Every day the kidneys filter nearly 200 liters of fluid from the bloodstream, allowing toxins, metabolic wastes, and excess ions to leave the body in urine while returning needed substances to the blood. Much like a water purification plant that keeps a city’s water drinkable and disposes of its wastes, the kidneys are usually unappreciated until they malfunction and body fluids become contaminated. Although the lungs and skin also participate in excretion, the kidneys are the major excretory organs.

As the kidneys perform these excretory functions, they also act as essential regulators of the volume and chemical makeup of the blood, maintaining the proper balance between water and salts and...
between acids and bases. Frankly, this would be tricky work for a chemical engineer, but the kidneys do it efficiently most of the time.

Other renal functions include
- Gluconeogenesis during prolonged fasting (see p. 930).
- Producing the hormones renin and erythropoietin (see Chapter 16). Renin (re’n; ren = kidney) acts as an enzyme to help regulate blood pressure and kidney function. Erythropoietin (é-rith’ro-po’i-tin) stimulates red blood cell production.
- Metabolizing vitamin D to its active form (see Chapter 16).

Besides the urine-forming kidneys, the urinary system includes the urinary bladder, a temporary storage reservoir for urine, plus three tubelike organs—the paired ureters (u-re’ters) and the urethra (u-re’thrah), all three of which furnish transportation channels for urine (Figure 25.1).

**Kidney Anatomy**

- Describe the gross anatomy of the kidney and its coverings.

**Location and External Anatomy**

The bean-shaped kidneys lie in a retroperitoneal position (between the dorsal body wall and the parietal peritoneum) in the superior lumbar region (Figure 25.2). Extending approximately from T12 to L3, the kidneys receive some protection from the lower part of the rib cage (Figure 25.2b). The right kidney is crowded by the liver and lies slightly lower than the left. An adult’s kidney has a mass of about 150 g (5 ounces) and its average dimensions are 12 cm long, 6 cm wide, and 3 cm thick—about the size of a large bar of soap. The lateral surface is convex. The medial surface is concave and has a vertical cleft called the renal hilum that leads into an internal space within the kidney called the renal sinus. The ureter, renal blood vessels, lymphatics, and nerves all join each kidney at the hilum and occupy the sinus. Atoph each kidney is an adrenal (or suprarenal) gland, an endocrine gland that is functionally unrelated to the kidney.

Three layers of supportive tissue surround each kidney (Figure 25.2a):

1. The renal fascia, an outer layer of dense fibrous connective tissue that anchors the kidney and the adrenal gland to surrounding structures
2. The perirenal fat capsule, a fatty mass that surrounds the kidney and cushions it against blows
3. The fibrous capsule, a transparent capsule that prevents infections in surrounding regions from spreading to the kidney

**HOMEOSTATIC IMBALANCE**

The fatty encasement of the kidneys is important in holding the kidneys in their normal body position. If the amount of fatty tissue dwindles (as with extreme emaciation or rapid weight loss), one or both kidneys may drop to a lower position, an event called renal ptosis (to’sis; “a fall”). Renal ptosis may cause a ureter to become kinked, which creates problems because the urine, unable to drain, backs up into the kidney and exerts...
pressure on its tissue. Backup of urine from ureteral obstruction or other causes is called hydronephrosis (hi’drō-nē-fro’sis; “water in the kidney”). Hydronephrosis can severely damage the kidney, leading to necrosis (tissue death) and renal failure.

Internal Anatomy

A frontal section through a kidney reveals three distinct regions: cortex, medulla, and pelvis (Figure 25.3). The most superficial region, the renal cortex, is light in color and has a granular appearance. Deep to the cortex is the darker, reddish-brown renal medulla, which exhibits cone-shaped tissue masses called medullary or renal pyramids. The broad base of each pyramid faces toward the cortex, and its apex, or papilla (“nipple”), points internally. The pyramids appear striped because they are formed almost entirely of parallel bundles of microscopic urine-collecting tubules and capillaries. The renal columns, inward extensions of cortical tissue, separate the pyramids. Each pyramid and its surrounding cortical tissue constitutes one of approximately eight lobes of a kidney.

The renal pelvis, a funnel-shaped tube, is continuous with the ureter leaving the hilum. Branching extensions of the pelvis form two or three major calyces (ka’lih-sēz; singular: calyx). Each one subdivides to form several minor calyces, cup-shaped areas that enclose the papillae.

The calyces collect urine, which drains continuously from the papillae, and empty it into the renal pelvis. The urine then flows through the renal pelvis and into the ureter, which moves it to the bladder to be stored. The walls of the calyces, pelvis, and ureter contain smooth muscle that contracts rhythmically to propel urine along its course by peristalsis.

Figure 25.2 Position of the kidneys against the posterior body wall. (a) Cross-section viewed from inferior direction. Note the retroperitoneal position and the supportive tissue layers of the kidney. (b) Posterior in situ view showing relationship of the kidneys to the 12th rib pair.
Infection of the renal pelvis and calyces produces the condition called pyelitis (pi'el-i-tis). Infections or inflammations that affect the entire kidney are pyelonephritis (pi'el-o-ne-prif'tis). Kidney infections in females are usually caused by fecal bacteria that spread from the anal region to the urinary tract. Less often they result from bloodborne bacteria (traveling from other infected sites) that lodge and multiply in the kidneys. In severe cases of pyelonephritis, the kidney swells, abscesses form, and the pelvis fills with pus. Untreated, the kidneys may be severely damaged, but antibiotic therapy can usually treat the infection successfully.

**Blood and Nerve Supply**

Trace the blood supply through the kidney.

The kidneys continuously cleanse the blood and adjust its composition, and so it is not surprising that they have a rich blood supply. Under normal resting conditions, the large renal arteries deliver one-fourth of the total cardiac output (about 1200 ml) to the kidneys each minute.

The renal arteries issue at right angles from the abdominal aorta, and the right renal artery is longer than the left because the aorta lies to the left of the midline. As each renal artery approaches a kidney, it divides into five segmental arteries (Figure 25.4). Within the renal sinus, each segmental artery branches further to form several interlobar arteries.

At the medulla-cortex junction, the interlobar arteries branch into the arcuate arteries (ar'ku-ät) that arch over the bases of the medullary pyramids. Small cortical radiate arteries radiate outward from the arcuate arteries to supply the cortical tissue. More than 90% of the blood entering the kidney perfuses the renal cortex.

Afferent arterioles branching from the cortical radiate arteries begin a complex arrangement of microscopic blood vessels. These vessels are key elements of kidney function, and we will examine them in detail later when we describe the nephron.

Veins pretty much trace the pathway of the arterial supply in reverse (Figure 25.4). Blood leaving the renal cortex drains...
sequentially into the cortical radiate, arcuate, interlobar, and finally renal veins. (There are no segmental veins.) The renal veins issue from the kidneys and empty into the inferior vena cava. Because the inferior vena cava lies to the right of the vertebral column, the left renal vein is about twice as long as the right.

The renal plexus, a variable network of autonomic nerve fibers and ganglia, provides the nerve supply of the kidney and its ureter. An offshoot of the celiac plexus, the renal plexus is largely supplied by sympathetic fibers from the most inferior thoracic and first lumbar splanchnic nerves, which course along with the renal artery to reach the kidney. These sympathetic vasomotor fibers regulate renal blood flow by adjusting the diameter of renal arterioles and also influence the urine-forming role of the nephrons.

CHECK YOUR UNDERSTANDING

1. Roger is hit in the lower back by an errant baseball. What protects his kidneys from this mechanical trauma?
2. From inside to outside, list the three layers of supportive tissue that surround each kidney. Where is the parietal peritoneum in relation to these layers?
3. The lumen of the ureter is continuous with a space inside the kidney. This space has branching extensions. What are the names of this space and its extensions?

For answers, see Appendix G.

Nephrons

- Describe the anatomy of a nephron.

Nephrons (nē’fronz) are the structural and functional units of the kidneys. Each kidney contains over 1 million of these tiny blood-processing units, which carry out the processes that form urine (Figure 25.5). In addition, there are thousands of collecting ducts, each of which collects fluid from several nephrons and conveys it to the renal pelvis.

Each nephron consists of a glomerulus (glo-mer’u-lus; glom = ball of yarn), which is a tuft of capillaries, and a renal tubule. The renal tubule has a cup-shaped end, the glomerular capsule (or Bowman’s capsule), which is blind and completely surrounds the glomerulus, much as a well-worn baseball glove encloses a ball. Collectively, the glomerular capsule and the enclosed glomerulus are called the renal corpuscle.

The endothelium of the glomerular capillaries is fenestrated (penetrated by many pores), which makes them exceptionally porous. This allows large amounts of solute-rich, virtually protein-free fluid to pass from the blood into the glomerular capsule. This plasma-derived fluid or filtrate is the raw material that the renal tubules process to form urine.

The external parietal layer of the glomerular capsule is simple squamous epithelium (Figures 25.5, 25.8, and 25.9). This layer simply contributes to the capsule structure and plays no part in forming filtrate.
Figure 25.5 Location and structure of nephrons. Schematic view of a nephron depicting the structural characteristics of epithelial cells forming its various regions.
The visceral layer, which clings to the glomerular capillaries, consists of highly modified, branching epithelial cells called podocytes (pod’o-sit; “foot cells”) (see Figure 25.9). The octopus-like podocytes terminate in foot processes, which intertwine as they cling to the basement membrane of the glomerulus. The clefts or openings between the foot processes are called filtration slits. Through these slits, filtrate enters the capsular space inside the glomerular capsule.

The remainder of the renal tubule is about 3 cm (1.2 inches) long and has three major parts. It leaves the glomerular capsule as the elaborately coiled proximal convoluted tubule (PCT), makes a hairpin loop called the loop of Henle (also called the nephron loop or Henle’s loop), and then winds and twists again as the distal convoluted tubule (DCT) before emptying into a collecting duct. The terms proximal and distal indicate the relationship of the convoluted tubules to the renal corpuscle—filtrate from the renal corpuscle passes through the PCT first and then the DCT, which is thus “further away” from the renal corpuscle. The meandering nature of the renal tubule increases its length and enhances its filtrate processing capabilities.

The collecting ducts, each of which receives filtrate from many nephrons, run through the medullary pyramids and give them their striped appearance. As the collecting ducts approach the renal pelvis, they fuse together and deliver urine into the minor calyces via papillae of the pyramids.

Throughout its length, the renal tubule consists of a single layer of polar epithelial cells on a basement membrane, but each of its regions has a unique cellular anatomy that reflects its role in processing filtrate. The walls of the PCT are formed by cuboidal epithelial cells with large mitochondria, and their luminal (exposed) surfaces bear dense microvilli (Figure 25.5 and Figure 25.6). Just as in the intestine, this brush border dramatically increases the surface area and capacity for reabsorbing water and solutes from the filtrate and secreting substances into it.

The U-shaped loop of Henle has descending and ascending limbs. The proximal part of the descending limb is continuous with the proximal tubule and its cells are similar. The rest of the descending limb, called the thin segment, is a simple squamous epithelium freely permeable to water. The epithelium becomes cuboidal or even low columnar in the ascending part of the loop of Henle, which therefore becomes the thick segment. In some nephrons, the thin segment is found only in the descending limb. In others, it extends into the ascending limb as well.

The epithelial cells of the DCT, like those of the PCT, are cuboidal and confined to the cortex, but they are thinner and almost entirely lack microvilli (Figure 25.5). The transition between the DCT and the collecting duct is marked by the appearance of a heterogeneous collection of cells. The two cell types seen in the collecting ducts are intercalated cells, cuboidal cells with abundant microvilli, and the more numerous principal cells, which have sparse, short microvilli. The two varieties (type A and B) of intercalated cells play a major role in maintaining the acid-base balance of the blood. The principal cells help maintain the body’s water and Na⁺ balance.

Nephrons are generally divided into two major groups. Cortical nephrons represent 85% of the nephrons in the kidneys. Except for small parts of their loops of Henle that dip into the outer medulla, they are located entirely in the cortex. The remaining juxtamedullary nephrons (juks”ta-me’duh-re) originate close to (juks = near to) the cortex-medulla junction, and they play an important role in the kidneys’ ability to produce concentrated urine. Their loops of Henle deeply invade the medulla, and their thin segments are much more extensive than those of cortical nephrons. Figure 25.7a compares the anatomy of these two types of nephrons.

**Nephron Capillary Beds**

The renal tubule of every nephron is closely associated with two capillary beds: the glomerulus and the peritubular capillaries (Figure 25.7). The glomerulus, in which the capillaries run in parallel, is specialized for filtration. It differs from all other capillary beds in the body in that it is both fed and drained by arterioles—the afferent arteriole and the efferent arteriole, respectively.
Chapter 25  The Urinary System

25

• Has short loop of Henle and glomerulus further from the corticomedullary junction
  Cortical nephron
• Efferent arteriole supplies peritubular capillaries

• Has long loop of Henle and glomerulus closer to the corticomedullary junction
  Juxtamedullary nephron
• Efferent arteriole supplies vasa recta

Figure 25.7  Blood vessels of cortical and juxtamedullary nephrons. (a) Arrows indicate direction of blood flow. Capillary beds from adjacent nephrons (not shown) overlap. (b) Scanning electron micrograph of a cast of blood vessels associated with nephrons (60×). View looking down onto the cortex.

SOURCE: (b) Kessel and Kardon/Visuals Unlimited.
The afferent arterioles arise from the cortical radiate arteries that run through the renal cortex. The blood pressure in the glomerulus is extraordinarily high for a capillary bed because (1) arterioles are high-resistance vessels and (2) the afferent arteriole has a larger diameter than the efferent. This high blood pressure easily forces fluid and solutes out of the blood into the glomerular capsule. Most of the resulting filtrate (99%) is reabsorbed by the renal tubule cells and returned to the blood in the peritubular capillary beds.

The peritubular capillaries arise from the efferent arterioles draining the glomeruli. These capillaries cling closely to adjacent renal tubules and empty into nearby venules. They are low-pressure, porous capillaries that readily absorb solutes and water from the tubule cells as these substances are reclaimed from the filtrate.

Notice in Figure 25.7a that the efferent arterioles serving the juxtamedullary nephrons tend not to break up into meandering peritubular capillaries. Instead they form bundles of long straight vessels called vasa recta (va’sah rek’tah; “straight vessels”) that extend deep into the medulla paralleling the longest loops of Henle. The thin-walled vasa recta play an important role in forming concentrated urine, as we will describe shortly.

In summary, the microvasculature of the nephrons consists of two capillary beds separated by intervening efferent arterioles. The first capillary bed (glomerulus) produces the filtrate. The second (peritubular capillaries) reclaims most of that filtrate.

Vascular Resistance in the Microcirculation

Blood flowing through the renal circulation encounters high resistance, first in the afferent and then in the efferent arterioles. As a result, renal blood pressure declines from approximately 95 mm Hg in the renal arteries to 8 mm Hg or less in the renal veins. The resistance of the afferent arterioles protects the glomeruli from large fluctuations in systemic blood pressure. Resistance in the efferent arterioles reinforces the high glomerular pressure and reduces the hydrostatic pressure in the peritubular capillaries.

Juxtaglomerular Apparatus

Each nephron has a region called a juxtaglomerular apparatus (JGA) (juks’tah-glo-mer’u-lar), where the most distal portion of the ascending limb of the loop of Henle lies against the afferent arteriole feeding the glomerulus (and sometimes the efferent arteriole) (Figure 25.8). Both the ascending limb and the efferent arteriole are modified at the point of contact.

The JGA includes two cell populations that play important roles in regulating the rate of filtrate formation and systemic blood pressure, as we will describe shortly. In the arteriole walls are the granular cells, also called juxtaglomerular (JG) cells, which are enlarged, smooth muscle cells with prominent secretory granules containing renin. Granular cells act as mechanoreceptors that sense the blood pressure in the afferent arteriole. The macula densa (mak’u-lah den’sah; “dense spot”)
is a group of tall, closely packed cells of the ascending limb of the loop of Henle that lies adjacent to the granular cells (Figure 25.8). The macula densa cells are chemoreceptors that respond to changes in the NaCl content of the filtrate. A third population of cells, the extraglomerular mesangial cells, is also part of the JGA. These cells are interconnected by gap junctions and may pass signals between macula densa and granular cells.

**The Filtration Membrane**

The filtration membrane lies between the blood and the interior of the glomerular capsule. It is a porous membrane that allows free passage of water and solutes smaller than plasma proteins. As Figure 25.9c shows, its three layers are: (1) the fenestrated endothelium of the glomerular capillaries; (2) the visceral membrane of the glomerular capsule, made of podocytes which have filtration slits between their foot processes; and between these two layers, (3) the basement membrane composed of the fused basal laminae of the two other layers.

The fenestrations (capillary pores) allow passage of all plasma components but not blood cells. The basement membrane restricts all but the smallest proteins while permitting most other solutes to pass. The structural makeup of the gel-like basement membrane also confers electrical selectivity on the filtration process. Most of the proteins in the membrane are negatively charged glycoproteins that repel other macromolecular anions and hinder their passage into the tubule. Because most plasma proteins also bear a net negative charge, this electrical repulsion reinforces the plasma protein blockage imposed by molecular size.

Almost all macromolecules that do manage to make it through the basement membrane are prevented from traveling further by thin membranes (slit diaphragms) that extend across the filtration slits. Macromolecules that get “hung up” in the filtration membrane are engulfed and degraded by mesangial cells within the glomerulus. These extraglomerular mesangial cells can also contract, changing the total surface area of the capillaries available for filtration.

**CHECK YOUR UNDERSTANDING**

4. Name the tubular components of a nephron in the order that filtrate passes through them.
5. What are the structural differences between juxtamedullary and cortical nephrons?
6. What type of capillaries are the glomerular capillaries? What is their function?

For answers, see Appendix G.

**Kidney Physiology: Mechanisms of Urine Formation**

Urine formation and the adjustment of blood composition involve three major processes: **glomerular filtration** by the glomeruli, and **tubular reabsorption** and **tubular secretion** in the renal tubules (Figure 25.10). In addition, the collecting ducts work in concert with the nephrons to make concentrated or dilute urine.
Let’s first look at the big picture to see how the kidneys use these three processes to maintain the volume and chemical makeup of the blood—in other words, how do they “clean” the blood? Conceptually, it’s really very simple. The kidneys “dump” (by glomerular filtration, Figure 25.10, 1) cell- and protein-free blood into a separate “container” (the renal tubules and collecting ducts). From this container, the kidneys reclaim (by tubular reabsorption, Figure 25.10, 2) everything the body needs to keep. This is almost everything—all of the glucose and amino acids, and some 99% of the water, salt, and other components. Anything that is not reabsorbed becomes urine. In addition, some things are selectively added to the container (by tubular secretion, Figure 25.10, 3), fine-tuning the body’s chemical balance.

The volume of blood processed by the kidneys each day is enormous. Of the approximately 1200 ml of blood that passes through the glomeruli each minute, some 650 ml is plasma, and about one-fifth of this (120–125 ml) is forced into the renal tubules. This is equivalent to filtering out your entire plasma volume more than 60 times each day! Considering the magnitude of their task, it is not surprising that the kidneys (which account for only 1% of body weight) consume 20–25% of all oxygen used by the body at rest.

Filtrate and urine are quite different. Filtrate contains everything found in blood plasma except proteins. Urine contains mostly metabolic wastes and unneeded substances. The kidneys process about 180 L (47 gallons!) of blood-derived fluid daily. Of this amount, less than 1% (1.5 L) typically leaves the body as urine; the rest returns to the circulation.

**Step 1: Glomerular Filtration**

- Describe the forces (pressures) that promote or counteract glomerular filtration.
- Compare the intrinsic and extrinsic controls of the glomerular filtration rate.

**Glomerular filtration** is a passive process in which hydrostatic pressure forces fluids and solutes through a membrane (see Chapter 19). The glomeruli can be viewed as simple mechanical filters because filtrate formation does not consume metabolic energy.

The glomerulus is a much more efficient filter than are other capillary beds. One reason is that its filtration membrane has a large surface area and is thousands of times more permeable to water and solutes (Figure 25.9). Furthermore, glomerular blood pressure is much higher than that in other capillary beds (approximately 55 mm Hg as opposed to 18 mm Hg or less), resulting in a much higher net filtration pressure, which we will discuss shortly. As a result of these differences, the kidneys produce about 180 L of filtrate daily, in contrast to the 2 to 4 L formed daily by all other capillary beds of the body combined.

Molecules smaller than 3 nm in diameter—such as water, glucose, amino acids, and nitrogenous wastes—pass freely from the blood into the glomerular capsule. As a result, these substances...
usually show similar concentrations in the blood and the glomerular filtrate. Larger molecules pass with greater difficulty, and those larger than 5 nm are generally barred from entering the tubule. Keeping the plasma proteins in the capillaries maintains the colloid osmotic (oncotic) pressure of the glomerular blood, preventing the loss of all its water to the renal tubules. The presence of proteins or blood cells in the urine usually indicates a problem with the filtration membrane.

Net Filtration Pressure

The net filtration pressure (NFP), responsible for filtrate formation, involves forces acting at the glomerular bed (Figure 25.11). Glomerular hydrostatic pressure (HPg), which is essentially glomerular blood pressure, is the chief force pushing water and solutes out of the blood and across the filtration membrane. Although theoretically the colloid osmotic pressure in the capsular space of the glomerular capsule “pulls” the filtrate into the tubule, this pressure is essentially zero because virtually no proteins enter the capsule.

The HPg is opposed by two forces that inhibit fluid loss from glomerular capillaries. These filtration-opposing forces are (1) colloid osmotic (oncotic) pressure of glomerular blood (OPg) and (2) capsular hydrostatic pressure (HPc) exerted by fluids in the glomerular capsule. Using the values shown in the key to Figure 25.11, we calculate the NFP responsible for forming renal filtrate from plasma as 10 mm Hg:

\[ \text{NFP} = \text{HP}_g - (\text{OP}_g + \text{HP}_c) \]
\[ = 55 \text{ mm Hg} - (30 \text{ mm Hg} + 15 \text{ mm Hg}) \]
\[ = 10 \text{ mm Hg} \]

Glomerular Filtration Rate

The glomerular filtration rate or GFR is the volume of filtrate formed each minute by the combined activity of all 2 million glomeruli of the kidneys. Factors governing filtration rate at the capillary beds are (1) total surface area available for filtration,

Figure 25.10 A schematic, uncoiled nephron showing the three major renal processes that adjust plasma composition. A kidney actually has more than a million nephrons acting in parallel.

Figure 25.11 Forces determining glomerular filtration and filtration pressure. The glomerular hydrostatic (blood) pressure is the major force forcing fluids and solutes out of the blood. This pressure is opposed by the colloid osmotic pressure of the blood and the hydrostatic pressure in the glomerular capsule. The pressure values cited in the diagram are approximate.
(2) filtration membrane permeability, and (3) NFP. In adults the normal GFR in both kidneys is 120–125 ml/min. Because glomerular capillaries are exceptionally permeable and have a huge surface area (collectively equal to the surface area of the skin), huge amounts of filtrate can be produced even with the usual modest NFP of 10 mm Hg. The opposite side of this “coin” is that a drop in glomerular pressure of only 18% stops filtration altogether.

The GFR is directly proportional to the NFP, so any change in any of the pressures acting at the filtration membrane changes both the NFP and the GFR. In the absence of regulation, an increase in arterial (and glomerular) blood pressure in the kidneys increases the GFR. As we shall see in the next section however, GFR is tightly regulated.

Regulation of Glomerular Filtration
GFR is regulated by both intrinsic and extrinsic controls. These two types of controls serve two different (and sometimes opposing) needs. The kidneys need a relatively constant GFR in order to do their job and maintain extracellular homeostasis. On the other hand, the body as a whole needs a constant blood pressure, and therefore a constant blood volume.

Intrinsic controls (renal autoregulation) act locally within the kidney to maintain GFR, while extrinsic controls by the nervous and endocrine systems maintain blood pressure. In extreme changes of blood pressure (mean arterial pressure less than 80 or greater than 180 mm Hg), extrinsic controls take precedence over intrinsic controls. Next we examine both types of control.

Intrinsic Controls: Renal Autoregulation
By adjusting its own resistance to blood flow, a process called renal autoregulation, the kidney can maintain a nearly constant GFR despite fluctuations in systemic arterial blood pressure. Renal autoregulation entails two types of controls: (1) a myogenic mechanism and (2) a tubuloglomerular feedback mechanism (Figure 25.12, left side).

1. Myogenic mechanism. The myogenic mechanism (mi’o-jen’ik) reflects the tendency of vascular smooth muscle to contract when stretched. Increasing systemic blood pressure causes the afferent arterioles to constrict, which restricts blood flow into the glomerulus and prevents glomerular blood pressure from rising to damaging levels. Declining systemic blood pressure causes dilation of afferent arterioles and raises glomerular hydrostatic pressure. Both responses help maintain a normal GFR.

2. Tubuloglomerular feedback mechanism. Autoregulation by the flow-dependent tubuloglomerular feedback mechanism is “directed” by the macula densa cells of the juxtamedullary apparatus (see Figure 25.8). These cells, located in the walls of the ascending limb of Henle’s loop, respond to filtrate NaCl concentration (which varies directly with filtrate flow rate). When GFR increases, there is insufficient time for reabsorption and the concentration of NaCl in the filtrate remains high. This causes the macula densa cells to release a vasoconstrictor chemical (probably ATP) that causes intense constriction of the afferent arteriole. This constriction hinders blood flow into the glomerulus, which decreases the NFP and GFR, allowing more time for filtrate processing (NaCl reabsorption).

On the other hand, when the macula densa cells are exposed to slowly flowing filtrate with its low NaCl concentration, ATP release is inhibited, causing vasodilation of the afferent arterioles, as shown in Figure 25.12. This allows more blood to flow into the glomerulus, thus increasing the NFP and GFR.

Autoregulatory mechanisms maintain a relatively constant GFR over an arterial pressure range from about 80 to 180 mm Hg. Consequently, our normal day-to-day activities (such as exercise, sleep, or changes in posture) do not cause large changes in water and solute excretion. However, the intrinsic controls cannot handle extremely low systemic blood pressure, such as might result from serious hemorrhage (hypovolemic shock). Once the mean arterial pressure drops below 80 mm Hg, autoregulation ceases.

Extrinsic Controls: Neural and Hormonal Mechanisms
The purpose of the extrinsic controls regulating the GFR is to maintain systemic blood pressure—sometimes to the detriment of the kidneys (Figure 25.12, right side).

1. Sympathetic nervous system controls. Neural renal controls serve the needs of the body as a whole. When the volume of the extracellular fluid is normal and the sympathetic nervous system is at rest, the renal blood vessels are dilated and renal autoregulation mechanisms prevail. However, during extreme stress or emergency when it is necessary to shunt blood to vital organs, neural controls may overcome renal autoregulatory mechanisms.

Norepinephrine released by sympathetic nerve fibers (and epinephrine released by the adrenal medulla) acts on alpha-adrenergic receptors on vascular smooth muscle, strongly constricting afferent arterioles, thereby inhibiting filtrate formation. This, in turn, indirectly trips the renin-angiotensin mechanism by stimulating the macula densa cells. The sympathetic nervous system also directly stimulates the granular cells to release renin, as we discuss next.

2. Renin-angiotensin mechanism. The renin-angiotensin mechanism is triggered when various stimuli cause the granular cells to release the hormone renin. Renin acts enzymatically on angiotensinogen, a plasma globulin made by the liver, converting it to angiotensin I. This, in turn, is converted to angiotensin II by angiotensin converting enzyme (ACE) associated with the capillary endothelium in various body tissues, particularly the lungs.

Angiotensin II acts in five ways to stabilize systemic blood pressure and extracellular fluid volume. (1) As a potent vasoconstrictor, angiotensin II activates smooth muscle of arterioles throughout the body, raising mean arterial blood pressure. (2) Angiotensin II stimulates reabsorption of sodium, both directly by acting on renal tubules and indirectly by triggering the release of aldosterone from the adrenal cortex. Because water follows sodium osmotically, blood volume and blood pressure rise (Figure 25.12). (3) Angiotensin II stimulates the hypothalamus to release
antidiuretic hormone and activates the hypothalamic thirst center, both of which increase blood volume (see Chapter 26). (4) Angiotensin II also increases fluid reabsorption by decreasing peritubular capillary hydrostatic pressure. This pressure drop occurs because the efferent arterioles constrict, and the downstream drop in hydrostatic pressure allows more fluid to move back into the peritubular capillary bed. (5) Finally, angiotensin II targets the glomerular mesangial cells, causing them to contract and reduce the GFR by decreasing the total surface area of glomerular capillaries available for filtration.

While this seems like a daunting list at first, it will help if you remember that all of the effects of angiotensin II are aimed at restoring blood volume and blood pressure. Of angiotensin II’s many effects, the first two are the most important.
Several factors acting independently or collectively can trigger renin release.

- **Reduced stretch of the granular cells.** A drop in mean systemic blood pressure below 80 mm Hg (as might be due to hemorrhage, dehydration, etc.) reduces the stretch of the granular cells and stimulates them to release more renin.

- **Stimulation of the granular cells by input from activated macula densa cells.** When macula densa cells sense low NaCl concentration (slowly moving filtrate), they signal the granular cells to release renin. This signal may be decreased release of ATP (also thought to be the tubuloglomerular feedback messenger), increased release of the prostaglandin PGE₂, or both.

- **Direct stimulation of granular cells via β₁-adrenergic receptors by renal sympathetic nerves.**

**Other Factors Affecting GFR** Renal cells produce a battery of chemicals, many of which act as paracines (local signaling molecules).

1. **Prostaglandin E₂ (PGE₂):** The vasodilatory paracrine PGE₂, in addition to its role discussed above, counteracts vasoconstriction by norepinephrine and angiotensin II within the kidney. The adaptive value of these opposing actions is to prevent renal damage while responding to body demands to increase peripheral resistance.

2. **Intrarenal angiotensin II:** Although we usually think of angiotensin II as a hormone, the kidney makes its own, locally acting angiotensin II that reinforces the effects of hormonal angiotensin II. It also dampens the resulting renal vasoconstriction by causing PGE₂ release.

3. **Adenosine:** Adenosine can be released as such or produced extracellularly from ATP released by macula densa cells. Although it functions as a vasodilator systemically, adenosine constricts the renal vasculature.

**HOMEOSTATIC IMBALANCE** Abnormally low urinary output (less than 50 ml/day), called **anuria** (ah-nu’re-ah), may indicate that glomerular blood pressure is too low to cause filtration. However, renal failure and anuria can result from situations in which the nephrons cease to function for a variety of other reasons, including acute nephritis, transfusion reactions, and crush injuries.

**CHECK YOUR UNDERSTANDING**

7. Extrinsic and intrinsic controls of GFR serve two different purposes. What are they?

8. Calculate net filtration pressure given the following values: glomerular hydrostatic pressure = 50 mm Hg, blood colloid osmotic pressure = 25 mm Hg, capsular hydrostatic pressure = 20 Hg.

9. Describe two main ways in which angiotensin II increases blood pressure and blood volume.

For answers, see Appendix G.

**Step 2: Tubular Reabsorption**

- Describe the mechanisms underlying water and solute reabsorption from the renal tubules into the peritubular capillaries.

- Describe how sodium and water reabsorption is regulated in the distal tubule and collecting duct.

Our total plasma volume filters into the renal tubules about every 22 minutes, so all our plasma would be drained away as urine in less than 30 minutes were it not for the fact that most of the tubule contents are quickly reclaimed and returned to the blood. This reclamation process, called **tubular reabsorption,** is a selective **transepithelial process** that begins as soon as the filtrate enters the proximal tubules. To reach the blood, reabsorbed substances follow either the **transcellular or paracellular route** (Figure 25.13). In the transcellular route, transported substances move through the **luminal membrane,** the cytosol, and the **basolateral membrane** of the tubule cell and then the endothelium of the peritubular capillaries. Movement of substances in the paracellular route between the tubule cells is limited because these cells are connected by tight junctions. In the proximal nephron, however, these tight junctions are “leaky” and allow some important ions (Ca²⁺, Mg²⁺, K⁺, and some Na⁺) through the paracellular route.

Given healthy kidneys, virtually all organic nutrients such as glucose and amino acids are completely reabsorbed to maintain or restore normal plasma concentrations. On the other hand, the reabsorption of water and many ions is continuously regulated and adjusted in response to hormonal signals. Depending on the substances transported, the reabsorption process may be passive (no ATP required) or active (at least one of its steps is driven by ATP directly or indirectly).

**Sodium Reabsorption**

Sodium ions are the single most abundant cation in the filtrate, and about 80% of the energy used for active transport is devoted to their reabsorption. Sodium reabsorption is almost always active and via the transcellular route.

In general, two basic processes that promote active Na⁺ reabsorption occur in each tubule segment. First, Na⁺ is actively transported out of the tubule cell by **primary active transport**—a Na⁺-K⁺ ATPase pump present in the basolateral membrane (Figure 25.14, 1). From there, Na⁺ is swept along by the bulk flow of water into adjacent peritubular capillaries. This bulk flow of water and solutes into the peritubular capillaries is rapid because the blood there has low hydrostatic pressure and high osmotic pressure (remember, most proteins remain in the blood instead of being filtered out into the tubule).

Second, active pumping of Na⁺ from the tubule cells results in a strong electrochemical gradient that favors its passive entry at the luminal face via **secondary active transport** (symport or antiport) carriers (Figure 25.14, 2, 3) or via facilitated diffusion through channels. This occurs because (1) the pump maintains the intracellular Na⁺ concentration at low levels, and (2) the K⁺ pumps into the tubule cells almost immediately diffuses out into the interstitial fluid via leakage channels, leaving the interior of the tubule cell with a net negative charge.
Passive transport
the substance they transport—the excess is excreted in urine.

Reabsorption of Nutrients, Water, and Ions
The reabsorption of Na\(^+\) by primary active transport provides the energy and the means for reabsorbing almost every other substance, including water. Substances reabsorbed by secondary active transport (the “push” comes from the gradient created by Na\(^+\)-K\(^+\) pumping at the basolateral membrane) include glucose, amino acids, lactate, and vitamins. In nearly all these cases, a luminal carrier moves Na\(^+\) down its concentration gradient as it cotransports (symports) another solute (Figure 25.14, 3). Cotransported solutes diffuse (via different transport proteins) across the basolateral membrane before moving into the peritubular capillaries. Although there is some overlap of carriers, the transport systems for the various solutes are quite specific and limited.

There is a transport maximum (T\(_m\)) for nearly every substance that is reabsorbed using a transport protein in the membrane. The T\(_m\) (reported in mg/min) reflects the number of transport proteins in the renal tubules available to ferry each particular substance. In general, there are plenty of transporters and therefore high T\(_m\) values for substances such as glucose that need to be retained, and few or no transporters for substances of no use to the body.

When the transporters are saturated—that is, all bound to the substance they transport—the excess is excreted in urine. This is what happens in individuals who become hyperglycemic because of uncontrolled diabetes mellitus. As plasma levels of glucose approach and exceed 180 mg/dl, the glucose T\(_m\) is exceeded and large amounts of glucose may be lost in the urine even though the renal tubules are still functioning normally.

In passive tubular reabsorption, which encompasses osmosis, diffusion, and facilitated diffusion, substances move down their electrochemical gradients without the use of ATP. The movement of Na\(^+\) and other solutes establishes a strong osmotic gradient, and water moves by osmosis into the peritubular capillaries, a process aided by transmembrane proteins called aquaporins that form water channels across cell membranes (Figure 25.14, 4). In continuously water-permeable regions of the renal tubules, such as the PCT, aquaporins are constant components of the tubule cell membranes. Because these channels are always present, the body is “obliged” to absorb water in the proximal nephron regardless of its state of over- or underhydration. This water flow is referred to as obligatory water reabsorption. Aquaporins are virtually absent in the luminal membranes of the collecting duct unless antidiuretic hormone (ADH) is present.

As water leaves the tubules, the concentration of solutes in the filtrate increases and, if able, they too begin to follow their concentration gradients into the peritubular capillaries. This phenomenon of solutes following solvent explains the passive reabsorption of a number of solutes present in the filtrate, such as lipid-soluble substances, certain ions, and some urea (Figure 25.14, 5, 6). It also explains in part why lipid-soluble drugs and environmental toxins are difficult to excrete: Since lipid-soluble compounds can generally pass through membranes,
they will follow their concentration gradients and be reabsorbed, even if this is "not desirable."

As they move through the tubule cells into the peritubular capillary blood, Na\(^+\) ions also establish an electrical gradient that favors passive reabsorption of anions (primarily Cl\(^-\)/H\(_2\)O\(_2\)) to restore electrical neutrality in the filtrate and plasma (Figure 25.14).

Any plasma proteins that squeeze through the filtration membrane are removed from the filtrate in the proximal tubule by endocytosis and digested to their amino acids, which are moved into the peritubular blood.

Reabsorptive Capabilities of the Renal Tubules and Collecting Ducts

Table 25.1 compares the reabsorptive abilities of various regions of the renal tubules and collecting ducts.

**Proximal Convoluted Tubule** The entire renal tubule is involved in reabsorption to some degree, but the PCT cells are by far the most active “reabsorbers” and the events just described occur mainly in this tubular segment. Normally, the PCT reabsorbs all of the glucose, lactate, and amino acids in the filtrate and 65% of the Na\(^+\) and water. Additionally, 80% of the filtered bicarbonate (HCO\(_3^-\)), 60% of the Cl\(^-\), and about 55% of the K\(^+\) are reclaimed in the PCT. The bulk of the reabsorption of electrolytes is accomplished by the time the filtrate reaches the loop of Henle. Nearly all of the uric acid and about half of the urea are reabsorbed in the proximal tubule, but both are later secreted back into the filtrate.

**Loop of Henle** Beyond the PCT, the permeability of the tubule epithelium changes dramatically. Here, for the first time, water reabsorption is not coupled to solute reabsorption. Water can leave the descending limb of the loop of Henle but not the ascending limb, where aquaporins are scarce or absent in the tubule membrane. For reasons that we will explain shortly, these permeability differences play a vital role in the kidneys’ ability to form dilute and concentrated urine.

The rule for water is that it leaves the descending (but not the ascending) limb of Henle’s loop, and the opposite is true for solutes. Virtually no solute reabsorption occurs in the descending
### Table 25.1  Reabsorption Capabilities of Different Segments of the Renal Tubules and Collecting Ducts

<table>
<thead>
<tr>
<th>TUBULE SEGMENT</th>
<th>SUBSTANCE REABSORBED</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal Convoluted Tubule</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium ions (Na⁺)</td>
<td>Primary active transport via basolateral Na⁺-K⁺ pump; sets up electrochemical gradient for passive solute diffusion, osmosis, and secondary active transport (cotransport) with Na⁺</td>
<td></td>
</tr>
<tr>
<td>Virtually all nutrients (glucose, amino acids, vitamins)</td>
<td>Secondary active transport with Na⁺</td>
<td></td>
</tr>
<tr>
<td>Cations (K⁺, Mg²⁺, Ca²⁺, and others)</td>
<td>Passive paracellular diffusion driven by electrochemical gradient</td>
<td></td>
</tr>
<tr>
<td>Cl⁻</td>
<td>Passive paracellular diffusion driven by electrochemical gradient</td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>Secondary active transport linked to H⁺ secretion and Na⁺ reabsorption (see Chapter 26)</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>Osmosis; driven by solute reabsorption (obligatory)</td>
<td></td>
</tr>
<tr>
<td>Lipid-soluble solutes</td>
<td>Passive diffusion driven by the concentration gradient created by reabsorption of water</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>Passive paracellular diffusion driven by chemical gradient; some transcellular facilitated diffusion may also occur</td>
<td></td>
</tr>
<tr>
<td>Small proteins</td>
<td>Endocytosed by tubule cells and digested to amino acids within tubule cells</td>
<td></td>
</tr>
<tr>
<td><strong>Loop of Henle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending limb</td>
<td>Water</td>
<td>Osmosis</td>
</tr>
<tr>
<td>Ascending limb</td>
<td>Na⁺, Cl⁻, K⁺</td>
<td>Secondary active transport of Cl⁻, Na⁺, and K⁺ via Na⁺-Cl⁻ cotransporter in thick portion; paracellular diffusion; Na⁺-H⁺ antiport</td>
</tr>
<tr>
<td>Ca²⁺, Mg²⁺</td>
<td>Passive paracellular diffusion driven by electrochemical gradient</td>
<td></td>
</tr>
<tr>
<td><strong>Distal Convoluted Tubule</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺, Cl⁻</td>
<td>Primary active Na⁺ transport at basolateral membrane; secondary active transport at luminal membrane via Na⁺-Cl⁻ symporter and channels; aldosterone-regulated at distal portion</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Passive uptake via PTH-modulated channels in luminal membrane; primary and secondary active transport (antiport with Na⁺) in basolateral membrane</td>
<td></td>
</tr>
<tr>
<td><strong>Collecting Duct</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺, H⁺, K⁺, HCO₃⁻, Cl⁻</td>
<td>Primary active transport of Na⁺ (requires aldosterone); passive paracellular diffusion of some Cl⁻; cotransport of H⁺, Cl⁻, and HCO₃⁻; K⁺ is both reabsorbed and secreted (aldosterone dependent), usually resulting in net K⁺ secretion</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>Osmosis; controlled (facultative) water reabsorption; ADH required to insert aquaporins</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>Facilitated diffusion in response to concentration gradient in the deep medulla region; recycles and contributes to medullary osmotic gradient</td>
<td></td>
</tr>
</tbody>
</table>
limb, but both active and passive reabsorption of solute occurs in the ascending limb. In the thin portion of the ascending limb, Na\(^+\) moves passively down the concentration gradient created by water reabsorption. A Na\(^+\)-K\(^+\)-2Cl\(^-\) symporter is the main means of Na\(^+\) entry at the luminal surface in the thick portion of the ascending limb. A Na\(^+\)-K\(^+\) ATPase operates at the basolateral membrane to create the ionic gradient that drives the symporter. The thick ascending limb also has Na\(^+\)-H\(^+\) antiporters. In addition, some 50% of Na\(^+\) passes via the paracellular route in this region.

**Distal Convoluted Tubule and Collecting Duct** By the time the DCT is reached, only about 10% of the originally filtered NaCl and 25% of the water remain in the tubule. Most reabsorption from this point depends on the body’s needs at the time and is regulated by hormones (mainly aldosterone for Na\(^+\), ADH for water, and PTH for Ca\(^{2+}\) as we will describe in Chapter 26). If necessary, nearly all of the water and Na\(^+\) reaching these regions can be reclaimed.

In the absence of antidiuretic hormone (ADH), the collecting ducts are relatively impermeable to water. Reabsorption of more water depends on the presence of ADH, which makes the collecting ducts more permeable to water by inserting aquaporins into the collecting duct luminal membranes.

Aldosterone “fine-tunes” reabsorption of the remaining Na\(^+\). Decreased blood volume or blood pressure, low extracellular Na\(^+\) concentration (hyponatremia), or high extracellular K\(^+\) concentration (hyperkalemia) can cause the adrenal cortex to release aldosterone to the blood. Except for hyperkalemia (which directly stimulates the adrenal cortex to secrete aldosterone), these conditions promote the renin-angiotensin mechanism, which in turn prompts the release of aldosterone (see Figure 25.12). Aldosterone targets the principal cells of the collecting ducts and cells of the distal portion of the DCT (producing them to synthesize and retain more luminal Na\(^+\) and K\(^+\) channels, and more basolateral Na\(^+\)-K\(^+\) ATPases). As a result, little or no Na\(^+\) leaves the body in urine. In the absence of aldosterone, much less Na\(^+\) is reabsorbed by these segments, resulting in Na\(^+\) losses of about 2% of Na\(^+\) filtered daily, an amount incompatible with life.

Physiologically, aldosterone’s role is to increase blood volume, and therefore blood pressure, by enhancing Na\(^+\) reabsorption. In general, water follows Na\(^+\) if it can. Aldosterone also reduces blood K\(^+\) concentrations because aldosterone-induced reabsorption of Na\(^+\) is coupled to K\(^+\) secretion in the principal cells. That is, as Na\(^+\) enters, K\(^+\) moves into the lumen.

In contrast to aldosterone, which acts to conserve Na\(^+\), atrial natriuretic peptide (ANP) reduces blood Na\(^+\), thereby decreasing blood volume and blood pressure. Released by cardiac atrial cells when blood volume or blood pressure is elevated, ANP exerts several effects that lower blood Na\(^+\) content, including direct inhibition of Na\(^+\) reabsorption at the collecting ducts. These actions are described more fully in Chapter 26 (see Figure 26.9).

**Step 3: Tubular Secretion**

- Describe the importance of tubular secretion and list several substances that are secreted.

The failure of tubule cells to reabsorb some solutes is an important way of clearing plasma of unwanted substances. Another way is **tubular secretion**—essentially, reabsorption in reverse. Substances such as H\(^+\), K\(^+\), NH\(_4\)\(^+\), creatinine, and certain organic acids either move into the filtrate from the peritubular capillaries through the tubule cells or are synthesized in the tubule cells and secreted. As a result, the urine eventually excreted contains both filtered and secreted substances. With one major exception (K\(^+\)), the PCT is the main site of secretion, but the cortical parts of the collecting ducts are also active (see Figure 25.18, p. 983).

Tubular secretion is important for:

1. **Disposing of substances, such as certain drugs and metabolites, that are tightly bound to plasma proteins.** Because plasma proteins are generally not filtered, the substances they bind are not filtered and so must be secreted.

2. **Eliminating undesirable substances or end products that have been reabsorbed by passive processes.** Urea and uric acid, two nitrogenous wastes, are both handled in this way. Urea handling in the nephron is complicated and will be discussed on p. 981, but the net effect is that 40–50% of the urea in the filtrate is excreted.

3. **Ridding the body of excess K\(^+\).** Because virtually all K\(^+\) present in the filtrate is reabsorbed in the PCT and ascending loop of Henle, nearly all K\(^+\) in urine is from aldosterone-driven active tubular secretion into the late DCT and collecting ducts.

4. **Controlling blood pH.** When blood pH drops toward the acidic end of its homeostatic range, the renal tubule cells actively secrete more H\(^+\) into the filtrate and retain and generate more HCO\(_3^-\) (a base). As a result, the blood pH rises and the urine drains off the excess H\(^+\). Conversely, when blood pH approaches the alkaline end of its range, Cl\(^-\) is reabsorbed instead of HCO\(_3^-\), which is allowed to leave the body in urine. We will discuss the kidneys’ role in pH homeostasis in more detail in Chapter 26.

**CHECK YOUR UNDERSTANDING**

10. In what part of the nephron does the majority of reabsorption occur?

11. How are primary and secondary active transport processes (both shown in Figure 25.14) different?

12. How does the movement of Na\(^+\) drive the reabsorption of water and solutes?

13. List several substances that are secreted into the kidney tubules.

For answers, see Appendix G.

**Regulation of Urine Concentration and Volume**

- Describe the mechanisms responsible for the medullary osmotic gradient.

- Explain formation of dilute versus concentrated urine.
One crucial renal function is to keep the solute concentration of body fluids constant. We use osmolality to measure the amount of solutes in body fluids. A solution’s osmolality (oz’mo-lal’-it) is the number of solute particles dissolved in 1 kg of water and reflects the solution’s ability to cause osmosis. For any solution interfering with a selectively permeable membrane, this ability, called osmotic activity, is determined only by the number of solute particles unable to pass through the membrane (called nonpenetrating solute particles) and is independent of their type. For example, 10 sodium ions have the same osmotic activity as 10 glucose molecules or 10 amino acids in the same volume of water.

Because 1 osmol (equivalent to 1 mole of particles) is a fairly large unit, the milliosmol (mOsm) (mil’e-oz’mol), equal to 0.001 osmol, is generally used. In the discussion that follows, we use mOsm to mean mOsm/kg.

The kidneys keep the solute load of body fluids constant at about 300 mOsm, the osmotic concentration of blood plasma, by regulating urine concentration and volume. The kidneys accomplish this feat using countercurrent mechanisms. In the kidneys, the term countercurrent means that fluid flows in opposite directions through adjacent segments of the same tube connected by a hairpin turn (see Figure 25.16). These countercurrent mechanisms are (1) the interaction between the fluid of filtrate through the ascending and descending limbs of the long loops of Henle of juxtamedullary nephrons (the countercurrent multiplier), and (2) the flow of blood through the ascending and descending portions of the vasa recta blood vessels (the countercurrent exchanger).* These countercurrent mechanisms establish and maintain an osmotic gradient extending from the cortex through the depths of the medulla (Figure 25.15). This gradient allows the kidneys to vary urine concentration dramatically.

The osmolality of the filtrate entering the PCT is identical to that of plasma, about 300 mOsm. As we described earlier, because of PCT reabsorption of water and solutes, the filtrate is still isosmotic with plasma by the time it reaches the descending limb of the loop of Henle. However, its osmolality increases from 300 to about 1200 mOsm in the deepest part of the medulla (Figure 25.16a).

How does this increase in concentration occur? The answer lies in the unique workings of the long loops of Henle of the juxtamedullary nephrons, and the vasa recta. Notice in Figure 25.16 that in each case the fluids involved—filtrate in the loops of Henle and blood in the vasa recta—first descend and then ascend through parallel limbs.

The Countercurrent Multiplier

First, we will follow filtrate processing through the loop of Henle, as portrayed in Figure 25.16a, to see how the loop functions as a countercurrent multiplier to establish the osmotic gradient. The countercurrent multiplier functions because of two factors:

1. **The descending limb of the loop of Henle is relatively impermeable to solutes and freely permeable to water.** Water passes osmotically out of the filtrate all along this limb because the osmolality of the medullary interstitial fluid increases all along the descending limb. (We will explain the mechanism of this increase shortly.) The filtrate osmolality reaches its highest point (1200 mOsm) at the bend of the loop.

2. **The ascending limb is permeable to solutes, but not to water.** As the filtrate rounds the bend into the ascending limb, the tubule permeability changes, becoming impermeable to water and selectively permeable to salt. The Na⁺ and Cl⁻ concentration in the filtrate entering the ascending limb is very high (and interstitial fluid concentrations of these two ions are lower). Na⁺ and Cl⁻ reabsorption in
the ascending limb is both passive (mostly in the thin segment) and active (via the Na⁺-K⁺-2Cl⁻ cotransporter in the thick segment). As Na⁺ and Cl⁻ are extruded from the filtrate into the medullary interstitial fluid, they contribute to the high osmolality there. Because it loses salt but not water, the filtrate in the ascending limb becomes increasingly dilute. Finally, at 100 mOsm at the DCT, it is hypo-osmotic, or hypotonic, to blood plasma and cortical interstitial fluids.

Notice in Figure 25.16 that there is a constant difference in filtrate concentration (200 mOsm) between the two limbs of the loop of Henle, and between the ascending limb and the interstitial fluid. This difference reflects the power of the ascending limb’s NaCl pumps, which are just powerful enough to create a 200 mOsm difference between the inside and outside of the ascending limb. A 200 mOsm gradient by itself would not be enough to allow excretion of very concentrated urine. The beauty of this system lies in the fact that, because of countercurrent flow, the loop of

**Figure 25.16 Countercurrent mechanism for establishing and maintaining the medullary osmotic gradient.** Notice in (a) that the descending limb of the loop of Henle produces increasingly salty filtrate, while the ascending limb uses this high salt concentration to establish the high osmolality of the interstitial fluid in the medulla and the medullary osmotic gradient.
Henle is able to “multiply” these small changes in solute concentration into a gradient change along the vertical length of the loop (both inside and outside) that is closer to 900 mOsm (1200 mOsm – 300 mOsm). Although the two limbs of the loop of Henle are not in direct contact with each other, they are close enough to influence each other’s exchanges with the interstitial fluid they share. Water diffusing out of the descending limb leaves behind an increasingly “salty” filtrate that the ascending limb then uses to raise the osmolality of the medullary interstitial fluid. Furthermore, the more NaCl the ascending limb extrudes, the more water diffuses out of the descending limb and the saltier the filtrate in the descending limb becomes. This establishes a positive feedback cycle that produces the high osmolality of the fluids in the descending limb and the interstitial fluid.

Urea Recycling and the Medullary Osmotic Gradient
In addition to Na⁺, urea forms an important part of the medullary osmotic gradient. As shown in Figure 25.17, urea enters the filtrate by facilitated diffusion in the ascending thin limb of the loop of Henle. As the filtrate moves on, water is usually reabsorbed in the cortical collecting duct, leaving urea behind. When filtrate reaches the collecting duct in the deep medullary region, urea, now highly concentrated, is transported by facilitated diffusion out of the tubule into the interstitial fluid of the medulla, forming a pool of urea that recycles back into the thin limb of the loop of Henle. This pool of urea contributes substantially to the high osmolality in the medulla.

Antidiuretic hormone (ADH), which stimulates excretion of highly concentrated urine (as we will see shortly), enhances urea transport in the medullary collecting duct. When ADH is present, urea recycling is enhanced, the medullary osmotic gradient is enhanced, and more concentrated urine can be formed.

The Countercurrent Exchanger
As shown in Figure 25.16b, the vasa recta function as countercurrent exchangers, maintaining the osmotic gradient established by the cycling of salt while delivering blood to cells in the area and removing reabsorbed water and solutes. These vessels receive only about 10% of the renal blood supply, making blood flow through the vasa recta sluggish. Moreover, they are freely permeable to water and NaCl, allowing blood to make passive exchanges with the surrounding interstitial fluid. Consequently, as the blood flows into the medullary depths, it loses water and gains salt (becomes hypertonic). Then, as it emerges from the medulla into the cortex, the process is reversed: It picks up water and loses salt. The water picked up by the ascending vasa recta includes not only water lost from the descending vasa recta, but also water reabsorbed from the loop of Henle and collecting duct. As a result, the volume of blood at the end of the vasa recta is greater than at the beginning.

Because blood leaving and reentering the cortex via the vasa recta has nearly the same solute concentration, the vessels of the vasa recta act as countercurrent exchangers. This system does not create the medullary gradient, but it protects it by preventing rapid removal of salt from the medullary interstitial space, and by removing reabsorbed water.

Formation of Dilute or Concentrated Urine
As we have just seen, the kidneys go to a great deal of trouble to create the medullary osmotic gradient. What is its purpose? Without this gradient, you would not be able to raise the concentration of urine above 300 mOsm—the osmolality of interstitial fluid. As a result, you would not be able to excrete excess solutes to lower your body’s osmolality.

Controlling the reabsorption of water from filtrate in the collecting ducts in order to adjust the body’s osmolality is the job of antidiuretic hormone (ADH). As its name reveals, ADH inhibits diuresis (di’u-re’sis), or urine output. It accomplishes this via a second-messenger system using cyclic AMP that causes insertion of aquaporins into the luminal membrane of the principal cells of the collecting ducts. The amount of ADH determines the number of aquaporins in the collecting ducts and so the amount of water that is reabsorbed there.

Dilute Urine
Tubular filtrate is diluted as it travels through the ascending limb of the loop of Henle, so all the kidney needs to do to secrete dilute (hypo-osmotic) urine is allow the filtrate to continue on its way into the renal pelvis (Figure 25.17a). When ADH is not being released by the posterior pituitary, that is exactly what happens. The collecting ducts remain essentially impermeable to water due to the absence of aquaporins in their luminal cell membranes, and no further water reabsorption occurs. Moreover, as noted, Na⁺ and selected other ions can be removed from the filtrate by DCT and collecting duct cells so that urine becomes even more dilute before entering the renal pelvis. The osmolality of urine can plunge as low as 50 mOsm, about one-sixth the concentration of glomerular filtrate or blood plasma.

Concentrated Urine
The formation of concentrated urine depends on the medullary osmotic gradient and the presence of ADH. In the distal tubules, the filtrate osmolality is approximately 100 mOsm, but as the filtrate flows through the collecting ducts and is subjected to the hyperosmolar conditions in the medulla, water rapidly leaves the filtrate, followed by urea (Figure 25.17b and Figure 25.18e). Depending on the amount of ADH released (which is keyed to the level of body hydration), urine concentration may rise as high as 1200 mOsm, the concentration of interstitial fluid in the deepest part of the medulla. With maximal ADH secretion, up to 99% of the water in the filtrate is reabsorbed and returned to the blood, and half a liter per day of highly concentrated urine is excreted. The ability of our kidneys to produce such concentrated urine is critically tied to our ability to survive without water. Water reabsorption that depends on the presence of ADH is called facultative water reabsorption.

ADH is released more or less continuously unless the blood solute concentration drops too low. Release of ADH is enhanced by any event that raises plasma osmolality above 300 mOsm, such as sweating or diarrhea, or by greatly reduced blood volume or blood pressure (see Chapter 26). Although release of ADH is the “signal” to produce concentrated urine that opens
the door for water reabsorption (through aquaporins), the kidneys’ ability to respond to this signal depends on the high medullary osmotic gradient.

Diuretics

There are several types of diuretics, chemicals that enhance urinary output. An osmotic diuretic is a substance that is not reabsorbed and that carries water out with it (for example, the high blood glucose levels of a diabetes mellitus patient). Alcohol, essentially a sedative, encourages diuresis by inhibiting release of ADH. Other diuretics increase urine flow by inhibiting Na\(^+\) reabsorption and the obligatory water reabsorption that normally follows. Examples include caffeine (found in coffee, tea, and colas) and many drugs prescribed for hypertension or the edema of congestive heart failure. Common diuretics inhibit Na\(^+\)/H\(^+\) associated symporters. “Loop diuretics” [like furosemide (Lasix)] are powerful because they inhibit formation of the medullary gradient by acting at the ascending limb of Henle’s loop. Thiazides are less potent and act at the DCT.

Figure 25.17 Mechanisms for forming dilute and concentrated urine. (a) In the absence of ADH, dilute filtrate produced by the countercurrent mechanism remains dilute as it passes through the collecting duct. (b) In the presence of maximal ADH, concentrated urine is excreted. ADH causes insertion of aquaporins in luminal membranes of principal cells of the collecting duct. Consequently water rapidly leaves the filtrate in the collecting duct. ADH also enhances urea recycling by increasing the number of urea transporters. More urea diffuses out of the collecting duct, contributing to the medullary osmotic gradient.
Chapter 25  The Urinary System

Cortex

Outer medulla

Inner medulla

(a) Proximal convoluted tubule:
- 65% of filtrate volume reabsorbed
- Na⁺, glucose, amino acids, and other nutrients actively transported; H₂O and many ions follow passively
- H⁺ and NH₄⁺ secretion and HCO₃⁻ reabsorption to maintain blood pH (see Chapter 26)
- Some drugs are secreted

(b) Descending limb of loop of Henle
- Freely permeable to H₂O
- Not permeable to NaCl
- Filtrate becomes increasingly concentrated as H₂O leaves by osmosis

(c) Ascending limb of loop of Henle
- Impermeable to H₂O
- Permeable to NaCl
- Filtrate becomes increasingly dilute as salt is reabsorbed

(d) Distal convoluted tubule
- Na⁺ reabsorption regulated by aldosterone
- Ca²⁺ reabsorption regulated by parathyroid hormone (PTH)
- Cl⁻ cotransported with Na⁺

(e) Collecting duct
- H₂O reabsorption through aquaporins regulated by ADH
- Na⁺ reabsorption and K⁺ secretion regulated by aldosterone
- H⁺ and HCO₃⁻ reabsorption or secretion to maintain blood pH (see Chapter 26)
- Urea reabsorption increased by ADH

Figure 25.18 Summary of tubular reabsorption and secretion. The glomerulus provides the filtrate processed by the renal tubule. The various regions of the renal tubule carry out reabsorption and secretion and maintain a gradient of osmolality within the medullary interstitial fluid. Varying osmolality at different points in the interstitial fluid is symbolized by gradients of color in the overview figure at left. (a–d) The main transport functions of the four regions of the nephron tubule. (e) Summary of transport activities occurring in both the cortical and medullary regions of the collecting duct.
Renal Clearance

- Define renal clearance and explain how this value summarizes the way a substance is handled by the kidney.

Renal clearance refers to the volume of plasma that is cleared of a particular substance in a given time, usually 1 minute. Renal clearance tests are done to determine the GFR, which allows us to detect glomerular damage and follow the progress of renal disease.

The renal clearance rate (RC) of any substance, in ml/min, is calculated from the equation

\[ RC = UV/P \]

where

- \( U \) = concentration of the substance in urine (mg/ml)
- \( V \) = flow rate of urine formation (ml/min)
- \( P \) = concentration of the substance in plasma (mg/ml)

Because it is freely filtered and neither reabsorbed nor secreted by the kidneys, inulin (in’u-lin) is the standard used to determine the GFR. A polysaccharide with a molecular weight of approximately 5000, inulin has a renal clearance value equal to the GFR. When inulin is infused such that its plasma concentration is 1 mg/ml (\( P = 1 \) mg/ml), then generally \( U = 125 \) mg/ml, and \( V = 1 \) ml/min. Therefore, its renal clearance is \( RC = (125 \times 1)/1 = 125 \) ml/min, meaning that in 1 minute the kidneys have removed (cleared) all the inulin present in 125 ml of plasma.

The clearance value tells us about the net handling of a substance by the kidneys. There are three possible cases:

- A clearance value less than that of inulin means that a substance is reabsorbed. An example is urea with an RC of 70 ml/min, meaning that of the 125 ml of glomerular filtrate formed each minute, approximately 70 ml is completely cleared of urea, while the urea in the remaining 55 ml is recovered and returned to the plasma. If the RC is zero (such as for glucose in healthy individuals), reabsorption is complete or the substance is not filtered.
- If the RC is equal to that of inulin, there is no net reabsorption or secretion.
- If the RC is greater than that of inulin, the tubule cells are secreting the substance into the filtrate. This is the case with most drug metabolites. Knowing a drug’s renal clearance value is essential because if it is high, the drug dosage must also be high and administered frequently to maintain a therapeutic level.

Creatinine, which has an RC of 140 ml/min, is freely filtered but also secreted in small amounts. It is often used nevertheless to give a “quick and dirty” estimate of GFR.

**HOMEOSTATIC IMBALANCE**

Chronic renal disease, defined as a GFR of less than 60 ml/min for at least three months, often develops silently and insidiously over many years. Filtrate formation decreases gradually, nitrogenous wastes accumulate in the blood, and the blood pH drifts toward the acidic range. The leading cause of chronic renal disease is diabetes mellitus (44% of new cases), with hypertension a close second (28% of new cases). Other causes include repeated kidney infections, physical trauma, and chemical poisoning by heavy metals.

In renal failure (GFR < 15 ml/min), filtrate formation decreases or stops completely. Ionic and pH imbalances build up and wastes accumulate quickly in the blood. At this point, the treatment options are hemodialysis or a kidney transplant.

Hemodialysis uses an “artificial kidney” apparatus, passing the patient’s blood through a membrane tubing that is permeable only to selected substances. The tubing is immersed in a bathing solution that differs slightly from normal cleansed plasma. As blood circulates through the tubing, substances such as nitrogenous wastes and K⁺ present in the blood (but not in the bath) diffuse out of the blood into the surrounding solution, and substances to be added to the blood, mainly buffers for H⁺ (and glucose for malnourished patients), move from the bathing solution into the blood. In this way, needed substances are retained in the blood or added to it, while wastes and ion excesses are removed.

**CHECK YOUR UNDERSTANDING**

14. Describe the special characteristics of the descending and ascending limbs of the loop of Henle that cause the formation of the medullary osmotic gradient.

15. Under what conditions is ADH released from the posterior pituitary? What effect does ADH have on the collecting ducts?

16. What would you expect the normal clearance value for amino acids to be? Explain.

For answers, see Appendix G.

**Urine**

- Describe the normal physical and chemical properties of urine.
- List several abnormal urine components, and name the condition characterized by the presence of detectable amounts of each.

**Physical Characteristics**

**Color and Transparency**

Freshly voided urine is clear and pale to deep yellow. Its yellow color is due to urochrome (u’ro-krôm), a pigment that results from the body’s destruction of hemoglobin. The more concentrated the urine, the deeper the yellow color.

An abnormal color such as pink or brown, or a smoky tinge, may result from eating certain foods (beets, rhubarb) or may be due to the presence in the urine of bile pigments or blood. Additionally, some commonly prescribed drugs and vitamin supplements alter the color of urine. Cloudy urine may indicate a urinary tract infection.
Odor
Fresh urine is slightly aromatic, but if allowed to stand, it develops an ammonia odor as bacteria metabolize its urea solutes. Some drugs and vegetables alter the usual odor of urine, as do some diseases. For example, in uncontrolled diabetes mellitus the urine smells fruity because of its acetone content.

pH
Urine is usually slightly acidic (around pH 6), but changes in body metabolism or diet may cause the pH to vary from about 4.5 to 8.0. A predominantly acidic diet that contains large amounts of protein and whole wheat products produces acidic urine. A vegetarian (alkaline) diet, prolonged vomiting, and bacterial infection of the urinary tract all cause the urine to become alkaline.

Specific Gravity
Because urine is water plus solutes, a given volume has a greater mass than the same volume of distilled water. The ratio of the mass of a substance to the mass of an equal volume of distilled water is its specific gravity. The specific gravity of distilled water is 1.0 and that of urine ranges from 1.001 to 1.035, depending on its solute concentration.

Chemical Composition
Water accounts for about 95% of urine volume; the remaining 5% consists of solutes. The largest component of urine by weight, apart from water, is urea, which is derived from the normal breakdown of amino acids. Other nitrogenous wastes in urine include uric acid (an end product of nucleic acid metabolism) and creatinine (a metabolite of creatine phosphate, which stores energy for the regeneration of ATP and is found in large amounts in skeletal muscle tissue).

Normal solute constituents of urine, in order of decreasing concentration, are urea, Na⁺, K⁺, PO₄³⁻, SO₄²⁻, creatinine, and uric acid. Much smaller but highly variable amounts of Ca²⁺, Mg²⁺, and HCO₃⁻ are also present in urine.

Unusually high concentrations of any solute, or the presence of abnormal substances such as blood proteins, WBCs (pus), or bile pigments, may indicate pathology (Table 25.2). (Normal urine values are listed in Appendix F.)

Ureters
Describe the general location, structure, and function of the ureters.

The ureters are slender tubes that convey urine from the kidneys to the bladder (Figure 25.1 and Figure 25.19). Each ureter begins at the level of L₂ as a continuation of the renal pelvis.

![Figure 25.19 Pyelogram. This X-ray image was obtained using a contrast medium to show the ureters, kidneys, and bladder.](image-url)
From there, it descends behind the peritoneum and runs obliquely through the posterior bladder wall. This arrangement prevents backflow of urine during bladder filling because any increase in bladder pressure compresses and closes the distal ends of the ureters.

Histologically, the ureter wall has three layers. The transitional epithelium of its lining mucosa is continuous with that of the kidney pelvis superiorly and the bladder medially. Its middle muscularis is composed chiefly of two smooth muscle sheets: the internal longitudinal layer and the external circular layer. An additional smooth muscle layer, the external longitudinal layer, appears in the lower third of the ureter. The adventitia covering the ureter’s external surface is typical fibrous connective tissue (Figure 25.20).

The ureter plays an active role in transporting urine. Incoming urine distends the ureter and stimulates its muscle fibers to contract, propelling urine into the bladder. (Urine does not reach the bladder through gravity alone.) The strength and frequency of the peristaltic waves are adjusted to the rate of urine formation. Each ureter is innervated by both sympathetic and parasympathetic fibers, but neural control of peristalsis appears to be insignificant compared to the way ureteral smooth muscle responds to stretch.

**HOMEOSTATIC IMBALANCE**

On occasion, calcium, magnesium, or uric acid salts in urine may crystallize and precipitate in the renal pelvis, forming renal calculi (kal’ku-li; calculus = little stone), or kidney stones. Most calculi are under 5 mm in diameter and pass through the urinary tract without causing problems. However, larger calculi can obstruct a ureter and block urine drainage. Increasing pressure in the kidney causes excruciating pain, which radiates from the flank to the anterior abdominal wall on the same side. Pain also occurs when the contracting ureter wall closes in on the sharp calculi as they are being eased through a ureter by peristalsis.

Predisposing conditions are frequent bacterial infections of the urinary tract, urine retention, high blood levels of calcium, and alkaline urine. Surgical removal of calculi has been almost entirely replaced by shock wave lithotripsy, a noninvasive procedure that uses ultrasonic shock waves to shatter the calculi. The pulverized, sandlike remnants of the calculi are then painlessly eliminated in the urine. People with a history of kidney stones are encouraged to acidify their urine by drinking cranberry juice and to ingest enough water to keep the urine dilute.

**CHECK YOUR UNDERSTANDING**

17. What are the three major nitrogenous wastes excreted in the urine?
18. A kidney stone blocking a ureter would interfere with urine flow to which organ? Why would the pain occur in waves?

For answers, see Appendix G.

**Urinary Bladder**

Describe the general location, structure, and function of the urinary bladder.

The urinary bladder is a smooth, collapsible, muscular sac that stores urine temporarily. It is located retroperitoneal on the pelvic floor just posterior to the pubic symphysis. The prostate (part of the male reproductive system) lies inferior to the bladder neck, which empties into the urethra. In females, the bladder is anterior to the vagina and uterus.

The interior of the bladder has openings for both ureters and the urethra (Figure 25.21). The smooth, triangular region of the bladder base outlined by these three openings is the trigone (tri’gôn; trigon = triangle), important clinically because infections tend to persist in this region.

The bladder wall has three layers: a mucosa containing transitional epithelium, a thick muscular layer, and a fibrous adventitia (except on its superior surface, where it is covered by the peritoneum). The muscular layer, called the detrusor muscle (de-tru’sor; “to thrust out”), consists of intermingled smooth muscle fibers arranged in inner and outer longitudinal layers and a middle circular layer.

The bladder is very distensible and uniquely suited for its function of urine storage. When empty, the bladder collapses into its basic pyramidal shape and its walls are thick and thrown into folds (rugae). As urine accumulates, the bladder expands, becomes pear shaped, and rises superiorly in the abdominal cavity. The muscular wall stretches and thins, and rugae disappear. These changes allow the bladder to store more urine without a significant rise in internal pressure.

A moderately full bladder is about 12 cm (5 inches) long and holds approximately 500 ml (1 pint) of urine, but it can hold nearly double that if necessary. When tense with urine, it can be palpated well above the pubic symphysis. The maximum capacity of the bladder is 800–1000 ml and when it is
overdistended, it may burst. Although urine is formed continuously by the kidneys, it is usually stored in the bladder until its release is convenient.

Urethra

- Describe the general location, structure, and function of the urethra.
- Compare the course, length, and functions of the male urethra with those of the female.

The urethra is a thin-walled muscular tube that drains urine from the bladder and conveys it out of the body. The epithelium of its mucosal lining is mostly pseudostratified columnar

epithelium. However, near the bladder it becomes transitional epithelium, and near the external opening it changes to a protective stratified squamous epithelium.

At the bladder-urethra junction a thickening of the detrusor smooth muscle forms the internal urethral sphincter (Figure 25.21). This involuntary sphincter keeps the urethra closed when urine is not being passed and prevents leaking between voiding. This sphincter is unusual in that contraction opens it and relaxation closes it.

The external urethral sphincter surrounds the urethra as it passes through the urogenital diaphragm. This sphincter is formed of skeletal muscle and is voluntarily controlled. The levator ani muscle of the pelvic floor also serves as a voluntary constrictor of the urethra (see Table 10.7, pp. 344–345).

The length and functions of the urethra differ in the two sexes. In females the urethra is only 3–4 cm (1.5 inches) long and tightly bound to the anterior vaginal wall by fibrous connective tissue. Its external opening, the external urethral orifice, lies anterior to the vaginal opening and posterior to the clitoris.

In males the urethra is approximately 20 cm (8 inches) long and has three regions. The prostatic urethra, about 2.5 cm (1 inch) long, runs within the prostate. The membranous urethra, which runs through the urogenital diaphragm, extends about 2 cm from the prostate to the beginning of the penis. The spongy urethra, about 15 cm long, passes through the penis and opens at its tip via the external urethral orifice. The male urethra has a double function: It carries semen as well as urine out of the body. We discuss the reproductive function of the male urethra in Chapter 27.
Because the female’s urethra is very short and its external orifice is close to the anal opening, improper toilet habits (wiping back to front after defecation) can easily carry fecal bacteria into the urethra. Actually, most urinary tract infections occur in sexually active women, because intercourse drives bacteria from the vagina and external genital region toward the bladder. The use of spermicides magnifies this problem, because the spermicide kills helpful bacteria, allowing infectious fecal bacteria to colonize the vagina. Overall, 40% of all women get urinary tract infections.

The urethral mucosa is continuous with that of the rest of the urinary tract, and an inflammation of the urethra (urethritis) can ascend the tract to cause bladder inflammation (cystitis) or even renal inflammations (pyelitis or pyelonephritis). Symptoms of urinary tract infection include dysuria (painful urination), urinary urgency and frequency, fever, and sometimes cloudy or blood-tinged urine. When the kidneys are involved, back pain and a severe headache often occur. Most urinary tract infections are easily cured by antibiotics.

**Micturition**

Define micturition and describe its neural control.

Micturition (mik”tu-rish’un; mictur = urinate), also called urination or voiding, is the act of emptying the urinary bladder. In order for micturition to occur, three things must happen simultaneously: (1) the detrusor muscle must contract, (2) the internal urethral sphincter must open, and (3) the external urethral sphincter must open. The detrusor muscle and its internal urethral sphincter are composed of smooth muscle and are innervated by both the parasympathetic and sympathetic nervous systems, which have opposing actions. The external urethral sphincter, in contrast, is skeletal muscle, and therefore is innervated by the somatic nervous system.

How are the three events required for micturition coordinated? Micturition is most easily understood in infants where a spinal reflex coordinates the process. As urine accumulates, distension of the bladder activates stretch receptors in its walls. Impulses from the activated receptors travel via visceral afferent fibers to the sacral region of the spinal cord. Visceral afferent impulses, relayed by sets of interneurons, excite parasympathetic neurons and inhibit sympathetic neurons (Figure 25.22). As a result, the detrusor muscle contracts and the internal sphincter opens. Visceral afferent impulses also inhibit tonically active somatic afferents that keep the external urethral sphincter closed, allowing it to relax and urine to flow.

Between ages two and three, descending circuits from the brain have matured enough to begin to override reflexive urination. The pons has two centers that participate in control of micturition. The pontine storage center inhibits micturition, whereas the pontine micturition center promotes this reflex. Afferent impulses from bladder stretch receptors are relayed to the pons, as well as to higher brain centers that provide the conscious awareness of bladder fullness.

Lower bladder volumes primarily activate the pontine storage center, which acts to inhibit urination by suppressing parasympathetic and enhancing sympathetic output to the bladder. When a person chooses not to void, reflex bladder contractions subside within a minute or so and urine continues to accumulate. Because the external sphincter is voluntarily controlled, we can choose to keep it closed and postpone bladder emptying temporarily. After additional urine has collected, the micturition reflex occurs again and, if urination is delayed again, is damped once more. The urge to void gradually becomes greater and greater, and micturition usually occurs before urine volume exceeds 400 ml. After normal micturition, only about 10 ml of urine remains in the bladder.

**Homeostatic Imbalance**

After the toddler years, incontinence is usually a result of emotional problems, physical pressure during pregnancy, or nervous system problems. In stress incontinence, a sudden increase in intra-abdominal pressure (during laughing and coughing) forces urine through the external sphincter. This condition is common during pregnancy when the heavy uterus stretches the muscles of the pelvic floor and the urogenital diaphragm that support the external sphincter. In overflow incontinence, urine dribbles from the urethra whenever the bladder overfills.

In urinary retention, the bladder is unable to expel its contained urine. Urinary retention is normal after general anesthesia (it seems that it takes a little time for the detrusor muscle to regain its activity). Urinary retention in men often reflects hypertrophy of the prostate, which narrows the urethra, making it difficult to void. When urinary retention is prolonged, a slender rubber drainage tube called a catheter (kath’ér-ter) must be inserted through the urethra to drain the urine and prevent bladder trauma from excessive stretching.

**Check Your Understanding**

19. What is the trigone of the bladder, and which landmarks define its borders?
20. Name the three regions of the male urethra.
21. How does the detrusor muscle respond to increased firing of the parasympathetic fibers that innervate it? How does this affect the internal urethral sphincter?

For answers, see Appendix G.

**Developmental Aspects of the Urinary System**

Trace the embryonic development of the urinary organs.

List several changes in urinary system anatomy and physiology that occur with age.

As the kidneys develop in a young embryo, it almost seems as if they are unable to “make up their mind” how to go about it. As illustrated in Figure 25.23, three different sets of kidneys develop from the urogenital ridges, paired elevations of the intermediate
mesoderm that give rise to both the urinary organs and the reproductive organs. Only the last set persists to become adult kidneys.

During the fourth week of development, the first tubule system, the pronephros (pro-nef’ros; “prekidney”), forms and then quickly degenerates as a second, lower set appears. Although the pronephros never functions and is gone by the sixth week, the pronephric duct that connects it to the cloaca persists and is used by the later-developing kidneys. (The cloaca is the terminal part of the gut that opens to the body exterior.)

As the second renal system, the mesonephros (mez’o-nef’ros; “middle kidney”), claims the pronephric duct, it comes to be called the mesonephric duct (Figure 25.23a, b). The mesonephric kidneys degenerate (with remnants incorporated into the male reproductive system) once the third set, the metanephros (met’ah-nef’ros; “after kidney”), makes its appearance (Figure 25.23b, c).

The metanephros starts to develop at about five weeks as hollow ureteric buds that push superiorly from the mesonephric duct into the urogenital ridge, inducing the mesoderm there to form nephrons. The distal ends of the ureteric buds form the renal pelves, calyces, and collecting ducts, and their unexpanded proximal parts, now called the ureteric ducts, become the ureters (Figure 25.23d).

Because the kidneys develop in the pelvis and then ascend to their final position, they receive their blood supply from successively higher sources. Although the lower blood vessels usually degenerate, they sometimes persist so that multiple renal arteries are common. The metanephric kidneys are excreting urine by the third month of fetal life, and most of the amniotic fluid that surrounds a developing fetus is fetal urine. Nonetheless, the fetal kidneys do not work nearly as hard as they will after birth because exchange through the placenta allows the mother’s urinary system to clear most of the undesirable substances from the fetal blood.

As the metanephros is developing, the cloaca subdivides to form the future rectum and anal canal and the urogenital sinus, into which the urinary and genital ducts empty. The urinary bladder and the urethra then develop from the urogenital sinus (Figure 25.23b–d).

**HOMEOSTATIC IMBALANCE**

Three of the most common congenital abnormalities of the urinary system are horseshoe kidney, hypospadias, and polycystic kidney.

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**Figure 25.22 Control of micturition.**
When ascending from the pelvis the kidneys are very close together, and in 1 out of 600 people they fuse across the midline, forming a single, U-shaped horseshoe kidney. This condition is usually asymptomatic, but it may be associated with other kidney abnormalities, such as obstructed drainage, that place a person at risk for frequent kidney infections.

Hypospadias (hi'po-spa-de-as), found in male infants only, is the most common congenital abnormality of the urethra. It occurs when the urethral orifice is located on the ventral surface of the penis. This problem is corrected surgically when the child is around 12 months old.

Poly cystic kidney disease (PKD) is a group of disorders characterized by the presence of many fluid-filled cysts in the kidneys, which interfere with renal function, ultimately leading to renal failure. These disorders can be grouped into two general forms. The less severe form is inherited in an autosomal dominant manner and is much more common, affecting 1 in 500 people. The cysts develop so gradually that they produce no symptoms until about 40 years of age. Then both kidneys begin to enlarge as blisterlike cysts containing fluid accumulate. The damage caused by these cysts progresses slowly, and many victims live without problems until their 60s. Ultimately, however, the kidneys become “knobby” and grossly enlarged, reaching a mass of up to 14 kg (30 lb) each.

The much less common and more severe form follows an autosomal recessive pattern of inheritance. Almost half of newborns with recessive PKD die just after birth, and survivors generally develop renal failure in early childhood. Recessive PKD results from a mutation in a single huge gene, but the dominant form of PKD (described above) is usually caused by a mutation in one of two different genes, which code for proteins involved in cell signaling. It is not yet clear how defects in these proteins lead to cyst formation. As yet, the only treatments are the usual treatments for kidney failure—renal dialysis or a kidney transplant.

Because its bladder is very small and its kidneys are less able to concentrate urine for the first two months, a newborn baby voids 5 to 40 times daily, depending on fluid intake. By 2 months of age, the infant is voiding approximately 400 ml/day, and the amount steadily increases until adolescence, when adult urine output (about 1500 ml/day) is achieved.

Incontinence, the inability to control micturition, is normal in infants because they have not yet learned to control the external urethral sphincter. Reflex voiding occurs each time a baby’s bladder fills enough to activate the stretch receptors. Control of

Figure 25.23 Development of the urinary system of the embryo. Direction of metanephros migration as it develops is indicated by red arrows.
the voluntary urethral sphincter goes hand in hand with nervous system development. By 15 months, most toddlers know when they have voided. By 18 months, they can usually hold urine for about two hours. By 24 months, some children are ready to begin toilet training. Daytime control usually is achieved first. It is unrealistic to expect complete nighttime control before age 4. From childhood through late middle age, most urinary system problems are infectious conditions. *Escherichia coli* (esh’e-rik’e-ah ko’li) bacteria are normal residents of the digestive tract and generally cause no problems there, but these bacteria account for 80% of all urinary tract infections. *Sexually transmitted diseases* can also inflame the urinary tract and clog some of its ducts. Childhood streptococcal infections such as strep throat and scarlet fever, if not treated promptly, may cause long-term inflammatory renal damage.

Only about 3% of elderly people have histologically normal kidneys, and kidney function declines with advancing age. The kidneys shrink as the nephrons decrease in size and number, and the tubule cells become less efficient. By age 80, the GFR is only half that of young adults, possibly due to atherosclerotic narrowing of the renal arteries. Diabetics are particularly at risk for renal disease, and nearly 50% of those who have had diabetes mellitus for 20 years are in renal failure.

The bladder of an aged person is shrunken, with less than half the capacity of a young adult (250 ml versus 600 ml). Loss of bladder tone causes an annoying increase in frequency of micturition. *Nocturia* (nok-tu’re-ah), the need to get up during the night to urinate, plagues almost two-thirds of this population. Many people eventually experience incontinence, which can usually be treated with exercise, medications, or surgery.

**CHECK YOUR UNDERSTANDING**

22. Name the three sets of embryonic kidneys in the order that they develop.

23. List two factors that might contribute to urinary retention in elderly men.

For answers, see Appendix G.

The ureters, urinary bladder, and urethra play important roles in transporting, storing, and eliminating urine from the body; but when the term “urinary system” is used, it is the kidneys that capture center stage. As summarized in Making Connections in Chapter 26, other organ systems of the body contribute to the well-being of the urinary system in many ways. In turn, without continuous kidney function, the electrolyte and fluid balance of the blood is dangerously disturbed, and internal body fluids quickly become contaminated with nitrogenous wastes. No body cell can escape the harmful effects of such imbalances.

Now that we have described renal mechanisms, we are ready to integrate kidney function into the larger topic of fluid and electrolyte balance in the body—the focus of Chapter 26.

**RELATED CLINICAL TERMS**

**Acute glomerulonephritis (GN)** (glo-mer’u-lo-nef’ri-tis) Inflammation of the glomeruli, leading to increased permeability of the filtration membrane. In some cases, circulating immune complexes (antibodies bound to foreign substances, such as streptococcal bacteria) become trapped in the glomerular basement membranes. In other cases, immune responses are mounted against one’s own kidney tissues, leading to glomerular damage. In either case, the inflammatory response that follows damages the filtration membrane, allowing blood proteins and even blood cells to pass into the renal tubules and into the urine. As the osmotic pressure of blood drops, fluid seeps from the bloodstream into the tissue spaces, causing bodywide edema. Renal shutdown requiring dialysis may occur temporarily, but normal renal function usually returns within a few months. If permanent glomerular damage occurs, chronic GN and ultimately renal failure result.

**Bladder cancer** Bladder cancer, three times more common in men than in women, accounts for about 2% of all cancer deaths. It usually involves neoplasms of the bladder’s lining epithelium and may be induced by carcinogens from the environment or the workplace that end up in urine. Smoking, exposure to industrial chemicals, and arsenic in drinking water also have been linked to bladder cancer. Blood in the urine is a common warning sign.

**Cystocele** (sis’to-se; cyst = a sac, the bladder; cele = hernia, rupture) Herniation of the urinary bladder into the vagina; a common result of tearing of the pelvic floor muscles during childbirth.

**Cystoscopy** (sis-tos’ko-pe; cyst = bladder; scopy = observation) Procedure in which a thin viewing tube is threaded into the bladder through the urethra to examine the bladder’s mucosal surface.

**Diabetes insipidus** (in.si-pi-dus; insipid = tasteless, bland) Condition in which large amounts (up to 40 L/day) of dilute urine flush from the body; results from malfunction or deficiency of aquaporins or ADH receptors in the collecting duct (nephrogenic diabetes insipidus), or little or no ADH release due to injury to, or a tumor in, the hypothalamus or posterior pituitary. Can lead to severe dehydration and electrolyte imbalances unless the individual drinks large volumes of liquids. See Chapter 16, p. 608.

**Intravenous pyelogram (IVP)** (pi’e-lo-gram; pyelo = kidney pelvis; gram = written) An X ray of the kidneys and ureters obtained after intravenous injection of a contrast medium (as in Figure 25.19). Allows assessment for obstructions, viewing of renal anatomy (pelvis and calyces), and determination of rate of excretion of the contrast medium.

**Nephrotoxin** A substance (heavy metal, organic solvent, or bacterial toxin) that is toxic to the kidney.

**Nocturnal enuresis (NE)** (en’u-re’sis) An inability to control urination at night during sleep; bed-wetting. In children over 6, called primary NE if control has never been achieved and secondary NE if control was achieved and then lost. Secondary NE often has psychological causes. Primary NE is more common and results from a combination of inadequate nocturnal ADH production, unusually sound sleep, or a small bladder capacity. Synthetic ADH often corrects the problem.