute molecules are transported from the lumen of the tubule into the interstitial fluid. Water follows the reabsorbed solutes by osmosis because the cells of the tubule wall are permeable to water.

2. Approximatley 15% of the filtrate volume is reabsorbed in the descending limb of the loop of Henle. The descending limb passes through the concentrated interstitial fluid of the medulla. Because the wall of the descending limb is permeable to water, water moves by osmosis from the tubule into the more concentrated interstitial fluid. By the time the filtrate reaches the apex of the medulla of the kidney, the concentration of the filtrate is equal to the concentration of the interstitial fluid.

The ascending limb of the loop of Henle is not permeable to water. Solutes diffuse out of the thin segment and Na^+, K^+, and Cl^- are actively transported from the filtrate of the thick segment into the interstitial fluid. Consequently, the volume of the filtrate doesn't change as it passes through the interstitial fluid, but the concentration is greatly reduced. By the time the filtrate reaches the cortex of the kidney, the concentration is approximately 100 mOsm/L, which is less concentrated than the interstitial fluid of the cortex (300 mOsm/L).

3. The distal tubule and collecting duct are permeable to water if ADH is present. If ADH is present, water moves by osmosis from the more concentrated filtrate into the interstitial fluid. By the time the filtrate has reached the apex of the medulla an additional 19% of the filtrate has been reabsorbed, and

4. 1% or less remains as urine.

Process Figure 26.16 Urine Concentrating Mechanism

Summary of the mechanisms responsible for the concentration of urine.

and its osmolality has increased to about 1200 mOsm/kg (figure 26.16). By the time the filtrate has reached the tips of the loops of Henle, at least 80% of the filtrate volume has been reabsorbed.

After passing through the descending limbs of the loops of Henle, the filtrate enters the ascending limbs, or the thick segments. The thick segments are impermeable to water; but Na^+, Cl^-, and K^+ are transported from the filtrate into the interstitial fluid (see figure 26.16). The movement of ions, but not water, across the wall of the ascending limbs causes the osmolality of the filtrate to decrease from 1200 to about 100 mOsm/kg by the time the filtrate again reaches the cortex of the kidney. As a result, the filtrate in the nephrons is dilute compared to the concentration of the surrounding interstitial fluid, which has an osmolality of about 300 mOsm/kg.

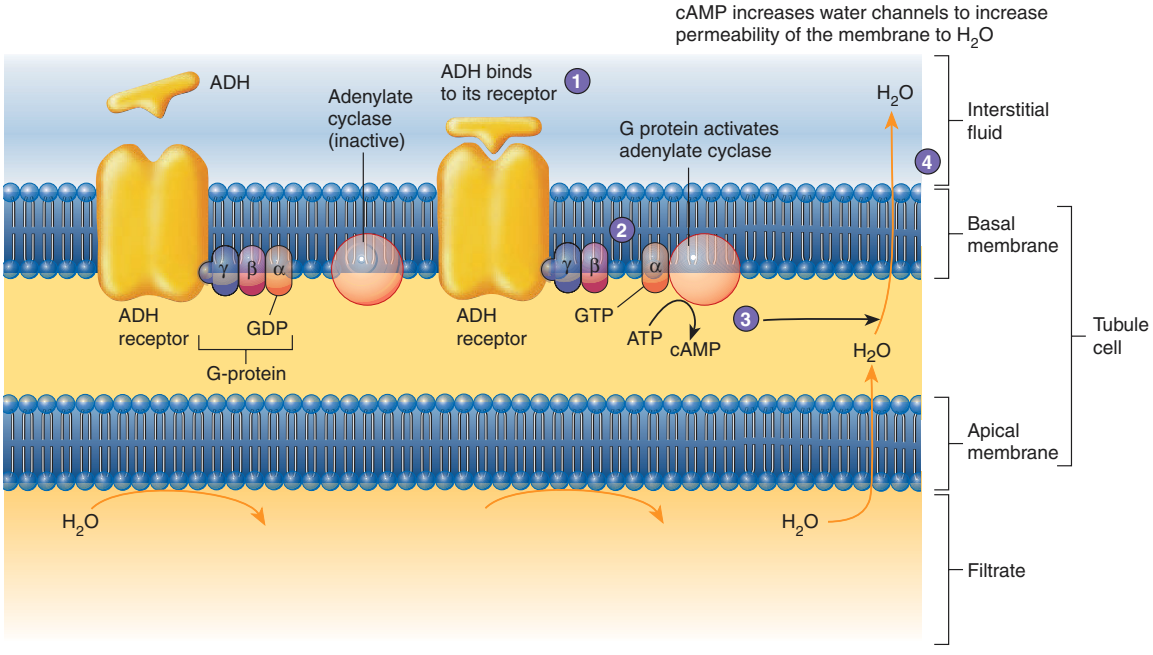
The changes just described are obligatory; that is, they occur regardless of the concentration and the volume of the urine that is finally produced by the kidney. The mechanisms by which concentrated and dilute urine are formed by the kidney are described in the following sections.

Formation of Concentrated Urine

Filtrate enters the distal tubules after passing through the loops of Henle and then passes through the collecting ducts. Near the ends of the distal tubules and collecting ducts, the wall of the tubules become very permeable to water, provided antidiuretic hormone (ADH) is present. Water then diffuses from the lumens of the nephrons into the more concentrated interstitial fluid.

ADH increases the permeability of the plasma membranes of the distal nephrons and collecting ducts to water. ADH binds to a membrane-bound receptor, activating a G protein mechanism that increases cAMP synthesis in the cells of the distal tubules and collecting ducts. Cyclic AMP increases the permeability of the plasma membranes of the distal tubules and collecting ducts to water by increasing the number of water channels in the plasma membrane (figure 26.17). When ADH is present, water moves by osmosis out of the distal tubules and collecting ducts, whereas in the absence of ADH, water remains within the nephrons and becomes urine. In the proximal tubules, 65% of the filtrate is reabsorbed, and 15% of the filtrate volume is reabsorbed in the thin segments of the descending limbs of the loops of Henle. About 80% of the volume of the filtrate is therefore reabsorbed in these structures.

The filtrate then flows into the distal tubules and collecting ducts that pass through the medulla of the kidney with its high concentration of solutes. If ADH is present, water diffuses from the collecting ducts into the interstitial fluid. By the time the filtrate passes through the collecting ducts, another 19% of the filtrate is reabsorbed. Thus, 1% of the filtrate remains as urine, and 99% of the



1. ADH binds to ADH receptors in the plasma membranes of the distal tubule cells and the collecting duct cells.
2. When ADH is bound to its receptor, a G protein mechanism is activated, which, in turn, activate adenylate cyclase.
3. The increase in the rate of cyclic adenosine monophosphate (cAMP) synthesis increases the permeability of the epithelial cells to water by increasing the number of water channels in their plasma membranes.
4. Water then moves out of the distal tubule and collecting duct into the interstitial fluid by osmosis, both decreasing the volume of the filtrate and increasing its concentration (osmolality).

Process Figure 26.17 The Effect of Antidiuretic Hormone (ADH) on the Nephron

filtrate is reabsorbed. The osmolality of the filtrate at the ends of the collecting ducts is approximately 1200 mOsm/kg (see figure 26.16).

In addition to the dramatic decrease in filtrate volume and the increase in filtrate osmolality, a marked alteration occurs in the filtrate composition. Waste products, such as creatinine and urea as well as K^+, H^+, phosphate, and sulfate ions, occur at a much higher concentration in urine than in the original filtrate because water has been removed from the filtrate. Many substances are selectively reabsorbed from the nephron, and others are secreted into the nephron so that beneficial substances are retained in the body and toxic substances are eliminated.

Formation of Dilute Urine

If ADH is not present or if its concentration is reduced, the distal tubules and collecting ducts have a low permeability to water. The amount of water moving by osmosis from the distal tubule and collecting duct, therefore, is low. The concentration of the urine produced is less than 1200 mOsm/kg, and the volume is increased. The volume of this more dilute urine can be much larger than 1% of the filtrate formed each day. If no ADH is secreted, the osmolality of the urine may be close to the osmolality of the filtrate in the distal tubule, and the volume of urine may approach 20–30 L/day.

In a healthy person, even when the kidney produces dilute urine, the concentration of waste products in the urine is large enough to maintain homeostasis in the body. Consequently, beneficial substances are retained, and both toxic substances and excess water are eliminated.

21. *What is a countercurrent system? How do the vasa recta help maintain the concentration gradient in the medulla?*
22. *How do the loops of Henle and collecting ducts contribute to the high medullary concentration gradient? How does urea contribute to the production of a high medullary concentration gradient?*
23. *Describe the net movement of water in the nephrons and collecting ducts.*
24. *Discuss the role of the distal tubules and collecting ducts in the formation of concentrated and dilute urine.*

Urine Concentration and Juxtamedullary Nephrons

Only the juxtamedullary nephrons have loops of Henle that descend deep into the medulla, but enough of them exist to maintain a high interstitial concentration of solutes in the interstitial fluid of the medulla. Not all of the nephrons need to have loops of Henle that descend into the medulla to effectively concentrate urine. The cortical nephrons function like the juxtamedullary nephrons, with the exception that their loops of Henle are not as efficient at concentrating urine. Because the filtrate from the cortical nephrons passes through the collecting ducts, however, water can diffuse out of the collecting ducts into the interstitial fluid. Thus the filtrate becomes concentrated. Animals that concentrate urine more effectively than humans have a greater percentage of nephrons that descend into the medulla of the kidney. For example, mammals that live in deserts have many nephrons that descend into the medulla of the kidney, and the renal pyramids are longer than in humans and most other mammals.

Regulation of Urine Concentration and Volume

Objectives

- *List and describe the hormonal mechanisms that regulate urine concentration and volume.*
- *Define autoregulation, and explain how it influences renal function.*
- *How does sympathetic stimulation affect filtrate production?*

Urine can be diluted or very concentrated, and it can be produced in large or small amounts. Urine concentration and volume are regulated by mechanisms that maintain the extracellular fluid osmolality and volume within narrow limits.

Filtrate reabsorption in the proximal tubules and the descending limbs of the loops of Henle is obligatory and therefore remains relatively constant. Filtrate reabsorption in the distal tubules and collecting ducts is regulated, however, and can change dramatically, depending on the conditions to which the body is exposed. If homeostasis requires the elimination of a large volume of dilute urine, a large volume of filtrate is produced, and the dilute filtrate in the distal tubules and collecting ducts can pass through them with little change in concentration. On the other hand, if conservation of water is required to maintain homeostasis, slightly less filtrate is produced, and water is reabsorbed from the filtrate as it passes through the distal tubules and collecting ducts. This results in the production of a small volume of very concentrated urine. Regulation of urine volume and concentration involves hormonal mechanisms, autoregulation, and the nervous system.

Hormonal Mechanisms

Antidiuretic Hormone

The distal tubules and the collecting ducts remain relatively impermeable to water in the absence of ADH (see figure 26.17). When little ADH is secreted, a large part of the 19% of the filtrate that's normally reabsorbed in the distal tubules and the collecting ducts becomes part of the urine. People who do not secrete sufficient ADH often produce 10–20 L of urine per day and develop major problems such as dehydration and ion imbalances. Insufficient ADH secretion results in a condition called **diabetes insipidus** (dī-ă-bē′tēz in-sip′i-dŭs); the word *diabetes* implies the production of a large volume of urine, and the word *insipidus* implies the production of a clear, tasteless, dilute urine. This condition is in contrast to **diabetes mellitus** (me-lī′tŭs), which implies the production of a large volume of urine that contains a high concentration of glucose. The word *mellitus* means "honeyed," or "sweet."

The posterior pituitary secretes ADH. Neurons with cell bodies primarily in the supraoptic nuclei of the hypothalamus have axons that course to the posterior pituitary gland. ADH is released into the circulatory system from these neuron terminals. Cells called **osmoreceptor cells** in the supraoptic nuclei are very sensitive to even slight changes in the osmolality of the interstitial fluid. If the osmolality of the blood and interstitial fluid increases,

these cells stimulate the ADH-secreting neurons. Action potentials are then propagated along the axons of the ADH-secreting neurons to the posterior pituitary gland, where the axons release ADH from their ends. Reduced osmolality of the interstitial fluid within the supraoptic nuclei inhibits ADH secretion from the posterior pituitary gland (see figure 18.5).

Baroreceptors that monitor blood pressure in the atria of the heart, large veins, carotid sinuses, and aortic arch also influence ADH secretion when the blood pressure increases or decreases in excess of 5%–10%. Decreases in blood pressure are detected by the baroreceptors, which consequently decrease the frequency of action potentials sent along the afferent pathways that ultimately extend to the supraoptic region of the hypothalamus. The result is an increase in ADH secretion.

When blood osmolality increases or when blood pressure declines significantly, ADH secretion increases and acts on the kidneys to increase the reabsorption of water. The reabsorption of water decreases blood osmolality. It also increases blood volume, which increases blood pressure. Conversely, when blood osmolality decreases or when blood pressure increases, ADH secretion declines. The reduced ADH levels cause the kidneys to reabsorb less water and to produce a larger volume of dilute urine. The increased loss of water in the urine increases blood osmolality and decreases blood pressure. ADH secretion occurs in response to small changes in osmolality while a substantial change in blood pressure is required to alter ADH secretion. Thus, ADH is more important in the regulation of blood osmolality than in the regulation of blood pressure.

PREDICT 5

Ethyl alcohol inhibits ADH secretion. Given this information, describe the mechanism by which alcoholic beverages affect urine production.

Renin-Angiotensin-Aldosterone

Renin is an enzyme secreted by cells of the juxtaglomerular apparatus. The rate of renin secretion increases if blood pressure in the afferent arteriole decreases, or if the Na^+ concentration of the filtrate decreases as it passes by the macula densa cells of the juxtaglomerular apparatuses. Renin enters the general circulation, acting on **angiotensinogen** and converting it to **angiotensin I.** Subsequently, a proteolytic enzyme called **angiotensin-converting enzyme (ACE)** converts angiotensin I to **angiotensin II** (figure 26.18). Angiotensin II is a potent vasoconstricting substance that increases peripheral resistance, causing blood pressure to increase. Angiotensin II also increases the rate of aldosterone secretion, the sensation of thirst, salt appetite, and ADH secretion.

The rate of renin secretion decreases if blood pressure in the afferent arteriole increases, or if the Na^+ concentration of the filtrate increases as it passes by the macula densa of the juxtaglomerular apparatuses.

A large decrease in the concentration of Na^+ in the interstitial fluids acts directly on the aldosterone-secreting cells of the adrenal cortex to increase the rate of aldosterone secretion. Angiotensin II is much more important than the blood level of Na^+, however, in regulating aldosterone secretion.

Aldosterone, a steroid hormone secreted by the cortical cells of the adrenal glands (see chapter 18), passes through the circulatory system from the adrenal glands to the cells in the distal tubules and the collecting ducts. Aldosterone molecules diffuse through the plasma membranes and bind to receptor molecules within the cells. The combination of aldosterone molecules with their receptor molecules increases synthesis of the transport protein molecules that increase the transport of Na^+ across the basal and apical membranes of nephron cells. As a result, the rate of Na^+ transport out of the filtrate back into the blood increases (see figure 26.18).

Reduced secretion of aldosterone decreases the rate of Na^+ transport. As a consequence, the concentration of Na^+ in the distal tubules and the collecting ducts remains high. Because the concentration of filtrate passing through the distal tubules and the collecting ducts has a greater-than-normal concentration of solutes, the capacity for water to move by osmosis from the distal tubules and the collecting ducts is diminished, urine volume increases, and the urine has a greater concentration of Na^+.

PREDICT 6

Drugs that increase urine volume are called diuretics. Some diuretics inhibit the active transport of Na^+ in the nephron. Explain how these diuretic drugs could cause increased urine volume.

Other Hormones

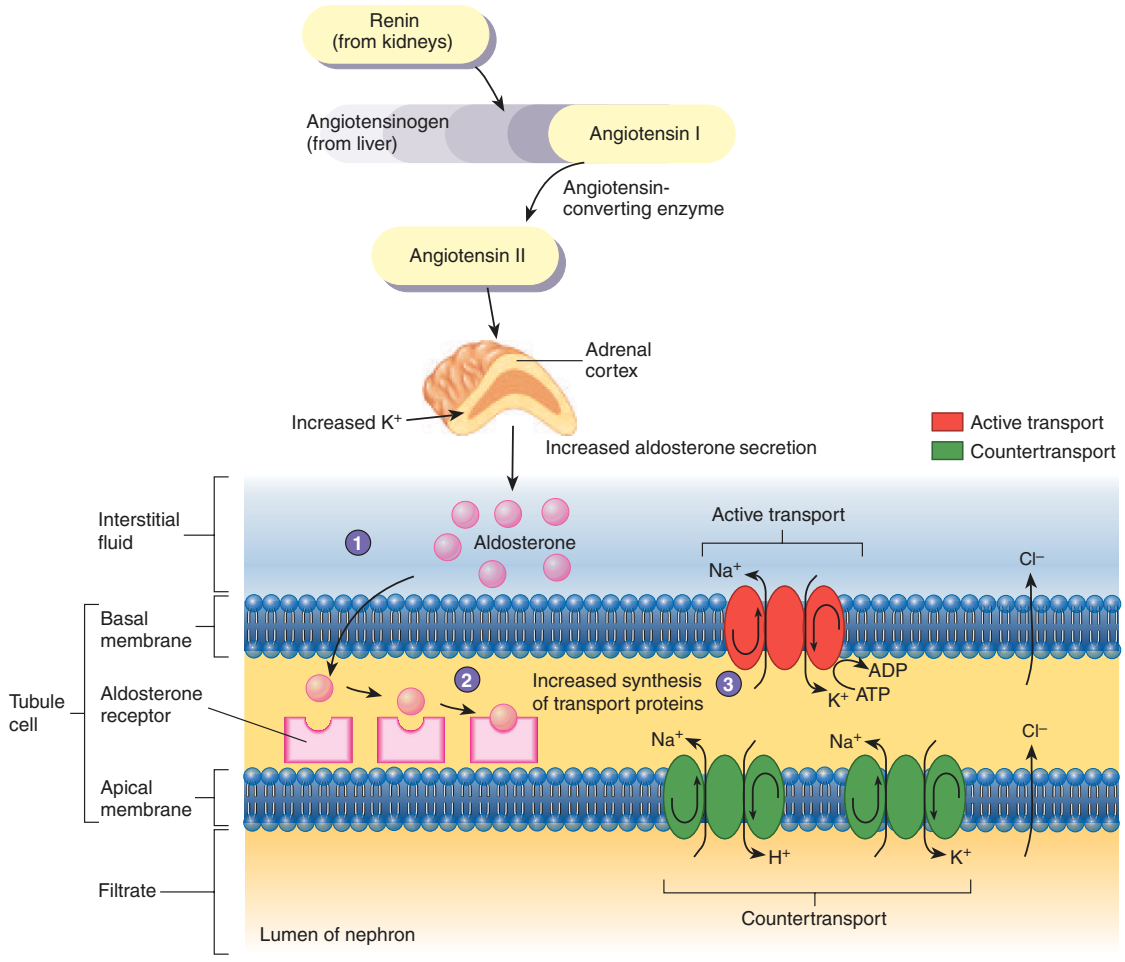
A polypeptide hormone called **atrial natriuretic** (nā′trē-ū-ret′ik) **hormone** is secreted from cardiac muscle cells in the right atrium of the heart when blood volume in the right atrium increases and stretches the cardiac muscle cells (see chapter 21). Atrial natriuretic hormone inhibits ADH secretion from the posterior pituitary gland and Na^+ reabsorption in the kidney, which leads to the production of a large volume of dilute urine. The resulting decrease in blood volume lowers blood pressure. Atrial natriuretic hormone also dilates arteries and veins, which reduces peripheral resistance and lowers blood pressure. Thus, a decrease occurs in venous return and blood volume in the right atrium.

Two other substances, prostaglandins and kinins, are formed in the kidneys and affect kidney function. Their roles are unclear, but both substances influence the rate of filtrate formation and Na^+ reabsorption. Prostaglandins probably moderate the sensitivity of the renal blood vessels to neural stimuli and to angiotensin II.

Autoregulation

Autoregulation is the maintenance, within the kidneys, of a relatively stable glomerular filtrate rate (GFR) over a wide range of systemic blood pressures. For example, GFR is relatively constant as the systemic blood pressure changes between 90 and 180 mm Hg.

Autoregulation involves changes in the degree of constriction in the afferent arterioles. The precise mechanism by which autoregulation is achieved is unclear, but, as systemic blood pressure increases, the afferent arterioles constrict and prevent an increase in renal blood flow and filtration pressure across the filtration membrane of the renal corpuscle. Conversely, a decrease in systemic blood pressure results in dilation of the afferent arterioles, thus preventing a decrease in renal blood flow and filtration pressure across the filtration membrane.



1. Aldosterone secreted from the adrenal cortex enters cells of the distal tubule.
2. Aldosterone binds to intracellular receptors and increases the synthesis of transport proteins of the apical and basal membranes.
3. Newly synthesized transport proteins increase the rate at which Na^+ are absorbed and K^+ and H^+ are secreted. Cl^- move with the Na^+ because they are attracted to the positive charge of Na^+.

Figure 26.18 Effect of Aldosterone on the Distal Tubule

Autoregulation is also influenced by the rate of flow of filtrate past cells of the macula densa. The macula densa detects an increased flow rate and sends a signal to the juxtaglomerular apparatus to constrict the afferent arteriole. The result is a decrease in the filtration pressure across the filtration membrane of the renal corpuscle.

Effect of Sympathetic Stimulation on Kidney Function

Sympathetic neurons with norepinephrine as their neurotransmitter innervate the blood vessels of the kidneys. Sympathetic stimulation constricts the small arteries and afferent arterioles, thereby decreasing renal blood flow and filtrate formation. Intense sympathetic stimulation, such as during shock or intense exercise, decreases the rate of filtrate formation to only a few milliliters per minute. Small changes in sympathetic stimulation have a minimal effect on renal blood flow and filtrate formation. Autoregulation maintains renal blood flow and filtrate formation at a relatively constant rate unless sympathetic stimulation is intense.

In response to severe stress or circulatory shock, renal blood flow can decrease to such low levels that the blood supply to the kidney is inadequate to maintain normal kidney metabolism. As a consequence, kidney tissues can be damaged and thus be unable to perform their normal functions. This is one of the reasons why shock should be treated quickly.

25. *Where is ADH produced? What factors stimulate an increase in ADH secretion?*
26. *What effect does ADH have on urine volume and concentration?*
27. *What are the effects of aldosterone on Na^+ and Cl^- transport? How does aldosterone affect urine concentration, urine volume, and blood pressure?*
28. *Where is aldosterone produced? What factors stimulate aldosterone secretion?*
29. *How is angiotensin II activated? What effects does it produce?*
30. *What factors cause an increase in renin production?*
31. *Where is atrial natriuretic hormone produced, and what effect does it have on urine production?*
32. *Describe autoregulation.*
33. *Explain the effect that sympathetic stimulation has on the kidney during rest, exercise, and shock.*

Clearance and Tubular Maximum

Objective

- *Define and explain plasma clearance, tubular load, and tubular maximum.*

Plasma clearance is a calculated value representing the volume of plasma that is cleared of a specific substance each minute. For example, if the clearance value is 100 mL/min for a substance, the substance is completely removed from 100 mL of plasma each minute.

Clearance

The plasma clearance can be calculated for any substance that enters the circulatory system according to the following formula:

$$\text{Plasma clearance (mL/min)} = \text{Quantity of urine (mL/min)} \times \frac{\text{Concentration of substance in urine}}{\text{Concentration of substance in plasma}}$$

Plasma clearance can be used to estimate GFR if the appropriate substance is monitored (see table 26.2). Such a substance must have the following characteristics: (1) it must pass through the filtration membrane of the renal corpuscle as freely as water or other small molecules, (2) it must not be reabsorbed, (3) it must not be secreted into the nephron, and (4) it must not be either metabolized or produced in the kidney. **Inulin** (in′ū-lin) is a polysaccharide that has these characteristics. As filtrate is formed, it has the same concentration of inulin as plasma; but, as the filtrate flows through the nephron, all the inulin remains in the nephron to enter the urine. As a consequence, all the volume of plasma that becomes filtrate is cleared of inulin, and the plasma clearance for inulin is equal to the rate of glomerular filtrate formation. GFR is reduced when the kidney fails. Measurement of the GFR indicates the degree to which kidney damage has occurred.

PREDICT 7

During surgery, a patient's blood pressure drops to very low levels, and ischemia of the kidney develops. Within 1 day following the surgery, the GFR and the urine volume decrease to very low levels. Given that the structure of the glomeruli did not dramatically change, but that the epithelium of nephrons suffered from ischemia and sloughed into the nephron to form casts of epithelial cells in the nephron, explain why the GFR was reduced.

Plasma clearance can also be used to calculate renal plasma flow (see table 26.2). Substances with the following characteristics, however, must be used: (1) the substance must pass through the filtration membrane of the renal corpuscle, and (2) it must be secreted into the nephron at a sufficient rate so that very little of it remains in the blood as the blood leaves the kidney. A substance that meets these requirements is *para*-aminohippuric acid (PAH). As blood flows through the kidney, essentially all the PAH is either filtered or secreted into the nephron. The clearance calculation for PAH is therefore a good estimate of the volume of plasma flowing through the kidney each minute. Also, if the hematocrit is known, the total volume of blood flowing through the kidney each minute can be easily calculated.

The concept of plasma clearance can be used to make the measurements described previously, or it can be used to determine the means by which drugs or other substances are excreted by the kidney. A plasma clearance value greater than the inulin clearance value suggests that the substance is secreted by the nephron into the filtrate.

PREDICT 8

A person is suspected of suffering from chronic renal failure. To assess kidney function, urea clearance is measured and found to be very low. Explain what a very low urea clearance indicates in a person suffering from chronic renal failure.

The **tubular load** of a substance is the total amount of the substance that passes through the filtration membrane into the nephrons each minute. Normally, glucose is almost completely reabsorbed from the nephron by the process of active transport. The capacity of the nephron to actively transport glucose across the epithelium of the nephron is limited, however. If the tubular load is greater than the capacity of the nephron to reabsorb it, the excess glucose remains in the urine.

The maximum rate at which a substance can be actively reabsorbed is called the **tubular maximum** (figure 26.19). Each substance that's reabsorbed has its own tubular maximum, determined by the number of active transport carrier molecules and the rate at which they are able to transport molecules of the substance. For example, in people suffering from diabetes mellitus the tubular load for glucose can exceed the tubular maximum by a substantial amount, thus allowing glucose to appear in the urine. Urine volume is also greater than normal because the glucose molecules in the filtrate reduce the effectiveness of water reabsorption by osmosis.

34. *Define and explain the significance of the terms plasma clearance, tubular load, and tubular maximum.*

Clinical Focus Diuretics

Diuretics (dī-ū-ret′iks) are agents that increase the rate of urine formation. Although the definition is simple, a number of different physiologic mechanisms are involved.

Diuretics are used to treat disorders like hypertension and several types of edema that are caused by congestive heart failure, cirrhosis of the liver, and other anomalies. Use of diuretics can lead to complications, however, including dehydration and electrolyte imbalances.

The action of **carbonic anhydrase** (karbon′ik an-hī′drās) **inhibitors** reduces the rate of hydrogen ion secretion and the reabsorption of bicarbonate ions. The bicarbonate ions increase tubular osmotic pressure, causing osmotic diuresis. With long-term use, the diuretic effect of carbonic anhydrase inhibitors tends to be lost. The diuretic effect of these inhibitors is useful in treating conditions such as glaucoma and altitude sickness.

Sodium ion reabsorption inhibitors include thiazide-type diuretics. They promote the loss of Na^+, Cl^-, and water in the urine. These diuretics are given to some people who have hypertension. Inhibitors of Na^+ reabsorption, such as bumetanide, furosemide, and ethacrynic acid, specifically inhibit transport in the ascending limb of the loop of Henle. These diuretics are frequently used to treat congestive heart failure, cirrhosis of the liver, and renal disease.

Potassium-sparing diuretics are antagonists to aldosterone or directly prevent Na^+ reabsorption in the distal tubules and collecting ducts. Thus they promote Na^+ and water loss in the urine. These diuretics are used to reduce the loss of potassium ions in the urine and therefore preserve, or "spare," these ions. They are often used in combination with Na^+ reabsorption inhibitors and are effective in preventing excess potassium loss in the urine.

Osmotic diuretics freely pass by filtration into the filtrate, and they undergo limited reabsorption by the nephron. These diuretics increase urine volume by elevating the osmotic concentration of the filtrate, thus reducing the amount of water moving by osmosis out of the nephron. Urea, mannitol, and glycerine have been used as osmotic diuretics. Although they are not commonly used, they are effective in treating people who are suffering from cerebral edema and edema in acute renal failure.

Xanthines (zan′thēnz), including caffeine and related substances, act as diuretics, partly because they increase renal blood flow and the rate of glomerular filtrate formation. They also influence the nephron by decreasing Na^+ and Cl^- reabsorption.

Alcohol acts as a diuretic, although it's not used clinically for that purpose. It inhibits ADH secretion from the posterior pituitary and results in increased urine volume.

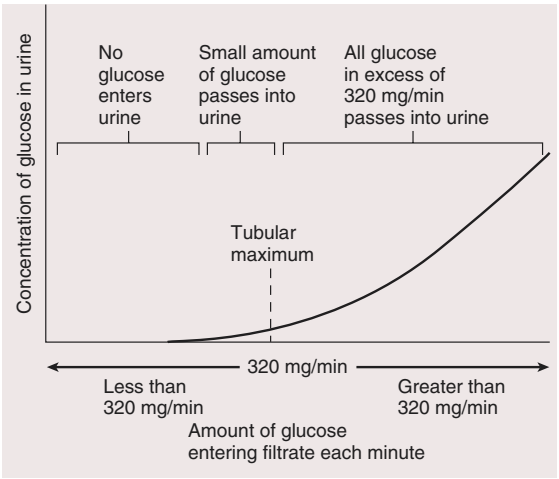


Figure 26.19 Tubular Maximum for Glucose

As the concentration of glucose increases in the filtrate, it reaches a point that exceeds the ability of the nephron to actively reabsorb it. That concentration is called the tubular maximum. Beyond that concentration, the excess glucose enters the urine.

Urine Movement

Objectives

- *Describe urine flow through the nephron and ureters.*
- *Describe the micturition reflex.*

Urine Flow Through the Nephron and the Ureters

Hydrostatic pressure averages 10 mm Hg in Bowman's capsule and nearly 0 mm Hg in the renal pelvis. This pressure gradient forces the filtrate to flow from Bowman's capsule through the nephron into the renal pelvis. Because the pressure is 0 mm Hg in the renal pelvis, no pressure gradient exists to force urine to flow to the urinary bladder through the ureters. The circular smooth muscle in the walls of the ureters exhibits peristaltic contractions that force urine to flow through the ureters. The peristaltic waves progress from the region of the renal pelvis to the urinary bladder. They occur from once every few seconds to once every 2–3 minutes. Parasympathetic stimulation increases their frequency, and sympathetic stimulation decreases it.

The peristaltic contractions of each ureter proceed at a velocity of approximately 3 cm/s and can generate pressures in excess of 50 mm Hg. At the point where the ureters penetrate the urinary bladder, they course obliquely through the trigone. Pressure inside the urinary bladder compresses that part of the ureter to prevent the backflow of urine.

When no urine is present in the urinary bladder, internal pressure is about 0 mm Hg. When the volume is 100 mL of urine, pressure is elevated to only 10 mm Hg. Pressure increases slowly as its volume increases to 400–500 mL, but above urinary bladder volumes of 500 mL the pressure rises rapidly.

Kidney Stones

Kidney stones are hard objects usually found in the pelvis of the kidney. They are normally 2–3 mm in diameter with either a smooth or jagged surface, but occasionally a large branching kidney stone called a **staghorn stone** forms in the renal pelvis. About 1% of all autopsies reveal kidney stones, and many of the stones occur without causing symptoms. The symptoms associated with kidney stones occur when a stone passes into the ureter, resulting in referred pain down the back, side, and groin area. The ureter contracts around the stone, causing the stone to irritate the epithelium and produce bleeding, which appears as blood in the urine, a condition called **hematuria.** In addition to causing intense pain, kidney stones can block the ureter, cause ulceration in the ureter, and increase the probability of bacterial infections.

About 65% of all kidney stones are composed of calcium oxylate mixed with calcium phosphate, 15% are magnesium ammonium phosphate, and 10% are uric acid or cystine; approximately 2.5% of each kidney stone is composed of mucoprotein.

The cause of kidney stones is usually obscure. Predisposing conditions include a concentrated urine and an abnormally high calcium concentration in the urine, although the cause of the high calcium concentration is usually unknown. Magnesium ammonium phosphate stones are often found in people with recurrent kidney infections, and uric acid stones often occur in people suffering from gout. Severe kidney stones must be removed surgically. Instruments that pulverize kidney stones with ultrasound or lasers, however, have replaced most traditional surgical procedures.

Micturition Reflex

The **micturition** (mik-choo-rish′un) **reflex** is activated when the urinary bladder wall is stretched and it results in **micturition,** which is the elimination of urine from the urinary bladder. Integration of the micturition reflex occurs in the sacral region of the spinal cord and it is modified by centers in the pons and cerebrum.

Urine filling the urinary bladder stimulates stretch receptors, which produce action potentials. The action potentials are carried by sensory neurons to the sacral segments of the spinal cord through the pelvic nerves. In response, action potentials are carried to the urinary bladder through parasympathetic fibers in the pelvic nerves (figure 26.20). The parasympathetic action potentials cause its wall to contract. In addition, decreased somatic motor action potentials cause the external urinary sphincter, which consists of skeletal muscle, to relax. Urine flows from the urinary bladder when the pressure there is great enough to force urine to flow through the urethra while the external urinary sphincter is relaxed. The micturition reflex normally produces a series of contractions of the urinary bladder.

Action potentials carried by sensory neurons from stretch receptors in the urinary bladder wall also ascend the spinal cord to a micturition center in the pons and to the cerebrum. Descending action potentials are sent from these areas of the brain to the sacral region of the spinal cord, where they modify the activity of the micturition reflex in the spinal cord. The micturition reflex, integrated in the spinal cord, predominates in infants. The ability to voluntarily inhibit micturition develops at the age of 2–3 years, and subsequently, the influence of the pons and cerebrum on the spinal micturition reflex predominates. The micturition reflex integrated in the spinal cord is automatic, but it is either stimulated or inhibited by descending action potentials. Higher brain centers prevent micturition by sending action potentials from the cerebrum and pons through spinal pathways to inhibit the spinal micturition reflex. Consequently, parasympathetic stimulation of the urinary bladder is inhibited and somatic motor neurons that keep the external urinary sphincter contracted are stimulated.

The pressure in the urinary bladder increases rapidly once its volume exceeds approximately 400–500 ml, and there is an increase in the frequency of action potentials carried by sensory neurons. The increased frequency of action potentials conducted by the ascending spinal pathways to the pons and cerebrum results in an increased desire to urinate.

Voluntary initiation of micturition involves an increase in action potentials sent from the cerebrum to facilitate the micturition reflex and to voluntarily relax the external urinary sphincter. In addition to facilitating the micturition reflex, there is an increased voluntary contraction of abdominal muscles, which causes an increase in abdominal pressure. This enhances the micturition reflex by increasing the pressure applied to the urinary bladder wall.

The desire to urinate normally results from stretch of the urinary bladder wall, but irritation of the urinary bladder or the urethra by bacterial infections or other conditions can also initiate the desire to urinate, even though the urinary bladder may be nearly empty.

35. *What is responsible for the movement of urine through the nephron and ureters?*
36. *Describe the micturition reflex. How is voluntary control of micturition accomplished?*

Automatic, Noncontracting, and Hyperexcitable Urinary Bladder

If the spinal cord is damaged above the sacral region, no micturition reflex exists for a time; but if the urinary bladder is emptied frequently, the micturition reflex eventually becomes adequate to cause it to empty. Some time is generally required for the micturition reflex integrated within the spinal cord to begin to operate. A typical micturition reflex can exist, but no conscious control exists over the onset or duration of it. This condition is called the **automatic bladder.**

Damage to the sacral region of the spinal cord or to the nerves that carry action potentials between the spinal cord and the urinary bladder can result in failure of the urinary bladder to contract although the external urinary sphincter is relaxed. As a result, the micturition reflex cannot occur. The bladder fills to capacity, and urine is forced in a slow dribble through the external urinary sphincter. In elderly people or in patients with damage to the brainstem or spinal cord, a loss of inhibitory action potentials to the sacral region of the spinal cord can occur. Without inhibition, the sacral centers are hyperexcitable, and even a small amount of urine in the bladder can elicit an uncontrollable micturition reflex.

Control of the micturition reflex by higher brain centers

A. Ascending pathways carry an increased frequency of action potentials up the spinal cord to the pons and cerebrum when the urinary bladder becomes stretched. This increases the conscious desire to urinate.

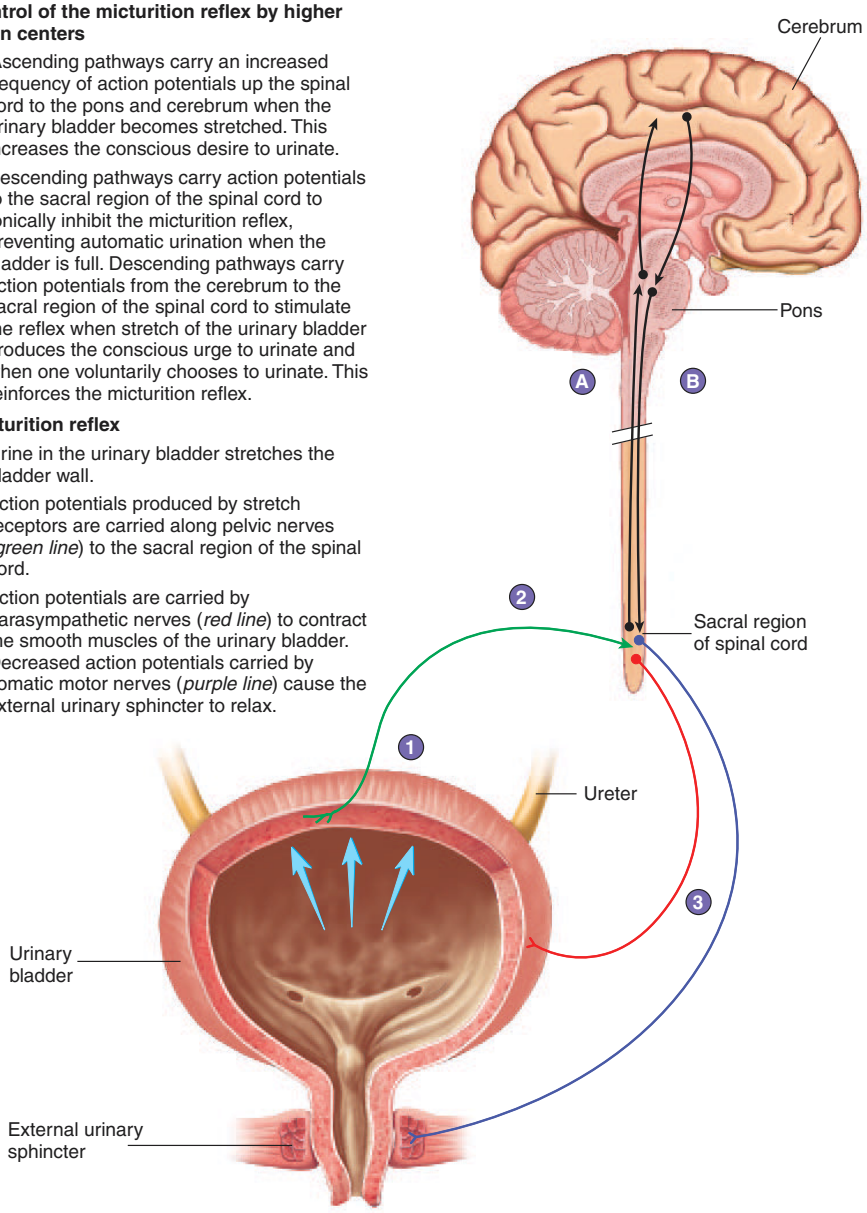
B. Descending pathways carry action potentials to the sacral region of the spinal cord to tonically inhibit the micturition reflex, preventing automatic urination when the bladder is full. Descending pathways carry action potentials from the cerebrum to the sacral region of the spinal cord to stimulate the reflex when stretch of the urinary bladder produces the conscious urge to urinate and when one voluntarily chooses to urinate. This reinforces the micturition reflex.

Micturition reflex

1. Urine in the urinary bladder stretches the bladder wall.

2. Action potentials produced by stretch receptors are carried along pelvic nerves (*green line*) to the sacral region of the spinal cord.

3. Action potentials are carried by parasympathetic nerves (*red line*) to contract the smooth muscles of the urinary bladder. Decreased action potentials carried by somatic motor nerves (*purple line*) cause the external urinary sphincter to relax.



Process Figure 26.20 Micturition Reflex

Effects of Aging on the Kidneys

Objective

- ***Describe the effect of aging on the kidneys.***

Aging causes a gradual decrease in the size of the kidneys that begins as early as age 20, becomes obvious by age 50, and continues until death. The loss of kidney size appears to be related to changes in the blood vessels of the kidney. The amount of blood flowing through the kidneys gradually decreases. Starting at age 20 there appears to be an approximately 10% decrease every 10 years. Small arteries including the afferent and efferent arterioles become irregular and twisted. Functional glomeruli are lost. By age 80, 40% of the glomeruli are not functioning. About 30% of the glomeruli that stop functioning no longer have a lumen through which blood flows. Other glomeruli thicken and assume a structure similar to arterioles. Some nephrons and collecting ducts become thicker,

Clinical Focus Renal Pathologies

Glomerular nephritis (glō-mār′ū-lăr ne-frī′tis) results from inflammation of the filtration membrane within the renal corpuscle. It's characterized by an increased permeability of the filtration membrane and the accumulation of numerous white blood cells in the area. As a consequence, a high concentration of plasma proteins enters the filtrate along with numerous white blood cells. A greater-than-normal urine volume accompanies the increase in plasma proteins in the urine.

Acute glomerular nephritis often occurs 1–3 weeks after a severe bacterial infection, such as streptococcal sore throat or scarlet fever. Antigen–antibody complexes associated with the disease become deposited in the filtration membrane and cause its inflammation. This acute inflammation normally subsides after several days.

Chronic glomerular nephritis is long term and usually progressive. The filtration membrane thickens and eventually is replaced by connective tissue. Although in the early stages chronic glomerular nephritis resembles the acute form, in the advanced stages many of the renal corpuscles are replaced by fibrous connective tissue, and the kidney eventually ceases to function.

Pyelonephritis (pī′ĕ-lō-ne-frī′tis) is inflammation of the renal pelvis, medulla, and cortex. It often begins as a bacterial infection of the renal pelvis and then extends into the kidney itself. It can result from several types of bacteria, including *Escherichia coli*. Pyelonephritis can destroy nephrons and renal corpuscles, but, because the infection starts in the pelvis of the kidney, it affects the medulla more than the cortex. As a consequence, the ability of the kidney to concentrate urine is dramatically affected.

Renal failure can result from any condition that interferes with kidney function. **Acute renal failure** occurs when kidney damage is extensive and leads to the accumulation of urea in the blood and to acidosis (see chapter 27). In complete renal failure, death can occur in 1–2 weeks. Acute renal failure can result from acute glomerular nephritis, or it can be caused by damage to or blockage of the renal tubules. Some poisons, such as mercuric ions or carbon tetrachloride, that are common to certain industrial processes cause necrosis of the nephron epithelium. If the damage doesn't interrupt the basement membrane surrounding the nephrons, extensive regeneration can occur within 2–3 weeks. Severe ischemia associated with circulatory shock resulting from sympathetic vasoconstriction of the renal blood vessels can cause necrosis of the epithelial cells of the nephron.

Chronic renal failure results when so many nephrons are permanently damaged that those nephrons remaining functional cannot adequately compensate. Chronic renal failure can result from chronic glomerular nephritis, trauma to the kidneys, absence of kidney tissue caused by congenital abnormalities, or tumors. Urinary tract obstruction by kidney stones, damage resulting from pyelonephritis, and severe arteriosclerosis of the renal arteries also cause degeneration of the kidney.

In chronic renal failure, the GFR is dramatically reduced, and the kidney is unable to excrete excess excretory products, including electrolytes and metabolic waste products. The accumulation of solutes in the body fluids causes water retention and edema. Potassium levels in the extracellular fluid are elevated, and acidosis occurs because the distal convoluted tubules and collecting ducts cannot excrete sufficient quantities of potassium and hydrogen ions. Acidosis, elevated potassium levels in the body fluids, and the toxic effects of metabolic waste products cause mental confusion, coma, and finally death when chronic renal failure is severe.

shorter, and more irregular in structure. The capacity to secrete and absorb declines, and whole nephrons stop functioning. The ability of the kidney to concentrate urine gradually declines. Eventually changes in the kidney increase the risk of dehydration because of the reduced ability of the kidney to produce a concentrated urine. There's also a decreased ability to eliminate uric acid, urea, creatine, and toxins from the blood.

There is an age-related loss of responsiveness to ADH and to aldosterone. The kidney decreases renin secretion. A reduced ability to participate in vitamin D synthesis occurs, which contributes to Ca^{2+} deficiency, osteoporosis, and bone fractures.

The age-related changes in the kidney cause a reduction in the reserve capacity of the kidney. Consequently, high blood pressure, atherosclerosis, and diabetes have greater adverse effects on the kidney in older people.

37. Describe the effect of aging on the kidneys. Why do the kidneys gradually decrease in size?

Systems Pathology

Acute Renal Failure

A large piece of machinery overturned at the construction site where Mr. H worked, trapping him beneath it. His legs were severely crushed, although they healed after several months. Mr. H nearly lost his life, however, because of the acute renal failure that developed as a result of his injury. Mr. H was trapped for several hours in a very difficult place to reach. During that time, his blood pressure decreased to very low levels because of the blood loss, the edema in the inflamed tissues, and emotional shock. After he was rescued, he received fluid replacement in the form of both intravenous saline solutions and blood transfusions, and his blood pressure returned to its normal range. Twenty-four hours after the accident, however, his urine volume began to decrease. His urinary Na^+ concentration increased, his urine osmolality decreased, his urine specific gravity decreased, and casts and cellular debris were evident in his urine.

For approximately 7 days, Mr. H exhibited oliguria (reduced urine production). During this period, renal dialysis was required to maintain Mr. H's blood volume and electrolyte concentrations within normal ranges (figure B). After approximately 7 days, his kidneys gradually began to produce large quantities of urine (a diuretic phase). Careful observation was required to keep his blood pressure and electrolyte concentrations within normal ranges. Substantial water, Na^+, and K^+ had to be administered to him. After about 3 weeks, the function of his kidneys slowly began to improve, although many months passed before his kidney function returned to normal.

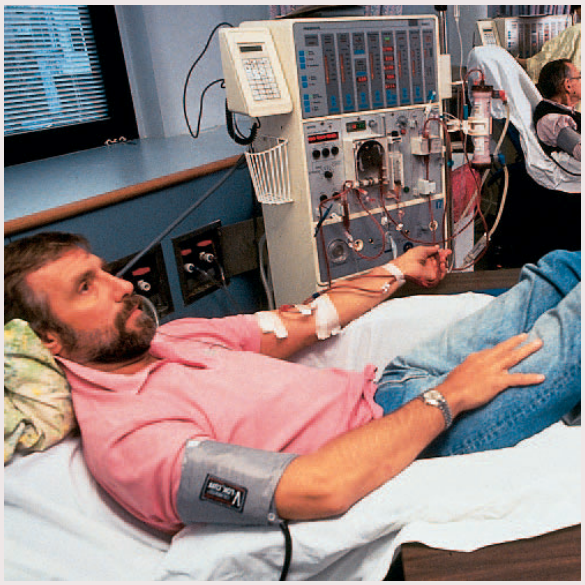


Figure B A Patient Undergoing Dialysis

Background Information

The events after 24 hours are consistent with acute renal failure caused by prolonged hypotension and ischemia of the kidney. While Mr. H was suffering from hypotension, blood flow to his kidneys was very low. The reduced blood flow was severe enough to result in damage to the epithelial lining of the kidney tubules (tubular necrosis). The period of reduced urine volume resulted from tubular damage. Renal ischemia results in necrosis of tubular cells, which then slough off into the tubules and block them so that filtrate cannot flow through the tubules. In addition, the filtrate leaks from the blocked or partially blocked tubules back into the interstitial spaces and, therefore, back into the circulatory system. As a result, the amount of filtrate that becomes urine is markedly reduced. Blood levels of urea and of creatine increase because of the reduction in filtrate formation and reduced function of the tubular epithelium. The kidneys' ability to eliminate metabolic waste products is therefore reduced. The small amount of urine produced has a high Na^+ concentration but an osmolality that's close to the concentration of the body fluids because the kidneys are not able to reabsorb Na^+ and because the urine-concentrating ability of the kidneys is severely damaged.

S U M M A R Y

The excretory system consists of the kidneys, the ureters, the urinary bladder, and the urethra.

Functions of the Urinary System (p. 947)

The urinary system eliminates wastes; regulates blood volume, ion concentration, and pH; and it is also involved with red blood cell and vitamin D production.

Kidney Anatomy and Histology (p. 947)

The kidney is surrounded by a renal capsule and perirenal fat and is held in place by the renal fascia.

Location and External Anatomy of the Kidneys

1. The kidneys lie behind the peritoneum on the posterior abdominal wall on either side of the vertebral column.

System Interactions The Effect of Acute Renal Failure on Other Systems

System	Interactions
Integumentary	Pallor results from anemia, and bruising results from reduced clotting proteins in the blood because they are lost in the urine. A waxy yellow caste develops to the skin of light-skinned people, an ashen gray caste in black-skinned people, or a yellowish brown caste in brown-skinned people due to accumulation of urinary pigments. When the urea concentration in the blood is very high, white crystals of urea, called uremic frost, may appear on areas of the skin where heavy perspiration occurs.
Skeletal	Changes in the skeletal system are not marked unless kidney damage results in chronic kidney failure. Bone resorption may result during a prolonged diuretic phase because of excessive loss of Ca^{2+} in the urine. Also, vitamin D levels may be reduced during both the oliguric and diuretic phases.
Muscular	Neuromuscular irritability results from the toxic effect of metabolic wastes on the central nervous system and ionic imbalances such as hyperkalemia. Involuntary jerking and twitching may occur as neuromuscular irritability develops. Tremors of the hands are an indication of the toxic effects of metabolic wastes on the cerebrum.
Nervous	Elevated blood K^+ levels and the toxic effects of metabolic wastes result in depolarization of neurons. Slowing of nerve conduction, burning sensations, pain, numbness, or tingling results. Also, decreased mental acuity, reduced ability to concentrate, apathy, and lethargy result. Periods of lethargy may alternate with restlessness and insomnia. In severe cases, the patient may become confused and comatose.
Endocrine	Major predictable hormone deficiencies include vitamin D deficiency. In addition, a decrease occurs in the secretion of reproductive hormones due to the effects of metabolic wastes and ionic imbalances on the hypothalamus.
Cardiovascular	Water and Na^+ retention may result in edema in peripheral tissues and in the lung. Also, hypertension and congestive heart failure may result. Hyperkalemia results in dysrhythmias and may cause cardiac arrest. Anemia due to decreased erythropoietin production by the damaged kidney and decreased half-life of red blood cells may result. Anemia is more likely because of the blood lost as a result of the crushing injury. Nosebleeds and bruising occur due to a reduced concentration of clottting factors because they are lost in the urine.
Lymphatic	No major direct effects occur to the lymphatic system with the exception that increased lymph flow happens as a result of edema.
Respiratory	Early during acute renal failure the depth of breathing increases, and it becomes labored as acidosis develops because the kidney is not able to secrete H^+. Pulmonary edema often develops because of water and Na^+ retention. The likelihood of pulmonary infection increases secondary to pulmonary edema.
Digestive	Anorexia, nausea, and vomiting result from altered gastrointestinal functions due to the effects of ionic imbalances on the nervous sytem. An odor of ammonia may occur on the breath and a metallic taste in the mouth. These effects are the result of the accumulation of metabolic waste products in the gastrointestinal tract, and the action of the normal gastrointestinal microorganisms on the waste products, which convert urea to ammonia. The ammonia and other metabolic waste products predispose the mouth to inflammation and infection.

During the diuretic phase, large quantities of urine were produced because the nephrons were partially healed and could produce urine, but the ability of the nephrons to concentrate urine was not yet normal. Large volumes of urine that contained significant amounts of Na^+ and K^+ were therefore produced. The kidneys were able to produce urine that was more concentrated than the body fluids, but the concentrating ability of the kidneys was still below normal. As time passed, the concentrating ability of the kidneys improved and eventually became normal once again.

PREDICT 9

Nine days after the accident, Mr. H began to appear pale, and he became dizzy and lethargic. His hematocrit was elevated and his heart was arrhythmic. He was very weak. Explain these manifestations.

2. The renal capsule surrounds each kidney, and the perirenal fat and the renal fascia surround each kidney and anchor it to the abdominal wall.
3. The hilum, on the medial side of each kidney, where blood vessels and nerves enter and exit the kidney, opens into the renal sinus containing fat and connective tissue.

Internal Anatomy and Histology of the Kidneys

1. The two layers of the kidney are the cortex and the medulla.
   - The renal columns extend toward the medulla between the renal pyramids.
   - The renal pyramids of the medulla project to the minor calyces.
2. The minor calyces open into the major calyces, which open into the renal pelvis. The renal pelvis leads to the ureter.
3. The functional unit of the kidney is the nephron. The parts of a nephron are the renal corpuscle, the proximal tubule, the loop of Henle, and the distal tubule.
   - The renal corpuscle is Bowman's capsule and the glomerulus. Materials leave the blood in the glomerulus and enter Bowman's capsule through the filtration membrane.
   - The nephron empties through the distal tubule into a collecting duct.

4. The juxtaglomerular apparatus consists of the macula densa (part of the distal tubule) and the juxtaglomerular cells of the afferent arteriole.

Arteries and Veins of the Kidneys

1. Arteries branch as follows: renal artery to segmental artery to interlobar artery to arcuate artery to interlobular artery to afferent arteriole.
2. Afferent arterioles supply the glomeruli.
3. Efferent arteries from the glomeruli supply the peritubular capillaries and vasa recta.
4. Veins form from the peritubular capillaries as follows: interlobular vein to arcuate vein to interlobar vein to renal vein.

Anatomy and Physiology of the Ureters and Urinary Bladder (p. 953)

1. Structure
   - The walls of the ureter and urinary bladder consist of the epithelium, the lamina propria, a muscular coat, and a fibrous adventitia.
   - The transitional epithelium permits changes in size.
2. Function
   - The ureters transport urine from the kidney to the urinary bladder.
   - The urinary bladder stores urine.

Urine Production (p. 954)

Urine is produced by the processes of filtration, reabsorption, and secretion.

Filtration

1. The renal filtrate is plasma minus blood cells and blood proteins. Most (99%) of the filtrate is reabsorbed.
2. The filtration membrane is fenestrated endothelium, basement membrane, and the slitlike pores formed by podocytes.
3. Filtration pressure is responsible for filtrate formation.
   - Filtration pressure is glomerular capillary pressure minus capsule pressure minus colloid osmotic pressure.
   - Filtration pressure changes are primarily caused by changes in glomerular capillary pressure.

Tubular Reabsorption

1. Filtrate is reabsorbed by passive transport, including simple diffusion, facilitated diffusion, active transport, and cotransport from the nephron into the peritubular capillaries.
2. Specialization of tubule segments
   - The thin segment of the loop of Henle is specialized for passive transport.
   - The rest of the nephron and collecting tubules perform active transport, cotransport, and passive transport.
3. Substances transported
   - Active transport moves mainly Na^+ across the wall of the nephron. Other ions and molecules are moved primarily by cotransport.
   - Passive transport moves water, urea, and lipid-soluble, nonpolar compounds.

Tubular Secretion

1. Substances enter the proximal or distal tubules and the collecting ducts.
2. H^+, K^+, and some substances not produced in the body are secreted by countertransport mechanisms.

Urine Concentration Mechanism

1. Countercurrent systems (e.g., vasa recta and loop of Henle) and the distribution of urea are responsible for the concentration gradient in the medulla. The concentration gradient is necessary for the production of concentrated urine.
2. Production of urine
   - In the proximal tubule Na^+ and other substances are removed by active transport. Water follows passively, filtrate volume is reduced 65%, and the filtrate concentration is 300 mOsm/L.
   - In the descending limb of the loop of Henle water exits passively, and solute enters. The filtrate volume is reduced 15%, and the filtrate concentration is 1200 mOsm/L.
   - In the ascending limb of the loop of Henle, Na^+, Cl^-, and K^+ are transported out of the filtrate, but water remains because this segment of the nephron is impermeable to water. The filtrate concentration is 100 mOsm/L.
   - In the distal tubules and collecting ducts, water movement out of them is regulated by ADH. If ADH is absent, water is not reabsorbed, and a dilute urine is produced. If ADH is present, water moves out, and a concentrated urine is produced.

Regulation of Urine Concentration and Volume (p. 970)

Hormonal Mechanisms

1. ADH is secreted by the posterior pituitary and increases water permeability in the distal tubules and the collecting ducts.
   - ADH decreases urine volume, increases blood volume, and thus increases blood pressure.
   - ADH release is stimulated by increased blood osmolality or a decrease in blood pressure.
2. Aldosterone is produced in the adrenal cortex and affects Na^+ and Cl^- transport in the nephron and the collecting ducts.
   - A decrease in aldosterone results in less Na^+ reabsorption and an increase in urine concentration and volume. An increase in aldosterone results in greater Na^+ reabsorption and a decrease in urine concentration and volume.
   - Aldosterone production is stimulated by angiotensin II, increased blood K^+ concentration, and decreased blood Na^+ concentration.
3. Renin, produced by the kidneys, causes the production of angiotensin II.
   - Angiotensin II acts as a vasoconstrictor and stimulates aldosterone secretion, causing a decrease in urine production and an increase in blood volume.
   - Decreased blood pressure or decreased Na^+ concentration stimulates renin production.
4. Atrial natriuretic hormone, produced by the heart when blood pressure increases, inhibits ADH production and reduces the ability of the kidney to concentrate urine.

Autoregulation

Autoregulation dampens systemic blood pressure changes by altering afferent arteriole diameter.

Effect of Sympathetic Stimulation on Kidney Function

Sympathetic stimulation decreases afferent arteriole diameter.

Clearance and Tubular Maximum (p. 973)

1. Plasma clearance is the volume of plasma that is cleared of a specific substance each minute.
2. The tubular load is the total amount of substance that enters the nephron each minute.
3. Tubular maximum is the fastest rate at which a substance is reabsorbed from the nephron.

Urine Movement (p. 974)

Urine Flow Through the Nephron and the Ureters

1. Hydrostatic pressure forces urine through the nephron.
2. Peristalsis moves urine through the ureters.

Micturition Reflex

1. Stretch of the urinary bladder stimulates a reflex that causes the bladder to contract and inhibits the urinary sphincters.
2. Higher brain centers can stimulate or inhibit the micturition reflex.

Effects of Aging on the Kidneys (p. 976)

1. There is a gradual decrease in the size of the kidney.
2. The decrease in kidney size is associated with a decrease in renal blood flow.
3. The number of functional nephrons decreases.
4. Renin secretion and vitamin D synthesis decrease.
5. The ability of the nephron to secrete and absorb declines.

REVIEW AND COMPREHENSION

1. Which of these is *not* a general function of the kidneys?
   a. regulation of blood volume
   b. regulation of solute concentration in the blood
   c. regulation of the pH of the extracellular fluid
   d. regulation of vitamin A synthesis
   e. regulation of red blood cell synthesis
2. The cortex of the kidney contains the
   a. hilus.
   b. glomeruli.
   c. perirenal fat.
   d. renal pyramids.
   e. renal pelvis.
3. A layer of fibrous connective tissue that surrounds each kidney is the
   a. hilum.
   b. renal pelvis.
   c. renal sinus.
   d. renal capsule.
   e. perirenal fat.
4. Given these structures:
   1. major calyx
   2. minor calyx
   3. renal papilla
   4. renal pelvis

   Choose the arrangement that lists the structures in order as urine leaves the collecting duct and travels to the ureter.
   a. 1,4,2,3
   b. 2,3,1,4
   c. 3,2,1,4
   d. 4,1,3,2
   e. 4,3,2,1
5. Which of these structures contains blood?
   a. glomerulus
   b. vasa recta
   c. distal tubule
   d. Bowman's capsule
   e. both a and b
6. Given these vessels:
   1. arcuate artery
   2. interlobar artery
   3. segmental artery

   A red blood cell has just passed through the renal artery. Choose the path the red blood cell must take to reach the interlobular artery.
   a. 1,2,3
   b. 2,1,3
   c. 2,3,1
   d. 3,1,2
   e. 3,2,1
7. The juxtaglomerular cells of the _____ and the macula densa cells of the _____ form the juxtaglomerular apparatus.
   a. afferent arteriole, proximal tubule
   b. afferent arteriole, distal tubule
   c. efferent arteriole, proximal tubule
   d. efferent arteriole, distal tubule
8. Given these blood vessels:
   1. afferent arteriole
   2. efferent arteriole
   3. glomerulus
   4. peritubular capillaries

   Choose the correct order as blood passes from an interlobular artery to an interlobular vein.
   a. 1,2,3,4
   b. 1,3,2,4
   c. 2,1,4,3
   d. 3,2,4,1
   e. 4,3,1,2
9. The urinary bladder
   a. is made up of skeletal muscle.
   b. is lined by simple columnar epithelium.
   c. is connected to the outside of the body by the ureter.
   d. is located in the pelvic cavity.
   e. has two urethras and one ureter attached to it.
10. Kidney function is accomplished by which of these means?
    a. filtration
    b. secretion
    c. reabsorption
    d. both a and b
    e. all of the above
11. The amount of plasma that enters Bowman's capsule per minute is the
    a. glomerular filtration rate.
    b. renal plasma flow.
    c. renal fraction.
    d. renal blood flow.
12. Given these structures:
    1. basement membrane
    2. fenestra
    3. filtration slit

    Choose the arrangement that lists the structures in the order a molecule of glucose encounters them as the glucose passes through the filtration membrane to enter Bowman's capsule.
    a. 1,2,3
    b. 2,1,3
    c. 2,3,1
    d. 3,1,2
    e. 3,2,1

13. If the glomerular capillary pressure is 40 mm Hg, the capsule pressure is 10 mm Hg, and the colloid osmotic pressure within the glomerulus is 30 mm Hg, the filtration pressure is
    a. −20 mm Hg.
    b. 0 mm Hg.
    c. 20 mm Hg.
    d. 60 mm Hg.
    e. 80 mm Hg.
14. Which of these conditions reduces filtration pressure in the glomerulus?
    a. elevated blood pressure
    b. constriction of the afferent arterioles
    c. decreased plasma protein in the glomerulus
    d. dilation of the afferent arterioles
    e. decreased capsule pressure
15. Glucose usually is completely reabsorbed from the filtrate by the time the filtrate has reached
    a. the end of the proximal tubule.
    b. the tip of the loop of Henle.
    c. the end of the distal tubule.
    d. the end of the collecting duct.
    e. Bowman's capsule.
16. The greatest volume of water is reabsorbed from the nephron by the
    a. proximal tubule.
    b. loop of Henle.
    c. distal tubule.
    d. collecting duct.
17. Water leaves the nephron by
    a. active transport.
    b. filtration into the capillary network.
    c. osmosis.
    d. facilitated diffusion.
    e. cotransport.
18. Potassium ions enter the _____ by _____.
    a. proximal tubule, diffusion
    b. proximal tubule, active transport
    c. distal tubule, diffusion
    d. distal tubule, counter transport
19. Reabsorption of most solute molecules from the proximal tubule is linked to the primary active transport of Na^+
    a. across the apical membrane and out of the cell.
    b. across the apical membrane and into the cell.
    c. across the basal membrane and out of the cell.
    d. across the basal membrane and into the cell.
20. Which of these ions is used to cotransport amino acids, glucose, and other solutes through the apical membrane of nephron epithelial cells?
    a. K^+
    b. Na^+
    c. Cl^-
    d. Ca^{2+}
    e. Mg^{2+}
21. Which of the following contribute to the formation of a hyperosmotic environment in the medulla of the kidney?
    a. effects of ADH on water permeability of the ascending limb of the loop of Henle
    b. impermeability of the ascending limb of the loop of Henle to water
    c. cotransport of Na^+, K^+, and Cl^- out of the ascending limb of the loop of Henle
    d. both a and c
    e. both b and c
22. At which of these sites is the osmolality lowest (lowest concentration)?
    a. glomerular capillary
    b. proximal tubule
    c. bottom of the loop of Henle
    d. initial section of the distal tubule
    e. collecting duct
23. Increased aldosterone causes
    a. decreased reabsorption of Na^+.
    b. decreased blood volume.
    c. decreased reabsorption of Cl^-.
    d. increased permeability of the distal tubule to water.
    e. decreased volume of urine.
24. Juxtaglomerular cells are involved in the secretion of
    a. ADH.
    b. angiotensin.
    c. aldosterone.
    d. renin.
25. ADH governs the
    a. Na^+ pump of the proximal tubules.
    b. water permeability of the loop of Henle.
    c. Na^+ pump of the vasa recta.
    d. water permeability of the distal tubules and collecting ducts.
    e. Na^+ reabsorption in the proximal tubule.
26. A decrease in blood osmolality results in which of these?
    a. increased ADH secretion
    b. increased permeability of the collecting ducts to water
    c. decreased urine osmolality
    d. decreased urine output
    e. all of the above
27. Angiotensin II
    a. causes vasoconstriction.
    b. stimulates aldosterone secretion.
    c. stimulates ADH secretion.
    d. increases the sensation of thirst.
    e. all of the above.
28. If blood pressure increases by 50 mm Hg,
    a. the afferent arterioles constrict.
    b. glomerular capillary pressure increases by 50 mm Hg.
    c. glomerular filtration rate increases dramatically.
    d. efferent arterioles constrict.
    e. all of the above.
29. The amount of a substance that passes through the filtration membrane into the nephrons per minute is the
    a. renal plasma flow.
    b. tubular load.
    c. plasma clearance.
    d. tubular maximum.
30. Given these events:
    1. loss of voluntary control of urination
    2. loss of the sensation of the desire to urinate
    3. loss of reflex emptying of the urinary bladder

    Which of these events occurs following transection of the spinal cord at level L5?
    a. 1
    b. 2
    c. 1,2
    d. 2,3
    e. 1,2,3

Answers in Appendix F

CRITICAL THINKING

1. To relax after an anatomy and physiology examination, Mucho Gusto goes to a local bistro and drinks 2 quarts of low-sodium beer. What effect does this beer have on urine concentration and volume? Explain the mechanisms involved.
2. A male eats a full bag of salty potato chips. What effect does this have on urine concentration and volume? Explain the mechanisms involved.
3. During severe exertion in a hot environment, a person can lose up to 4 L of hypoosmotic (less concentrated than plasma) sweat per hour. What effect does this loss have on urine concentration and volume? Explain the mechanisms involved.
4. Harry Macho is doing yard work one hot summer day and refuses to drink anything until he is finished. He then drinks glass after glass of plain water. Assume that he drinks enough water to replace all the water he lost as sweat. How does this much water affect urine concentration and volume? Explain the mechanisms involved.
5. A patient has the following symptoms: slight increase in extracellular fluid volume, large decrease in plasma sodium concentration, very concentrated urine, and cardiac fibrillation. An imbalance of what hormone is responsible for these symptoms? Are the symptoms caused by oversecretion or undersecretion of the hormone?
6. Propose as many ways as you can to decrease the GFR.
7. Design a kidney that can produce hypoosmotic urine, which is less concentrated than plasma, or hyperosmotic urine, which is more concentrated than plasma, by the active transport of water instead of Na^+. Assume that the anatomic structure of the kidney is the same as that in humans. Feel free to change anything else you choose.
8. If only a very small amount of urea were present in the interstitial fluid of the kidney instead of its normal concentration, how would it affect the kidney's ability to concentrate urine?
9. It is well known that some patients with hypertension are kept on a low-salt (sodium) diet. Propose an explanation for this therapy.
10. In studies of mammalian kidney function, it is known that animals with kidneys having relatively thicker medullas have a greater ability to conserve water. Explain why this is so.

Answers in Appendix G

ANSWERS TO PREDICT QUESTIONS

1. The urethra of females is much shorter than the urethra of males. In addition, the opening of the urethra in females is closer to the anus, which is a potential source of bacteria. The female urinary bladder is therefore more accessible to bacteria from the exterior. This accessibility is a major reason that urinary bladder infections are more common in females than in males.
2. If the cardiac output is 5600 mL of blood per minute, and the hematocrit is 45, renal plasma flow is 650 mL of plasma per minute (see table 26.2). If the filtration fraction increased from 19% to 22%, the GFR would be 143 mL of filtrate per minute (650 mL of plasma $\times$ 0.22). If 99.2% of the filtrate is reabsorbed, 0.8% becomes urine. Thus the urine produced is 1.14 mL of urine per minute (143 mL of filtrate $\times$ 0.008). Compared to the rate of urine production when the filtrate fraction was 19% (i.e., 1 mL per minute), the 3% increase in filtration fraction has caused a 14% increase in urine production. Converting 1.14 mL of urine per minute to liters of urine produced per day yields 1.64 L/day (1.14 mL/min $\times$ 1 L/1000 mL $\times$ 1440 min/day).
3. Even though hemoglobin is a smaller molecule than albumin, it doesn't normally enter the filtrate because hemoglobin is contained within red blood cells and these cells cannot pass through the filtration membrane. If red blood cells rupture, however, a process called hemolysis, the hemoglobin is released into the plasma, and large amounts of hemoglobin enter the filtrate. Conditions that cause red blood cells to rupture in the circulatory system result in large amounts of hemoglobin entering the urine.
4. Karl was suffering from plasma loss due to the extensive burns, which results in intense vasoconstriction, including vasoconstriction of arteries and arterioles that supply the kidneys. Constriction of the renal arteries and the renal afferent arterioles decreases the blood pressure in the glomeruli. As a consequence, the filtration pressure decreases. After an I.V. is administered and blood volume increases, the blood pressure returns to normal and renal arteries and arterioles once again dilate, thus blood pressure in the glomeruli increases to normal levels.
5. Inhibition of ADH secretion is one of the numerous effects alcohol has on the body. The lack of ADH secretion causes the distal tubules and the collecting ducts to be relatively impermeable to water. The water cannot therefore move by osmosis from the distal nephrons and collecting ducts and remains in the nephrons to become urine. In addition, because other fluids are normally consumed with the alcohol, the increased water intake also results in an increase in dilute urine production.
6. Without the normal active transport of Na^+, the concentration of Na^+ and ions cotransported with them remains elevated in the nephron. Movement of water by osmosis out of the nephron into the interstitial spaces is decreased, resulting in an increased volume of urine.
7. Anything that reduces the formation of filtrate reduces the GFR. If the epithelium of the nephrons sloughs off and forms casts in the nephrons, normal flow of filtrate through them is blocked. Consequently, the blocked flow of filtrate in the nephron causes the pressure in Bowman's capsule to increase enough so that the pressure inside of Bowman's capsule is close to the pressure in the glomerulus. Unless the pressure in the glomerulus is higher than the pressure in Bowman's capsule, no filtrate forms, and the GFR is very low. If very little filtrate forms, the volume of urine produced is reduced. Also, filtrate that enters a nephron that is block and with the epithelial lining of the nephron disrupted can flow directly into the peritubular capillaries.
8. Low urea clearance indicates that the amount of blood cleared of urea, a metabolic waste product, per minute is lower than normal. It's consistent with the reduction of the number of functional nephrons that occurs in advanced cases of renal failure. In addition, a low urea clearance is an indication that the GFR is reduced and that the blood levels of urea are increasing.

9. After 7 days Mr. H's kidney's began to produce a large volume of urine with larger-than-normal Na^+ and K^+ concentrations. The observations are consistent with Mr. H becoming dehydrated by day 10. Dehydration results in reduced blood volume. The pale skin was the result of vasoconstriction, which was triggered by the reduced blood pressure. Dizziness resulted from reduced blood flow to the brain when Mr. H tried to stand and walk. He was lethargic in part because of reduced blood volume but also because low blood levels of K^+ and Na^+. The arrythmia of his heart was due to low blood levels of K^+ and increased sympathetic stimulation, which also was triggered by low blood pressure.