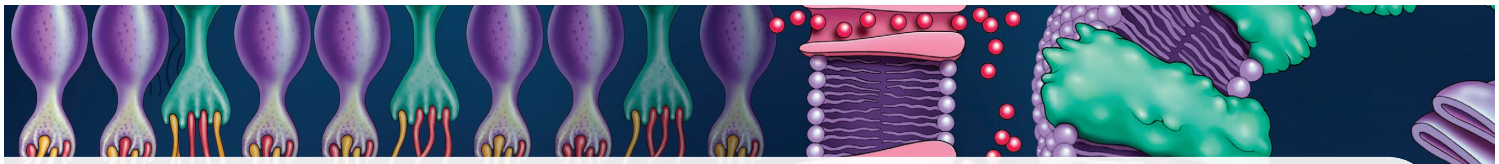


CHAPTER OUTLINE

CHAPTER 17

Physiology of the Kidneys

Refresh Your Memory

Before you begin this chapter, you may want to review these concepts from previous chapters:

- **Diffusion and Osmosis 133**
- **Carrier-Mediated Transport 142**
- **Carbon-Dioxide Transport 565**
- **Acid-Base Balance of the Blood 567**

Clinical Investigation

Lauren took lithium for her bipolar disorder and went to her physician because she felt dizzy upon standing. He told her that she was dehydrated, and urged her to increase her water intake. Lauren also took probenecid for her gout and hydrochlorothiazide for her hypertension. A month later she experienced muscle weakness, and upon examination was found to have a normal eGFR. However, her blood results revealed that she had moderate hypokalemia. Her urine tested negative for glucose. Her physician told her to stop taking the hydrochlorothiazide, and instead placed her on a different diuretic drug.

Some of the new terms and concepts you will encounter include:

- Countercurrent multiplication and countercurrent exchange
- Diabetes insipidus, renal reabsorption and secretion
- Glomerular filtration rate, renal plasma clearance, and diuretics

17.1 STRUCTURE AND FUNCTION OF THE KIDNEYS

Each kidney contains many tiny tubules that empty into a cavity drained by the ureter. Each of the tubules receives a blood filtrate from a capillary bed called the glomerulus. The filtrate is modified as it passes through different regions of the tubule and is thereby changed into urine.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. **Explain the functions of the kidneys.**
2. **Describe the gross and microscopic structure of the kidneys.**
3. **Trace the flow of blood and filtrate through the kidneys.**

The primary function of the kidneys is regulation of the extracellular fluid (plasma and interstitial fluid) environment in the body. This is accomplished through the formation of urine, which is a modified filtrate of plasma. In the process of urine formation, the kidneys regulate:

1. the volume of blood plasma (and thus contribute significantly to the regulation of blood pressure);
2. the concentration of waste products in the plasma;
3. the concentration of electrolytes (Na^+, K^+, HCO_3^- and other ions) in the plasma; and
4. the pH of plasma.

In order to understand how the kidneys perform these functions, a knowledge of kidney structure is required.

Gross Structure of the Urinary System

The paired **kidneys** lie on either side of the vertebral column below the diaphragm and liver. Each adult kidney weighs about 160 g and is about 11 cm (4 in.) long and 5 to 7 cm (2 to 3 in.) wide—about the size of a fist. Urine produced in the kidneys is drained into a cavity known as the *renal pelvis* (= basin) and then is channeled from each kidney via long ducts—the **ureters**—to the **urinary bladder** (fig. 17.1).

A coronal section of the kidney shows two distinct regions (fig. 17.2). The outer *cortex* is reddish brown and granular in appearance because of its many capillaries. The deeper region, or *medulla,* is striped in appearance due to the presence of microscopic tubules and blood vessels. The medulla is composed of 8 to 15 conical *renal pyramids* separated by *renal columns.*

The cavity of the kidney is divided into several portions. Each pyramid projects into a small depression called a *minor calyx* (the plural form is *calyces*). Several minor calyces unite to form a *major calyx.* The major calyces then join to form the funnel-shaped renal pelvis. The renal pelvis collects urine from the calyces and transports it to the ureters and urinary bladder (fig. 17.3).

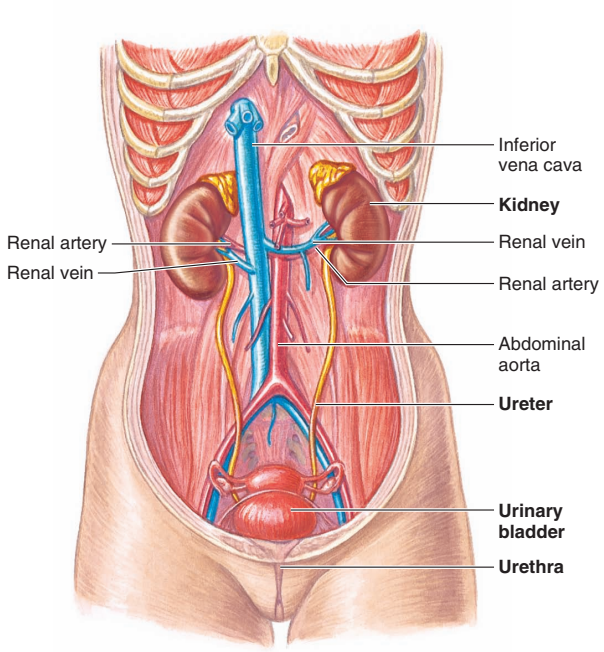


Figure 17.1 **The organs of the urinary system.** The urinary system of a female is shown; that of a male is the same, except that the urethra runs through the penis. AP|R

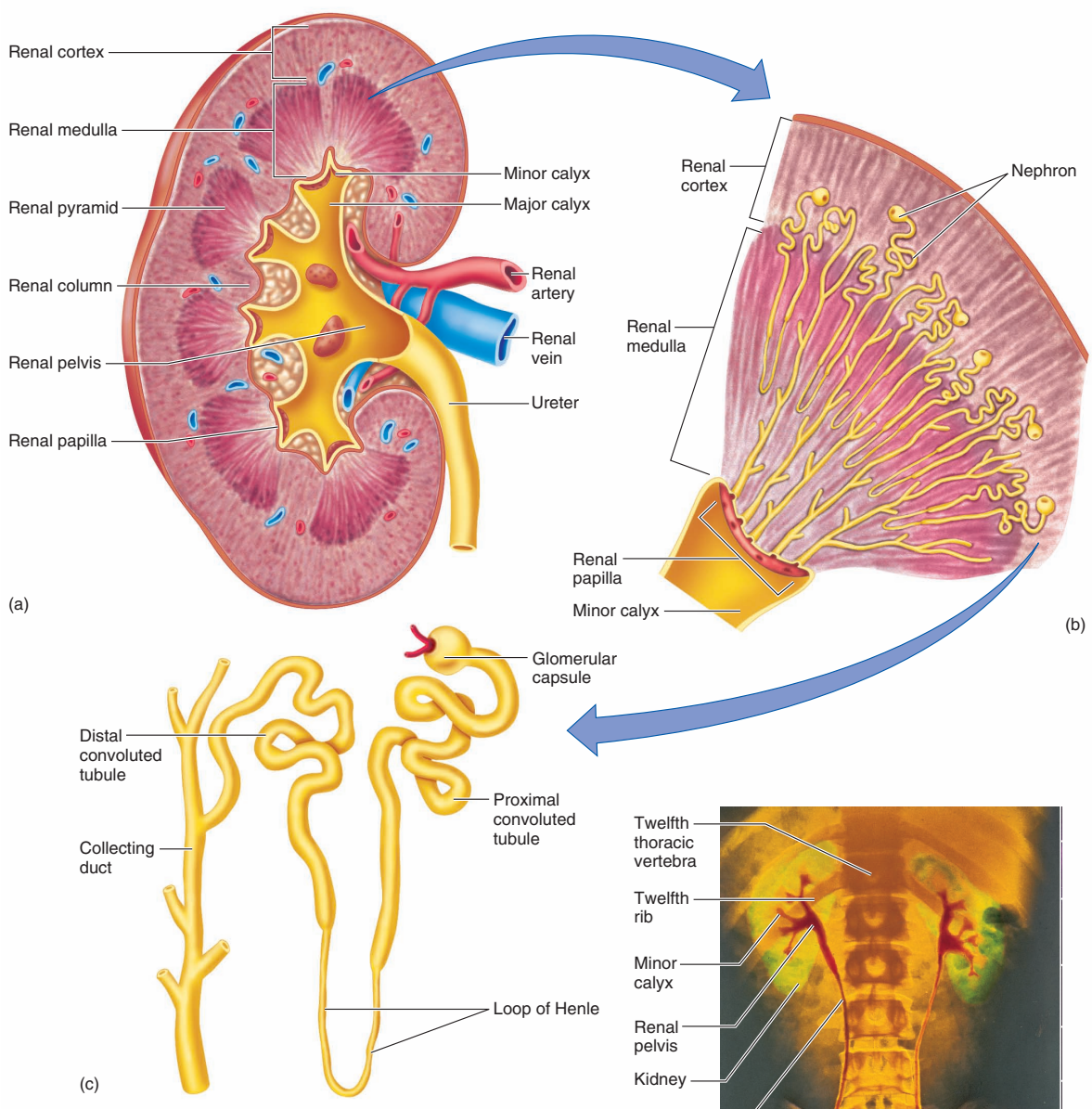


Figure 17.2 **The structure of a kidney.** The figure depicts (*a*) a coronal section of a kidney and (*b*) a magnified view of the contents of a renal pyramid. (*c*) A single nephron tubule, microscopic in actual size, is shown isolated. AP|R

Figure 17.3 **A pseudocolor radiograph of the urinary system.** In this photograph, shades of gray are assigned colors. The calyces of the kidneys, the renal pelvises, the ureters, and the urinary bladder are visible. AP|R

The ureter undergoes *peristalsis,* wavelike contractions similar to those that occur in the digestive tract. (This results in intense pain when a person passes a kidney stone.) Interestingly, the pacemaker of these peristaltic waves is located in the renal calyces and pelvis (see fig. 17.2), which contain smooth muscle. The calyces and pelvis also undergo rhythmic contractions, which may aid the emptying of urine from the kidney. Some scientists have suggested that these peristaltic contractions may affect the transport properties of the renal tubules, and thus influence the concentration of the urine.

CLINICAL APPLICATION

Nephrolithiasis (*lith* = stone), or **kidney stones,** are hard objects formed in the kidneys containing crystalized minerals or waste products. About 80% are *calcium stones,* composed of calcium phosphate or calcium oxalate. *Struvite stones* are crystals of magnesium ammonium phosphate that may result from certain urinary tract infections. *Uric acid stones* occur in people with gout, and *cysteine stones* (formed from an amino acid) occur in people with cystinuria. Because stones form when their components' concentrations exceed their solubility, the tendency to form stones is increased if a person is dehydrated. Large stones in the calyces or pelvis may obstruct urine flow, and smaller stones (usually less than 5 mm) that pass into a ureter can produce intense pain. Medications are available to help pass kidney stones, but if the stones do not pass, the person may need **lithotripsy.** In this procedure, energy generated by a lithotripter device produces shock waves that travel through body tissues to focus on the denser kidney stone and shatter it. If this noninvasive procedure is unsuccessful, surgery may be needed.

The **urinary bladder** is a storage sac for urine, and its shape is determined by the amount of urine it contains. An empty urinary bladder is pyramidal; as it fills, it becomes ovoid and bulges upward into the abdominal cavity. The urinary bladder is drained inferiorly by the tubular **urethra.** In females, the urethra is 4 cm (1.5 in.) long and opens into the space between the labia minora (chapter 20; see fig. 20.24). In males, the urethra is about 20 cm (8 in.) long and opens at the tip of the penis, from which it can discharge either urine or semen.

Control of Micturition

The urinary bladder has a muscular wall known as the **detrusor muscle.** Numerous gap junctions (electrical synapses; chapter 7; see fig. 7.21) interconnect its smooth muscle cells, so that action potentials can spread from cell to cell. Although action potentials can be generated automatically and in response to stretch, the detrusor muscle is densely innervated by parasympathetic neurons, and neural stimulation is required for the bladder to empty. The major stimulus for bladder emptying is acetylcholine (ACh) released by parasympathetic axons, which stimulate muscarinic ACh receptors in the detrusor muscle. As discussed in chapter 9, newer drugs that block specific muscarinic ACh receptors in the bladder are now available to treat an overactive bladder (detrusor muscle).

Two muscular sphincters surround the urethra. The upper sphincter, composed of smooth muscle, is called the *internal urethral sphincter;* the lower sphincter, composed of voluntary skeletal muscle, is called the *external urethral sphincter.* The actions of these sphincters are regulated in the process of urination, which is also known as **micturition.**

When the bladder is filling, sensory neurons in the bladder activated by stretch stimulate interneurons located in the S2 through S4 segments of the spinal cord. The spinal cord then controls the **guarding reflex,** in which parasympathetic nerves to the detrusor muscle are inhibited while the striated muscle of the external urethral sphincter is stimulated by somatic motor neurons. This prevents the involuntary emptying of the bladder. When the bladder is sufficiently stretched, sensory neuron stimulation can evoke a **voiding reflex.** During a voiding reflex, sensory information passes up the spinal cord to the pons, where a group of neurons functions as a *micturition center.* The micturition center activates the parasympathetic nerve to the detrusor muscle, causing rhythmic contractions. Inhibition of sympathetic neurons may also cause relaxation of the internal urethral sphincter. At this point, the person feels a sense of urgency but normally still has voluntary control over the external urethral sphincter, which is innervated by somatic motor neurons of the *pudendal nerve.* Incontinence would occur at a particular bladder volume unless higher brain regions inhibited the voiding reflex.

The guarding reflex permits bladder filling because higher brain regions inhibit the micturition center in the pons. These higher brain regions, including the prefrontal cortex and insula,

CLINICAL APPLICATION

Urinary incontinence, which is uncontrolled urination due to loss of bladder control, has many possible causes. *Stress urinary incontinence* is present when urine leakage occurs due to increased abdominal pressure, as during sneezing, coughing, and laughing. This happens in women when the pelvic floor no longer provides adequate support to the urethra due to childbirth or aging. It is often treated by a *sling surgery,* in which inserted mesh provides additional support for the urethra. In men, urinary incontinence frequently occurs as a result of treatments for prostate cancer. *Urgency incontinence* involves uncontrolled contractions of the detrusor muscle that produce a great urge to urinate and the leakage of a large volume of urine. This urgency is a hallmark of a person with an **overactive bladder,** who also usually experiences frequent urinations and other symptoms. Urinary incontinence can be diagnosed by *urodynamic testing.* This includes *cystometric tests,* in which bladder pressure and compliance (dispensability) are measured as the bladder is filled with warm water and the subject is asked to say when the urge to urinate is felt.

control the switch from the guarding to the voiding reflex, thereby allowing the person to have voluntary control of micturition. When the decision to urinate is made, the micturition center in the pons becomes activated by sensory information monitoring bladder stretch. As a result, pudendal nerve activity is inhibited so that the external urethral sphincter can relax. Then the parasympathetic nerve to the detrusor muscle is activated, causing contraction of the bladder and voiding of urine. The ability to voluntarily inhibit micturition generally develops between the ages of two and three.

Microscopic Structure of the Kidney

The **nephron** (see fig. 17.2) is the functional unit of the kidney responsible for the formation of urine. Each kidney contains more than a million nephrons. A nephron consists of small tubes, or **tubules,** and associated small blood vessels. Fluid formed by capillary filtration enters the tubules and is subsequently modified by transport processes; the resulting fluid that leaves the tubules is urine.

Renal Blood Vessels

Arterial blood enters the kidney through the *renal artery,* which divides into *interlobar arteries* (fig. 17.4) that pass between the pyramids through the renal columns. *Arcuate arteries* branch from the interlobar arteries at the boundary of the cortex and medulla.

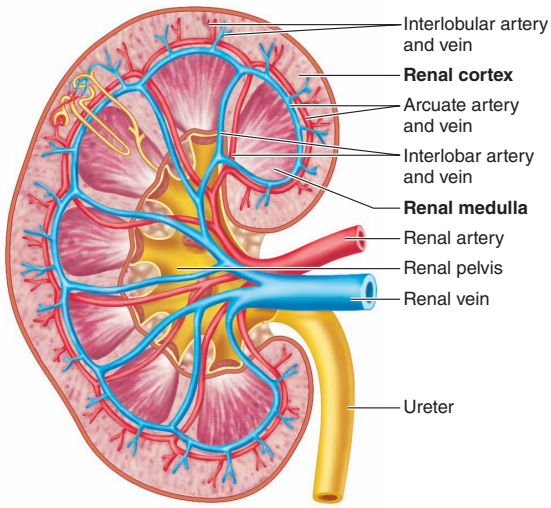


Figure 17.4 **Major blood vessels of the kidney.** The vessels carrying blood into the renal medulla and cortex, and those carrying blood out of the kidney, are illustrated. AP|R

A number of *interlobular arteries* radiate from the arcuate arteries into the cortex and subdivide into numerous **afferent arterioles** (fig. 17.5), which are microscopic. The afferent arterioles deliver blood into **glomeruli**—capillary networks that produce a blood

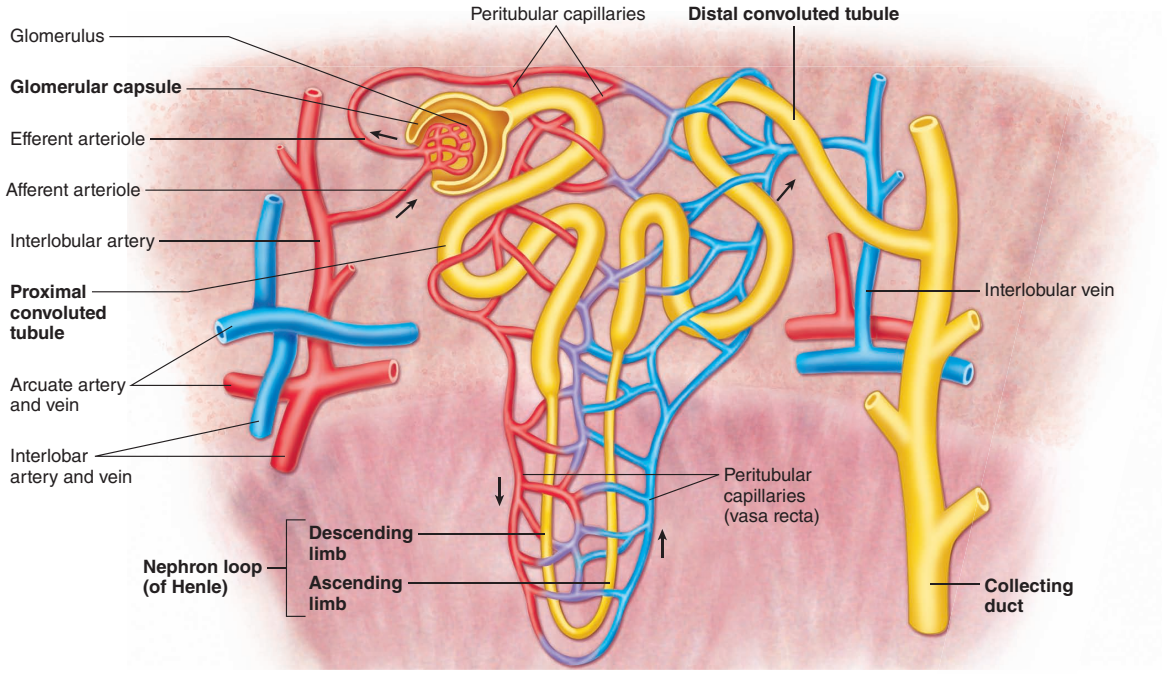


Figure 17.5 **The nephron tubules and associated blood vessels.** In this simplified illustration, the blood flow from a glomerulus to an efferent arteriole, to the peritubular capillaries, and to the venous drainage of the kidneys is indicated with arrows. The names for the different regions of the nephron tubules are indicated with boldface type. AP|R

filtrate that enters the urinary tubules. The blood remaining in a glomerulus leaves through an **efferent arteriole,** which delivers the blood into another capillary network—the **peritubular capillaries** surrounding the renal tubules.

This arrangement of blood vessels is unique. It is the only one in the body in which a capillary bed (the glomerulus) is drained by an arteriole rather than by a venule and delivered to a second capillary bed located downstream (the peritubular capillaries). Blood from the peritubular capillaries is drained into veins that parallel the course of the arteries in the kidney. These veins are called the *interlobular veins, arcuate veins,* and *interlobar veins.* The interlobar veins descend between the pyramids, converge, and leave the kidney as a single *renal vein,* which empties into the inferior vena cava.

Nephron Tubules

The tubular portion of a nephron consists of a *glomerular capsule,* a *proximal convoluted tubule,* a *descending limb of the loop of Henle,* an *ascending limb of the loop of Henle,* and a *distal convoluted tubule* (fig. 17.5).

The **glomerular (Bowman's) capsule** surrounds the glomerulus. The glomerular capsule and its associated glomerulus are located in the cortex of the kidney and together constitute the *renal corpuscle.* The glomerular capsule contains an inner visceral layer of epithelium around the glomerular capillaries and an outer parietal layer. The space between these two layers is continuous with the lumen of the tubule and receives the glomerular filtrate, as will be described in the next section.

Filtrate that enters the glomerular capsule passes into the lumen of the **proximal convoluted tubule.** The wall of the proximal convoluted tubule consists of a single layer of cuboidal cells containing millions of microvilli; these microvilli increase the surface area for reabsorption. In the process of reabsorption, salt, water, and other molecules needed by the body are transported from the lumen, through the tubular cells and into the surrounding peritubular capillaries.

The glomerulus, glomerular capsule, and convoluted tubule are located in the renal cortex. Fluid passes from the proximal convoluted tubule to the **nephron loop,** or **loop of Henle.** This fluid is carried into the medulla in the **descending limb** of the loop and returns to the cortex in the **ascending limb** of the loop. Back in the cortex, the tubule again becomes coiled and is called the **distal convoluted tubule.** The distal convoluted tubule is shorter than the proximal tubule and has relatively few microvilli. The distal convoluted tubule terminates as it empties into a collecting duct.

The two principal types of nephrons are classified according to their position in the kidney and the lengths of their loops of Henle. Nephrons that originate in the inner one-third of the cortex—called *juxtamedullary nephrons* because they are next to the medulla—have longer nephron loops than the more numerous *cortical nephrons,* which originate in the outer two-thirds of the cortex (fig. 17.6). The juxtamedullary nephrons play an important role in the ability of the kidney to produce a concentrated urine.

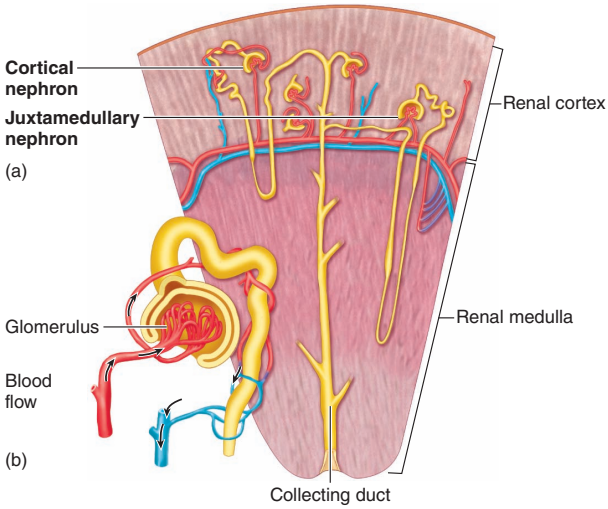


Figure 17.6 **The contents of a renal pyramid.** (*a*) The position of cortical and juxtamedullary nephrons is shown within the renal pyramid of the kidney. (*b*) The direction of blood flow in the vessels of the nephron is indicated with arrows. AP|R

CLINICAL APPLICATION

Polycystic kidney disease (**PKD**) is a congenital disorder in which the kidneys are enlarged by hundreds to thousands of fluid-filled cysts that form in all segments of the nephron and eventually separate from the tubules. **Autosomal dominant polycystic kidney disease** (**ADPKD**) accounts for most cases and affects almost 1 in 1,000 people. Because the trait is dominant, a child has a 50% chance of getting the disease if one parent is affected. Far less commonly, the disease may be inherited as an autosomal recessive trait in which the child has a 25% chance of getting the disease if both parents have the trait. The gene responsible for 85% of ADPKD is located on chromosome 16 and codes for a protein called *polycystin-1,* whereas a gene located on chromosome 4 that codes for *polycystin-2* is responsible for the other cases. Polycystin-1 and polycystin-2 in the epithelial cells of the renal tubules form a complex that is important for the sensory function of the *primary cilium.* The primary cilium extends into the lumen of the renal tubule and serves as a mechanosensor, where the flow of filtrate bends the cilium and results in the movement of Ca^{2+} into the cell. This is a second messenger in the regulation of many cell functions, and disruptions of these functions are believed to somehow produce polycystic kidney disease. There is no cure presently available, only treatments for the complications of this disease.

A **collecting duct** receives fluid from the distal convoluted tubules of several nephrons. Fluid is then drained by the collecting duct from the cortex to the medulla as the collecting

duct passes through a renal pyramid. This fluid, now called urine, passes into a minor calyx. Urine is then funneled through the renal pelvis and out of the kidney in the ureter.

CHECKPOINT

1. Describe the "theme" of kidney function in a single sentence and list the components of this functional theme.

2a. Draw and label the tubular components of a nephron and indicate which parts are in the cortex and which are in the medulla.

2b. Trace the course of tubular fluid from the glomerular capsules to the ureter.

3. Trace the course of blood flow through the kidney from the renal artery to the renal vein.

17.2 GLOMERULAR FILTRATION

The glomerular capillaries have large pores in their walls, and the layer of Bowman's capsule in contact with the glomerulus has filtration slits. Water, together with dissolved solutes, can thus pass from the blood plasma to the inside of the capsule and the nephron tubules.

LEARNING OUTCOMES

After studying this section, you should be able to:

4. Describe glomerular filtration and the structures and forces involved.
5. Explain the significance of the glomerular filtration rate (GFR) and how it is regulated.

Endothelial cells of the glomerular capillaries have large pores (200 to 500 Å in diameter) called fenestrae; thus, the glomerular endothelium is said to be *fenestrated.* As a result of these large pores, glomerular capillaries are 100 to 400 times more permeable to plasma water and dissolved solutes than are the capillaries of skeletal muscles. Although the pores of glomerular capillaries are large, they are still small enough to prevent the passage of red blood cells, white blood cells, and platelets into the filtrate.

Before the fluid in blood plasma can enter the interior of the glomerular capsule, it must pass through three layers that could serve as selective filters. The fluid entering the glomerular capsule is thus referred to as a *filtrate.* This is the fluid that will become modified as it passes through the different segments of the nephron tubules to become the urine.

The first potential filtration barrier is the **capillary fenestrae,** which are large enough to allow proteins to pass but are surrounded by charges that may present some barrier to plasma proteins. The second potential barrier is the **glomerular basement membrane,** a layer of collagen IV and proteoglycans (chapter 1, section 1.3) lying immediately outside the capillary endothelium. This may offer some barrier to plasma proteins, and indeed a genetic defect in collagen IV can produce inherited glomerulonephritis (*Alport's syndrome*). The glomerular basement membrane is more than five times as thick as the basement membrane of other vessels, and is the structure that most restricts the rate of fluid flow into the capsule lumen.

The filtrate must then pass through the inner (visceral) layer of the glomerular capsule, where the third potential filtration barrier is located. This layer is composed of **podocytes,** which are unique epithelial cells with a bulbous *cell body, primary processes* extending from the cell body, and thousands of *foot processes* (fig. 17.7) that branch from the primary processes. The podocyte processes are attached to the glomerular basement membrane, while their cell bodies float in the fluid within the glomerular capsules. The foot processes of neighboring podocytes interdigitate and surround the basement membrane of the glomerular capillaries. The narrow slits (30 to 50 nm wide) between adjacent foot processes provide passageways for molecules entering the interior of the glomerular capsule as glomerular filtrate (fig. 17.8). However, a **slit diaphragm** (fig. 17.9), analogous in composition to an adherens junction (chapter 6; see fig. 6.22), links the interdigitating foot processes and presents the last potential filtration barrier.

All dissolved plasma solutes pass easily through all three potential filtration barriers to enter the interior of the glomerular capsule. However, plasma proteins are mostly excluded from the filtrate because of their large sizes and net negative charges. Until recently most scientists believed that the glomerular basement membrane was the primary filter excluding plasma proteins from the filtrate. More recent evidence indicates that the slit diaphragm poses the major barrier to the

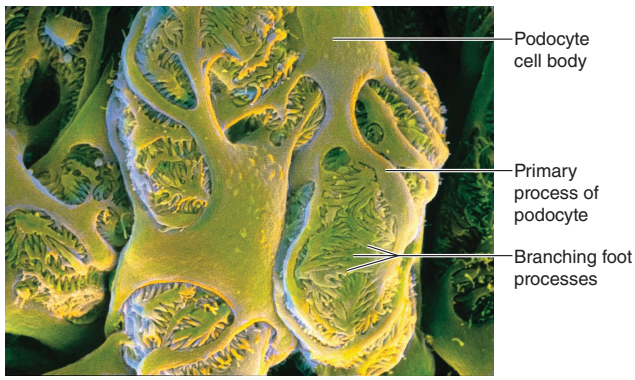


Figure 17.7 A scanning electron micrograph of the glomerular capillaries and capsule. The inner (visceral) layer of the glomerular (Bowman's) capsule is composed of podocytes, as shown in this scanning electron micrograph. Very fine extensions of these podocytes form foot processes that interdigitate around the glomerular capillaries. Spaces between adjacent foot processes form the "filtration slits" (see also fig. 17.8). AP|R

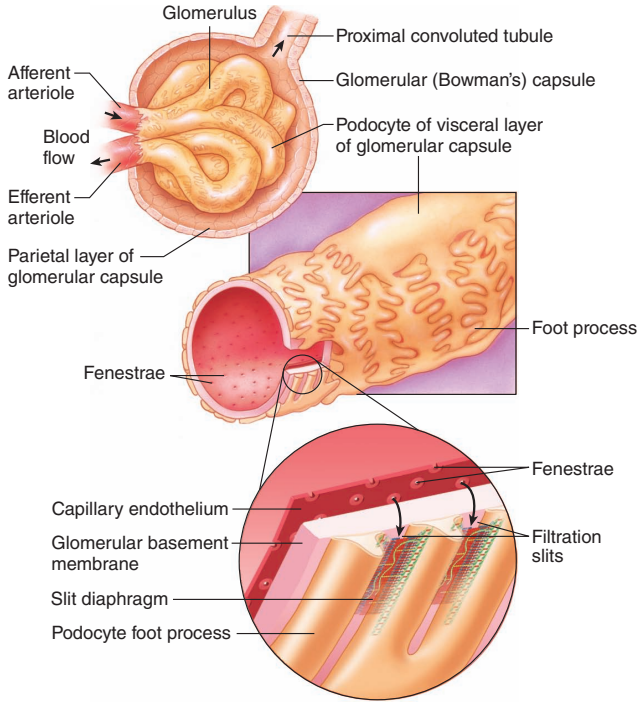


Figure 17.8 The structure of the glomerulus and capsule. An illustration of the relationship between the glomerular capillaries and the inner layer of the glomerular (Bowman's) capsule. Notice that filtered molecules pass out of the fenestrae of the capillaries and through the filtration slits to enter the cavity of the capsule. Plasma proteins are excluded from the filtrate by the glomerular basement membrane and the slit diaphragm. APR

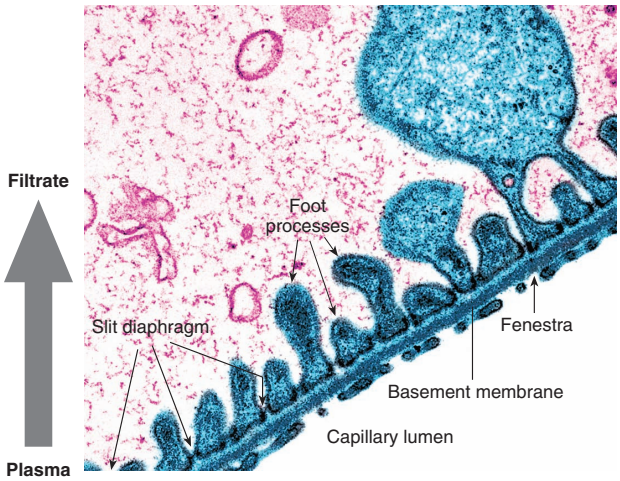


Figure 17.9 An electron micrograph of the filtration barrier. This electron micrograph shows the barrier separating the capillary lumen from the cavity of the glomerular (Bowman's) capsule. Note that, unlike the view in fig. 17.8, the glomerular capillary is shown below the capsule lumen in this photograph.

passage of plasma proteins into the filtrate. One source of evidence for this is based on the consequences of genetic defects in the proteins that compose the slit diaphragms. These defects in the slit diaphragm result in massive leakage of proteins into the filtrate, and thus in *proteinuria* (proteins in the urine).

Actually, a small amount of albumin (the major class of plasma proteins) does normally enter the filtrate, but less than 1% of this filtered amount is excreted in the urine. This is because most of the small amount of albumin that enters the filtrate is reabsorbed, or transported across the cells of the proximal tubule into the surrounding blood. In the case of filtered albumin, such reabsorption is accomplished by receptor-mediated endocytosis (chapter 3; see fig. 3.4). Proteinuria thus occurs when damage to the slit diaphragm filtration barrier causes more protein to enter the filtrate than can be reabsorbed in this way.

Glomerular Ultrafiltrate

The fluid that enters the glomerular capsule is called **filtrate,** or **ultrafiltrate** (fig. 17.10) because it is formed under pressure—the hydrostatic pressure of the blood. This process is similar to the formation of tissue fluid by other capillary beds in the body in response to Starling forces (see chapter 14; fig. 14.9). The force favoring filtration is opposed by a counterforce developed by the hydrostatic pressure of fluid in the glomerular capsule. Also, since the protein concentration of the tubular fluid is low (less than 2 to 5 mg per 100 ml) compared to that of plasma (6 to 8 g per 100 ml), the greater colloid osmotic pressure of plasma promotes the osmotic return of filtered water. When these opposing forces are subtracted from the hydrostatic pressure of the glomerular capillaries, a *net filtration pressure* of only about 10 mmHg is obtained.

Because glomerular capillaries are extremely permeable and have an extensive surface area, this modest net filtration pressure produces an extraordinarily large volume of filtrate. The **glomerular filtration rate (GFR)** is the volume of filtrate produced by both kidneys per minute. The GFR averages 115 ml per minute in women and 125 ml per minute in men. This is equivalent to 7.5 L per hour or 180 L per day (about 45 gallons)! Since the total blood volume averages about 5.5 L, this means that the total blood volume is filtered into the urinary tubules every 40 minutes. Most of the filtered water must obviously be returned immediately to the vascular system or a person would literally urinate to death within minutes.

Regulation of Glomerular Filtration Rate

Vasoconstriction or dilation of afferent arterioles affects the rate of blood flow to the glomerulus, and thus affects the glomerular filtration rate. Changes in the diameter of the afferent

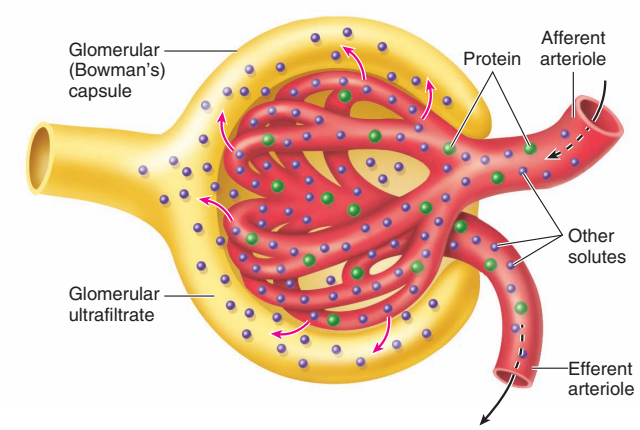


Figure 17.10 The formation of glomerular ultrafiltrate. Only a very small proportion of plasma proteins (*green spheres*) are filtered, but smaller plasma solutes (*purple spheres*) easily enter the glomerular ultrafiltrate. Arrows indicate the direction of filtration.

arterioles result from both extrinsic regulatory mechanisms (produced by sympathetic nerve innervation) and intrinsic regulatory mechanisms (those within the kidneys, also termed *renal autoregulation*). These mechanisms are needed to ensure that the GFR will be high enough to allow the kidneys to eliminate wastes and regulate blood pressure, but not so high as to cause excessive water loss.

Sympathetic Nerve Effects

An increase in sympathetic nerve activity, as occurs during the fight-or-flight reaction and exercise, stimulates constriction of afferent arterioles. This helps preserve blood volume and divert blood to the muscles and heart. A similar effect occurs during cardiovascular shock, when sympathetic nerve activity stimulates vasoconstriction. The decreased GFR and the resulting decreased rate of urine formation help compensate for the rapid drop in blood pressure under these circumstances (fig. 17.11).

Renal Autoregulation

When the direct effect of sympathetic stimulation is experimentally removed, the effect of systemic blood pressure on GFR can be observed. Under these conditions, surprisingly, the GFR remains relatively constant despite changes in mean arterial pressure within a range of 70 to 180 mmHg (normal mean arterial pressure is 100 mmHg). The ability of the kidneys to maintain a relatively constant GFR in the face of fluctuating blood pressures is called **renal autoregulation.**

In renal autoregulation, afferent arterioles dilate when the mean arterial pressure falls toward 70 mmHg and constrict when the mean arterial pressure rises above normal. Changes

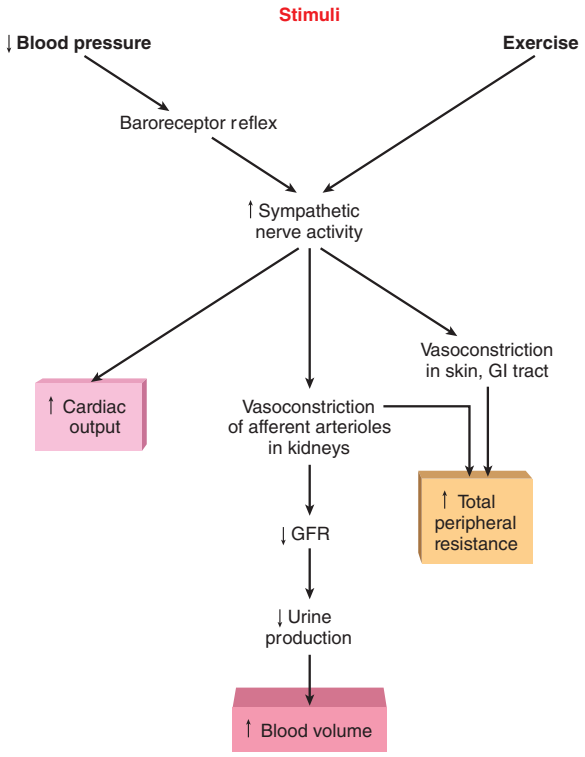


Figure 17.11 Sympathetic nerve effects. The effect of increased sympathetic nerve activity on kidney function and other physiological processes is illustrated.

that may occur in the efferent arterioles are believed to be of secondary importance.

Blood flow to the glomeruli and GFR can thus remain relatively constant within the autoregulatory range of blood pressure values. The effects of different regulatory mechanisms on the GFR are summarized in table 17.1.

Two general mechanisms are responsible for renal autoregulation: (1) *myogenic* constriction of the afferent arteriole, due to the ability of the smooth muscle to sense and respond to an increase in arterial pressure; and (2) the effects of locally produced chemicals on the afferent arteriole, which is part of a process called **tubuloglomerular feedback.** The sensor in tubuloglomerular feedback is a group of specialized cells called the **macula densa,** located in the thick portion of the ascending limb where it loops back and comes into contact with the afferent and efferent arterioles in the renal cortex. The macula densa here is part of a larger functional unit known as the *juxtaglomerular apparatus* (see fig. 17.26), which will be described in section 17.5.

When there is an increased delivery of NaCl and H_2O to the distal tubule (as occurs when increased arterial pressure causes a rise in the GFR), the macula densa releases a chemical signal

Table 17.1 | Regulation of the Glomerular Filtration Rate (GFR)

Regulation	Stimulus	Afferent Arteriole	GFR
Sympathetic nerves	Activation by baroreceptor reflex or by higher brain centers	Constricts	Decreases
Autoregulation	Decreased blood pressure	Dilates	No change
Autoregulation	Increased blood pressure	Constricts	No change

causing constriction of the afferent arteriole. Scientists now believe that ATP is the chemical released by the macula densa, although adenosine derived from ATP may more directly produce vasoconstriction of the afferent arteriole.

In summary, when there is increased salt and water flowing through the distal tubule, vasoconstriction of the afferent arteriole in response to ATP (or adenosine) from the macula densa lowers the GFR. This negative feedback response reduces the salt and water entering the nephron tubule and arriving at the distal tubule. Tubuloglomerular feedback may protect the late distal tubule and cortical collecting duct—structures that contribute to salt and water reabsorption—from becoming overloaded.

✔ | CHECKPOINT

4a. Describe the structures that plasma fluid must pass through before entering the glomerular capsule. Explain how proteins are excluded from the filtrate.

4b. Describe the forces that affect the formation of glomerular ultrafiltrate.

5a. Explain the significance of the glomerular filtration rate and how it is regulated by sympathetic nerves.

5b. Explain tubuloglomerular feedback and renal autoregulation of the GFR.

17.3 REABSORPTION OF SALT AND WATER

The reabsorption of water from the glomerular filtrate occurs by osmosis, which results from the transport of Na^+ and Cl^- across the tubule wall. The proximal tubule reabsorbs most of the filtered salt and water, and most of the remainder is reabsorbed across the wall of the collecting duct under ADH stimulation.

LEARNING OUTCOMES

After studying this section, you should be able to:

6. Describe the salt and water reabsorption properties of each nephron segment.

7. Explain the countercurrent multiplier system.

8. Explain how ADH acts to promote water reabsorption.

Although about 180 L of glomerular ultrafiltrate are produced each day, the kidneys normally excrete only 1 to 2 L of urine in a 24-hour period. Approximately 99% of the filtrate must thus be returned to the vascular system, while 1% is excreted in the urine. The urine volume, however, varies according to the needs of the body. When a well-hydrated person drinks a liter or more of water, urine production increases to 16 ml per minute (the equivalent of 23 L per day if this were to continue for 24 hours). In severe dehydration, when the body needs to conserve water, only 0.3 ml of urine per minute, or 400 ml per day, are produced. A volume of 400 ml of urine per day is the minimum needed to excrete the metabolic wastes produced by the body; this is called the **obligatory water loss.** When water in excess of this amount is excreted, the urine becomes increasingly diluted as its volume is increased.

Regardless of the body's state of hydration, it is clear that most of the filtered water must be returned to the vascular system to maintain blood volume and pressure. The return of filtered molecules from the tubules to the blood is called **reabsorption** (fig. 17.12). About 85% of the 180 L of glomerular filtrate formed per day is reabsorbed in a constant, unregulated fashion by the proximal tubules and descending limbs of the nephron loops. This reabsorption, as well as the regulated reabsorption of the remaining volume of filtrate, occurs by osmosis. A concentration gradient must thus be created between tubular filtrate and the plasma in the surrounding capillaries that promotes the osmosis of water back into the vascular system from which it originated.

Reabsorption in the Proximal Tubule

Because all plasma solutes, with the exception of proteins, are able to enter the glomerular ultrafiltrate freely, the total solute concentration (osmolality) of the filtrate is essentially the same as that of plasma. This total solute concentration is equal to 300 milliosmoles per liter, or 300 milliosmolal (300 mOsm), as described in chapter 6. The filtrate is thus said to be *isosmotic* with the plasma (chap ter 6, section 6.2). Reabsorption by osmosis cannot occur unless the solute concentrations of plasma in the peritubular capillaries and the filtrate are altered by active transport processes. This is achieved by the active transport of Na^+ from the filtrate to the peritubular blood.

Active and Passive Transport

The epithelial cells that compose the wall of the proximal tubule are joined together by tight junctions only toward

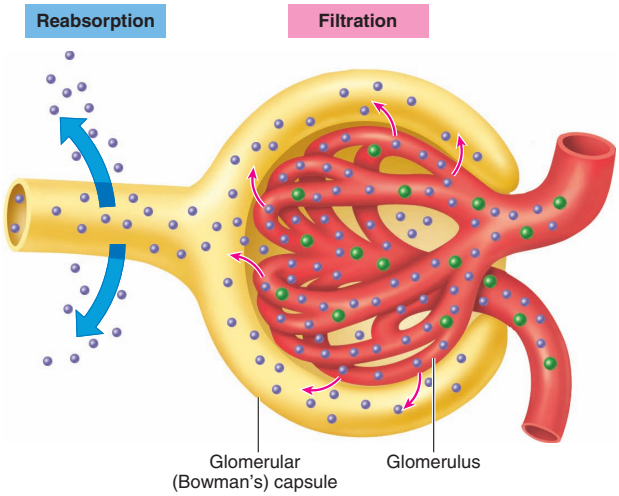


Figure 17.12 Filtration and reabsorption. Plasma water and its dissolved solutes (except proteins) enter the glomerular ultrafiltrate by filtration, but most of these filtered molecules are reabsorbed. The term *reabsorption* refers to the transport of molecules out of the tubular filtrate back into the blood.

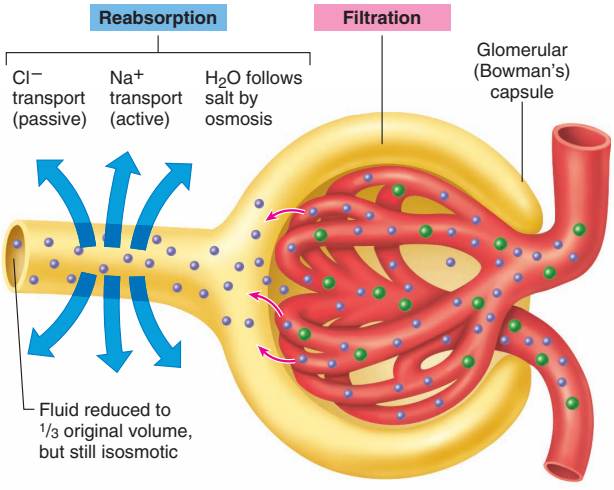


Figure 17.13 Salt and water reabsorption in the proximal tubule. Sodium is actively transported out of the filtrate (see fig. 17.24) and chloride follows passively by electrical attraction. Water follows the salt out of the tubular filtrate into the peritubular capillaries by osmosis.

their apical sides—that is, the sides of each cell that are closest to the lumen of the tubule (see fig. 17.24). Each cell has four exposed surfaces: the apical side facing the lumen, which contains microvilli; the basal side facing the peritubular capillaries; and the lateral sides facing the narrow clefts between adjacent epithelial cells.

The concentration of Na^+ in the glomerular ultrafiltrate—and thus in the fluid entering the proximal tubule—is the same as in plasma. The cytoplasm in epithelial cells of the tubule, however, has a much lower Na^+ concentration. This lower Na^+ concentration is partially due to the low permeability of the plasma membrane to Na^+ and partially due to the active transport of Na^+ out of the cells by Na^+/K^+ pumps (chapter 6, section 6.3). In the cells of the proximal tubule, the Na^+/K^+ pumps are located in the basal and lateral sides of the plasma membrane but not in the apical membrane. As a result of the action of these active transport pumps, a concentration gradient is created that favors the diffusion of Na^+ from the tubular fluid across the apical plasma membranes and into the epithelial cells of the proximal tubule. The Na^+ is then extruded into the surrounding interstitial (tissue) fluid by the Na^+/K^+ pumps.

The transport of Na^+ from the tubular fluid to the interstitial fluid surrounding the proximal tubule creates a potential difference across the wall of the tubule, with the lumen as the negative pole. This electrical gradient favors the passive transport of Cl^- toward the higher Na^+ concentration in the interstitial fluid. In the early proximal tubule, reabsorption of Cl^- occurs mainly by transcellular transport (through the epithelial cells). Despite this, Cl^- accumulates in the lumen, and by the late proximal tubule the tight junctions between epithelial cells are permeable to Cl^-. The Cl^- here can be passively reabsorbed by paracellular transport.

As a result of these processes, there is an accumulation of NaCl in the interstitial fluid surrounding the proximal tubule, particularly in the narrow spaces between epithelial cells. This raises the osmolality and osmotic pressure of the interstitial fluid above that of the tubular fluid, creating an osmotic gradient that drives the reabsorption of water through aquaporin channels in the plasma membrane of the epithelial cells. The salt and water that were reabsorbed from the proximal tubule can then move passively into the surrounding peritubular capillaries, and in this way be returned to the blood (fig. 17.13).

Significance of Proximal Tubule Reabsorption

Approximately 65% of the salt and water in the original glomerular ultrafiltrate is reabsorbed across the proximal tubule and returned to the vascular system. The volume of tubular fluid remaining is reduced accordingly, but this fluid is still isosmotic with the blood, which has a concentration of 300 mOsm. This is because the plasma membranes in the proximal tubule are freely permeable to water, so that water and salt are removed in proportionate amounts.

An additional smaller amount of salt and water (about 20%) is returned to the vascular system by reabsorption through the descending limb of the nephron loop. This reabsorption, like that in the proximal tubule, occurs constantly, regardless of the person's state of hydration. Unlike reabsorption in later regions of the nephron (distal tubule and collecting duct), it is

not subject to hormonal regulation. Therefore, approximately 85% of the filtered salt and water is reabsorbed in a constant fashion in the early regions of the nephron (proximal tubule and nephron loop). This reabsorption is very costly in terms of energy expenditures, accounting for as much as 6% of the calories consumed by the body at rest.

Since 85% of the original glomerular ultrafiltrate is reabsorbed in the early regions of the nephron, only 15% of the initial filtrate remains to enter the distal convoluted tubule and collecting duct. This is still a large volume of fluid—15% × GFR (180 L per day) = 27 L per day—that must be reabsorbed to varying degrees in accordance with the body's state of hydration. This "fine tuning" of the percentage of reabsorption and urine volume is accomplished by the action of hormones on the later regions of the nephron.

The Countercurrent Multiplier System

Water cannot be actively transported across the tubule wall, and osmosis of water cannot occur if the tubular fluid and surrounding interstitial fluid are isotonic to each other. In order for water to be reabsorbed by osmosis, the surrounding interstitial fluid must be hypertonic. The osmotic pressure of the interstitial fluid in the renal medulla is raised to more than four times that of plasma by juxtamedullary nephrons. This is partly due to the geometry of the nephron loops, which bend sharply so that descending and ascending limbs are in close enough proximity to interact. Because the ascending limb is the active partner in this interaction, its properties will be described before those of the descending limb.

Ascending Limb of the Loop of Henle

The ascending limb is divided into two regions: a *thin segment,* nearest the tip of the loop, and a *thick segment,* which carries the filtrate into the distal convoluted tubule in the renal cortex. Salt (NaCl) is actively extruded from the thick segment of the ascending limb into the surrounding interstitial fluid (fig. 17.14). This is accomplished differently from the way NaCl is reabsorbed from the proximal tubule. In the cells of the thick portion of the ascending limb, the movement of Na^+ down its electrochemical gradient from the filtrate into the cells powers the inward secondary active transport of K^+ and Cl^-. This occurs in a ratio of 1 Na^+ to 1 K^+ to 2 Cl^-. The Na^+ is then actively transported across the basolateral membrane to the interstitial fluid by the Na^+/K^+ pumps. Cl^- follows the Na^+ passively because of electrical attraction, and K^+ passively diffuses back into the filtrate (fig. 17.15).

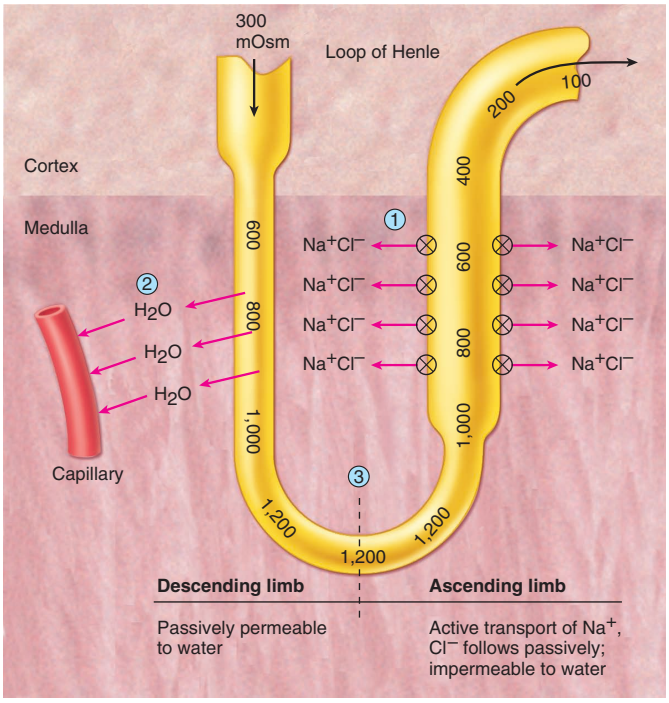


Figure 17.14 **The countercurrent multiplier system.** (1) The extrusion of sodium chloride from the ascending limb makes the surrounding interstitial fluid more concentrated. Multiplication of this concentration is due to the fact that (2) the descending limb is passively permeable to water, which causes its fluid to increase in concentration as the surrounding interstitial fluid becomes more concentrated. (3) The deepest region of the medulla reaches a concentration of 1,200 mOsm. (All numbers indicate milliosmolal units.)

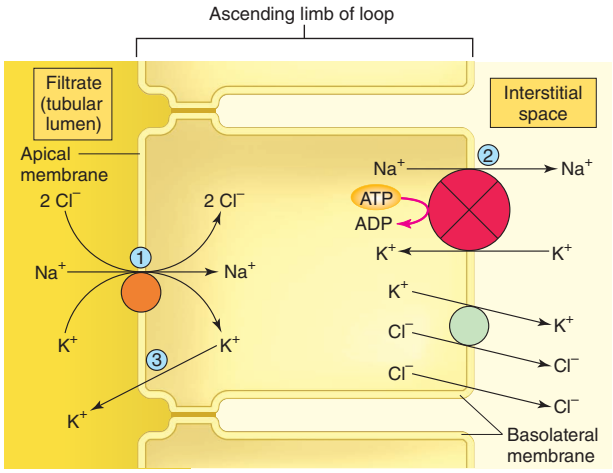


Figure 17.15 The transport of ions in the ascending limb. (1) In the thick segment of the ascending limb of the loop, Na^+ and K^+ together with two Cl^- enter the tubule cells. (2) Na^+ is then actively transported out into the interstitial space and Cl^- follows passively. (3) The K^+ diffuses back into the filtrate, and some also enters the interstitial space.

Although the mechanism of NaCl transport is different in the ascending limb than in the proximal tubule, the net effect is the same: salt (NaCl) is extruded into the interstitial fluid. Unlike the epithelial walls of the proximal tubule, however, the walls of the ascending limb of the nephron loop are *not permeable to water.* That is, water cannot follow the NaCl from the filtrate in the lumen of the ascending limb to the interstitial fluid surrounding the tubule. The filtrate in the ascending limb thus becomes increasingly dilute as it ascends into the cortex; by contrast, the interstitial fluid surrounding the nephron loops in the medulla becomes increasingly more concentrated. By means of these processes, the tubular fluid that enters the distal tubule in the cortex is made hypotonic (with a concentration of about 100 mOsm), whereas the interstitial fluid in the medulla is made hypertonic.

Descending Limb of the Loop of Henle

The deeper regions of the medulla, around the tips of the loops of juxtamedullary nephrons, reach a concentration of 1,200 mOsm. In order to reach a concentration this high, the salt pumped out of the ascending limb must accumulate in the interstitial fluid of the medulla. This occurs because of the properties of the descending limb, and because blood vessels around the loop do not carry back all of the extruded salt to the general circulation. The capillaries in the medulla are uniquely arranged to trap NaCl in the interstitial fluid, as will be discussed shortly.

The descending limb does not actively transport salt, and indeed is impermeable to the passive diffusion of salt. It is, however, permeable to water. Because the surrounding interstitial fluid is hypertonic to the filtrate in the descending limb, water is drawn out of the descending limb by osmosis and enters blood capillaries. The concentration of tubular fluid is thus increased, and its volume is decreased, as it descends toward the tips of the loops.

As a result of these passive transport processes in the descending limb, the fluid that "rounds the bend" at the tip of the loop has the same osmolality as that of the surrounding interstitial fluid (1,200 mOsm). There is, therefore, a higher salt concentration arriving in the ascending limb than there would be if the descending limb simply delivered isotonic fluid. Salt transport by the ascending limb is increased accordingly, so that the "saltiness" (NaCl concentration) of the interstitial fluid is multiplied (see fig. 17.14).

Countercurrent Multiplication

Countercurrent flow (flow in opposite directions) in the ascending and descending limbs and the close proximity of the two limbs allow for interaction between them. Because the concentration of the tubular fluid in the descending limb reflects the concentration of surrounding interstitial fluid, and the concentration of this fluid is raised by the active extrusion of salt from the ascending limb, a *positive feedback mechanism* is created. The more salt the ascending limb extrudes, the more concentrated will be the fluid that is delivered to it from the descending limb. This positive feedback mechanism, which multiplies the concentration of interstitial fluid and descending limb fluid, is called the **countercurrent multiplier system.**

Let's imagine that fluid goes through the loop of Henle in successive steps, one following the other. Flow is really continuous, but these hypothetical steps allow us to mentally picture the countercurrent multiplication mechanism. To start with, let's suppose that the fluid that leaves the descending limb and reaches the ascending limb is at first isosmotic (300 mOsm). Through active transport, the thick ascending limb pumps out some of the NaCl. This NaCl becomes trapped in the interstitial fluid by blood vessels called the *vasa recta.* The following progression of steps will occur:

1. The interstitial fluid is now a little hypertonic due to the NaCl pumped out of the thick segment of the ascending limb.
2. Because of the slightly hypertonic interstitial fluid, some water leaves the descending limb by osmosis (and enters the blood) as the filtrate goes deeper into the medulla. This makes the filtrate somewhat hypertonic when it reaches the ascending limb.
3. The now higher NaCl concentration of the filtrate that enters the ascending limb allows it to pump out more NaCl than it did before, because more NaCl is now available to the carriers. The interstitial fluid now becomes yet more concentrated.
4. Because the interstitial fluid is more concentrated than it was in step 2, more water is drawn out of the descending

limb by osmosis, making the filtrate even more hypertonic when it reaches the ascending limb.

5. Step 3 is repeated, but to a greater extent because of the higher NaCl concentration delivered to the ascending limb.
6. This progression continues until the maximum concentration is reached in the inner medulla. This maximum is determined by the capacity of the active transport pumps working along the lengths of the thick segments of the ascending limbs.

What does the countercurrent multiplier system accomplish? Most importantly, it increases the concentration of renal interstitial fluid from 300 mOsm in the cortex to 1,200 mOsm in the inner medulla. This great hypertonicity of the renal medulla is critical because it serves as the driving force for water reabsorption through the collecting ducts, which travel through the renal medulla to empty their contents of urine into the renal pelvis.

Vasa Recta

For the countercurrent multiplier system to be effective, most of the salt that is extruded from the ascending limbs must remain in the interstitial fluid of the medulla, while most of the water that leaves the descending limbs must be removed by the blood. This is accomplished by the **vasa recta,** vessels that parallel the nephron loops (fig. 17.18) and serve as the major vessels carrying blood into and out of the renal medulla. These vessels have *urea transporters* (for facilitated diffusion) and *aquaporin proteins* (water channels) in the plasma membranes (chapter 6, section 6.2). Because of this, the vasa recta are freely permeable to water, urea, and sodium chloride. As a result, the descending vessels of the vasa recta gain salt and urea while they lose water, whereas the ascending vessels lose salt and urea while they gain water (fig. 17.16).

The vasa recta maintain the hypertonicity of the renal medulla by means of a mechanism known as **countercurrent exchange.** Salt and other dissolved solutes (primarily urea, described in the next section) that are present at high concentrations in the interstitial fluid diffuse into the descending vasa recta. However, these same solutes then passively diffuse out of the ascending vasa recta and back into the interstitial fluid to complete the countercurrent exchange. They do this because, at each level of the medulla, the concentration of solutes is higher in the ascending vessels than in the interstitial fluid, and higher in the interstitial fluid than in the descending vessels. Solutes are thus recirculated and trapped within the medulla.

The net effect of countercurrent exchange is that the blood within the vasa recta approaches osmotic equilibrium with the interstitial fluid that surrounds each level in the medulla. The vasa recta deliver blood at an isotonic concentration to the cortex, while the blood in the medulla is nearly at the same concentration as its surroundings. When countercurrent exchange in the vasa recta is more efficient, the countercurrent multiplication of the nephron loops can more effectively maintain the concentration gradient of the medulla. For example, when blood flow in the ascending vasa recta is slowed during dehydration, there is more time for it to lose salt and urea and keep

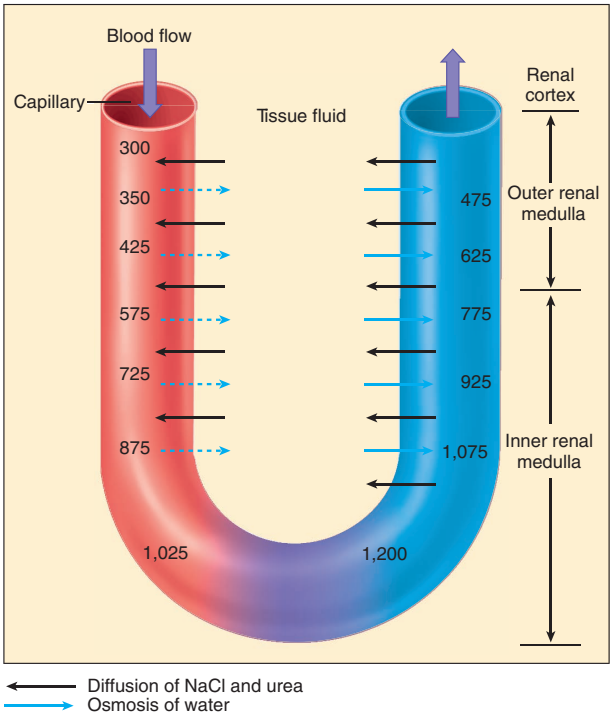


Figure 17.16 Countercurrent exchange in the vasa recta. The diffusion of salt and water first into and then out of these blood vessels helps to maintain the "saltiness" (hypertonicity) of the interstitial fluid in the renal medulla. (Numbers indicate osmolality.)

a maximally concentrated renal medulla. This helps to improve the ability of the kidneys to concentrate urine while retaining water.

The oncotic pressure of plasma proteins in the descending vasa recta would also be expected to draw water into these vessels. however, recent evidence indicates that water actually leaves the descending vasa recta, perhaps drawn out by a higher NaCl concentration of the interstitial fluid. The amount of water removed from the descending vasa recta is less than the amount of water that enters the ascending vasa recta, so the net action of the vasa recta is to remove water from the interstitial fluid of the renal medulla (fig. 17.16).

Effects of Urea

Countercurrent multiplication, produced by the active extrusion of NaCl without accompanying water from the thick ascending limbs, contributes most to the osmolality of the renal medulla. This is particularly true in the outer medulla, where the thick segments of the ascending limbs are located. However, the deepest portions of the medulla contain mainly thin segments of the ascending limbs, which do not actively extrude NaCl.

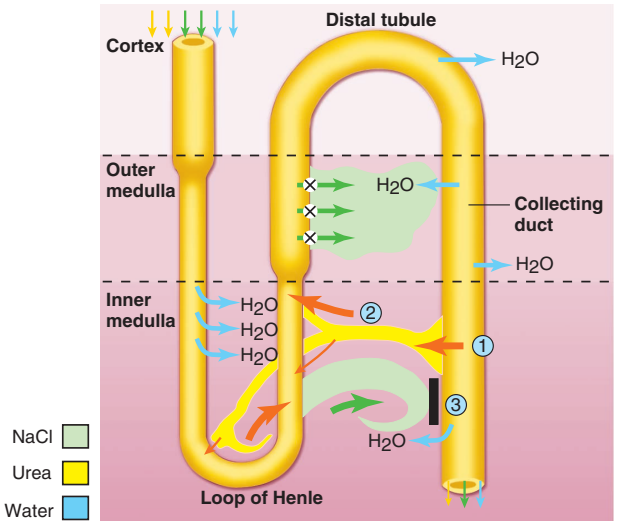


Figure 17.17 The role of urea in urine concentration. (1) Urea diffuses out of the inner collecting duct (in the renal medulla) into the interstitial fluid. (2) It can then pass into the ascending limb of the loop of Henle, so it recirculates in the interstitial fluid of the renal medulla. The urea and NaCl in the interstitial fluid of the renal medulla make it very hypertonic, so (3) water leaves the collecting duct by osmosis.

Here, **urea**—a waste product of amino acid metabolism (chapter 5; see fig. 5.16)—is believed to contribute significantly to the concentration of the interstitial fluid, although the mechanisms involved are not yet fully understood.

The terminal portions of the collecting ducts in the inner medulla are permeable to urea because they have specific urea channels. The urea that diffuses out of these portions of the collecting ducts becomes trapped in the interstitial fluid because of countercurrent exchange with the vasa recta and with the thin ascending limbs of the nephron loops (fig. 17.17). These structures recycle urea so that it can increase the osmolality of the interstitial fluid in the inner medulla.

The concentration of NaCl may be greater within the thin segments of the ascending limbs of the inner medulla than in the surrounding interstitial fluid. This would allow NaCl to passively diffuse out of these thin segments, allowing Na^+ and Cl^- to also increase the osmolality of the interstitial fluid surrounding the thin ascending limbs. Although the exact contribution of NaCl and urea to the concentration gradient of the inner medulla is still unsettled, countercurrent multiplication throughout the medulla produces a fourfold increase of concentrations (from 300 mOsm to 1200 mOsm) from the renal cortex to the inner renal medulla.

The transport properties of different tubule segments are summarized in table 17.2.

Collecting Duct: Effect of Antidiuretic Hormone (ADH)

As a result of active NaCl transport and countercurrent multiplication between the ascending and descending limbs and the recycling of urea between the collecting duct and the loop of Henle, the interstitial fluid is made very hypertonic. The collecting ducts must channel their fluid through this hypertonic environment in order to empty their contents of urine into the calyces. Whereas the fluid surrounding the collecting ducts in the medulla is hypertonic, the fluid that passes into the collecting ducts in the cortex is hypotonic because of the active extrusion of salt by the ascending limbs of the loops.

The collecting duct in the renal medulla is impermeable to the high concentration of NaCl that surrounds it. The wall of the collecting duct, however, is permeable to water. Because the surrounding interstitial fluid in the renal medulla is very hypertonic, water is drawn out of the collecting ducts by osmosis. This water does not dilute the surrounding interstitial fluid because

Table 17.2 | Transport Properties of Different Segments of the Renal Tubules and the Collecting Ducts

		Passive Transport		
Nephron Segment	**Active Transport**	**Salt**	**Water**	**Urea**
Proximal tubule	Na^+	Cl^-	Yes	Yes
Descending limb of Henle's loop	None	Maybe	Yes	No
Thin segment of ascending limb	None	NaCl	No	Yes
Thick segment of ascending limb	Na^+	Cl^-	No	No
Distal tubule	Na^+	Cl^-	No**	No
Collecting duct*	Slight Na^+	No	Yes (ADH) or slight (no ADH)	Yes

*The permeability of the collecting duct to water depends on the presence of ADH.
**The last part of the distal tubule, however, is permeable to water.

it is transported by capillaries to the general circulation. In this way, most of the water remaining in the filtrate is returned to the vascular system (fig. 17.18).

Note that it is the osmotic gradient created by the countercurrent multiplier system that provides the force for water reabsorption through the collecting ducts. Although this osmotic gradient is normally constant, the rate of osmosis across the walls of the collecting ducts can be varied by adjustments in their permeability to water. These adjustments are made by regulating the number of **aquaporins** (water channels) in the plasma membranes of the collecting duct epithelial cells.

The posterior pituitary secretes **arginine vasopressin,** the molecule that functions as the **antidiuretic hormone (ADH),** in response to as little as a 1% increase in plasma osmolality. When ADH binds to its membrane receptors in the cells of the collecting duct, it stimulates the production of cAMP as a second messenger (chapter 11, section 11.2). This initiates a chain of events that causes vesicles with aquaporins in their

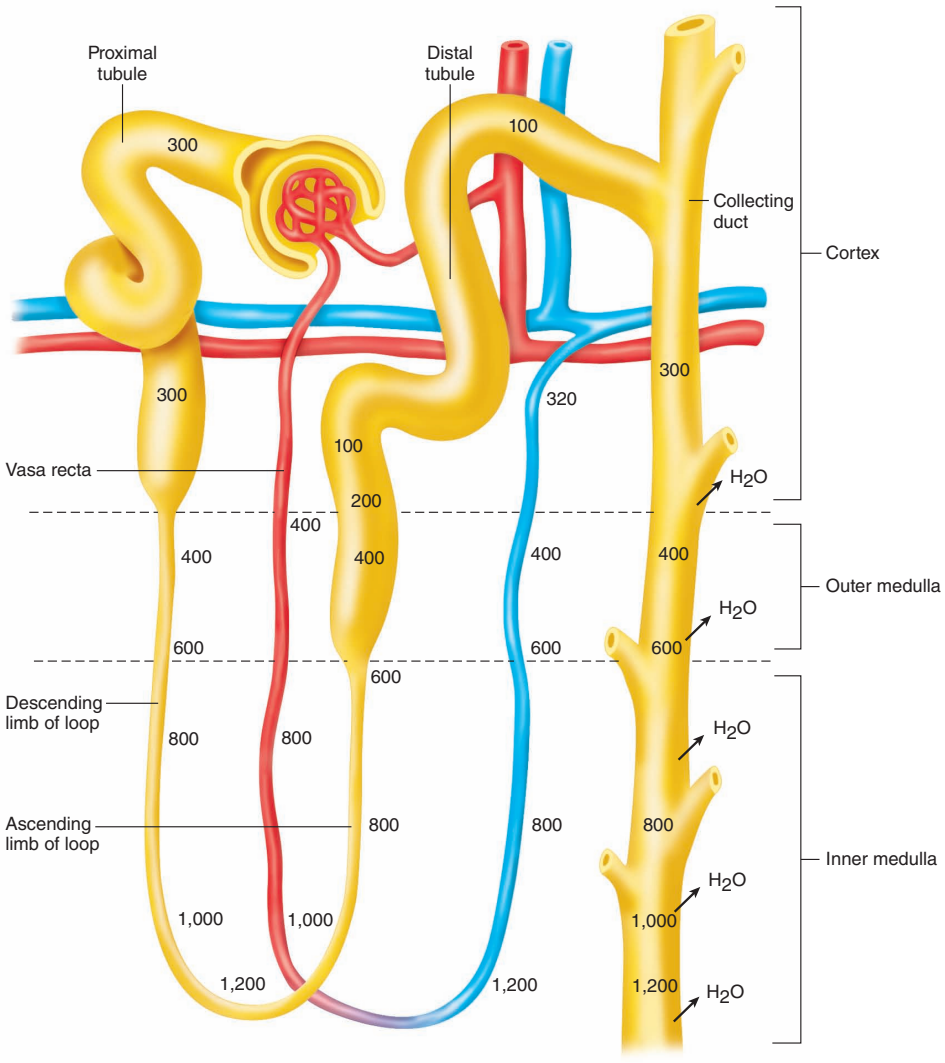


Figure 17.18 **The osmolality of different regions of the kidney.** The countercurrent multiplier system in the nephron loop and countercurrent exchange in the vasa recta help to create a hypertonic renal medulla. Under the influence of antidiuretic hormone (ADH), the collecting duct becomes more permeable to water, and thus more water is drawn out by osmosis into the hypertonic renal medulla and peritubular capillaries. (Numbers indicate osmolality.)

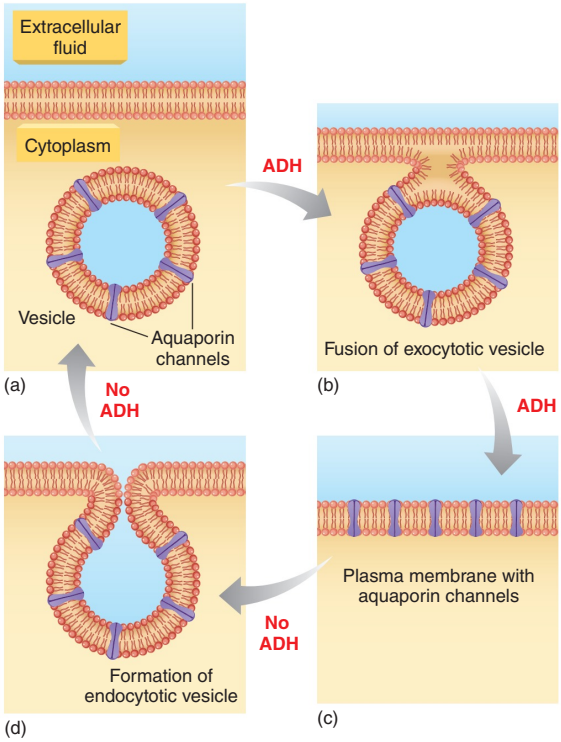


Figure 17.19 ADH stimulation of aquaporin channels. (*a*) When ADH is absent, aquaporin channels are located in the membrane of intracellular vesicles within collecting duct epithelial cells. (*b*) ADH stimulates the fusion of these vesicles with the plasma membrane and (*c*) the insertion of the aquaporin channels into the plasma membrane. (*d*) When ADH is withdrawn, the plasma membrane pinches inward (in endocytosis) to again form an intracellular vesicle and to remove the aquaporin channels from the plasma membrane.

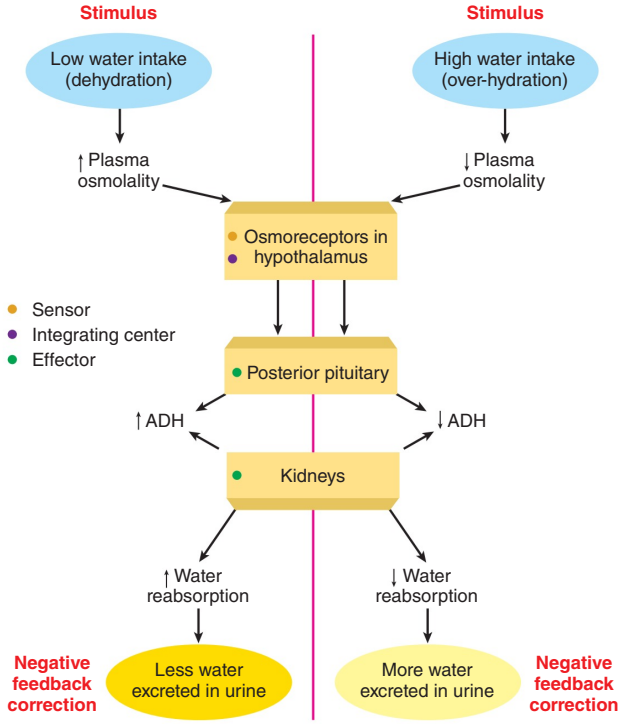


Figure 17.20 Homeostasis of plasma concentration is maintained by ADH. In dehydration (*left side of figure*), a rise in ADH secretion results in a reduction in the excretion of water in the urine. In overhydration (*right side of figure*), the excess water is eliminated through a decrease in ADH secretion. These changes provide negative feedback corrections, maintaining homeostasis of plasma osmolality and, indirectly, blood volume. AP|R

membranes to travel from the Golgi apparatus and fuse with the plasma membrane. This is similar to exocytosis, but instead of the secretion of cellular products, the process adds aquaporin channels to the plasma membrane in response to ADH stimulation.

In response to ADH, therefore, the collecting duct becomes more permeable to water. When ADH is no longer available to bind to its membrane receptors, the water channels are removed from the plasma membrane by a process of endocytosis (fig. 17.19). Endocytosis is the opposite of exocytosis; the plasma membrane invaginates to reform vesicles that again contain the water channels. Alternating exocytosis and endocytosis in response to the presence and absence of ADH, respectively, results in the recycling of water channels within the cell.

When the concentration of ADH is increased, the collecting ducts become more permeable to water and more water is reabsorbed. A decrease in ADH, conversely, results in less reabsorption of water and thus in the excretion of a larger volume of more dilute urine (fig. 17.20). ADH is produced by neurons in the hypothalamus and is released from the posterior pituitary (chapter 11; see fig. 11.13). The secretion of ADH is stimulated when osmoreceptors in the hypothalamus respond to an increase in blood osmolality above the normal range (generally 280–295 mOsm). During dehydration, therefore, when the plasma becomes more concentrated, increased secretion of ADH promotes increased permeability of the collecting ducts to water. In severe dehydration only the minimal amount of water needed to eliminate the body's wastes is excreted. This minimum, an *obligatory water loss* of about 400 ml per day, is limited by the fact that urine cannot become more concentrated than the medullary interstitial fluid surrounding the collecting ducts. Under these conditions about 99.8% of the initial glomerular ultrafiltrate is reabsorbed.

Table 17.3 | Antidiuretic Hormone Secretion and Action

Stimulus	Receptors	Secretion of ADH	Effects on Urine Volume	Effects on Blood
↑Osmolality (dehydration)	Osmoreceptors in hypothalamus	Increased	Decreased	Increased water retention; decreased blood osmolality
↓Osmolality	Osmoreceptors in hypothalamus	Decreased	Increased	Water loss increases blood osmolality
↑Blood volume	Stretch receptors in left atrium	Decreased	Increased	Decreased blood volume
↓Blood volume	Stretch receptors in left atrium	Increased	Decreased	Increased blood volume

A person in a state of normal hydration excretes about 1.5 L of urine per day, indicating that 99.2% of the glomerular ultra-filtrate volume is reabsorbed. Notice that small changes in percent reabsorption translate into large changes in urine volume. Drinking more water—and thus decreasing ADH secretion (fig. 17.20 and table 17.3)—results in correspondingly larger volumes of urine excretion. It should be noted, however, that even in the complete absence of ADH some water is still reabsorbed through the collecting ducts.

CLINICAL APPLICATION

Diabetes insipidus is characterized by *polyuria* (a large urine volume—from 3 to 10 L per day), thirst, and *polydipsia* (drinking a lot of fluids). The urine is dilute, with a hypotonic concentration of less than 300 mOsm. There are two major types of diabetes insipidus: (1) **central diabetes insipidus,** caused by inadequate secretion of ADH (arginine vasopressin); and (2) **nephrogenic diabetes insipidus,** caused by the inability of the kidneys to respond to ADH. These two types can be distinguished by measuring plasma arginine vasopressin, and by challenging the kidneys with a synthetic ADH called *desmopressin.* Nephrogenic diabetes insipidus may be caused by genetic defects in either the aquaporin channels or the ADH receptors. More commonly, it is acquired as a response to drug therapy (from lithium given to treat bipolar disorder, and from certain antibiotics) or other causes. People with central diabetes insipidus can take desmopressin when needed, and those with nephrogenic diabetes insipidus must drink a lot of water to prevent dehydration.

Clinical Investigation CLUES

Lauren was on lithium for her bipolar disorder and experienced dizziness upon standing.

- What condition likely caused Lauren's dizziness, and how is that related to dehydration?
- What treatment did the physician advise for this condition?

CHECKPOINT

6a. Describe the mechanisms for salt and water reabsorption in the proximal tubule.

6b. Compare the transport of Na^+, Cl^-, and water across the walls of the proximal tubule, ascending and descending limbs of the loop of Henle, and collecting duct.

7. Describe the interaction between the ascending and descending limbs of the loop and explain how this interaction results in a hypertonic renal medulla.

8. Explain how ADH helps the body conserve water. How do variations in ADH secretion affect the volume and concentration of urine?

17.4 RENAL PLASMA CLEARANCE

As blood passes through the kidneys, some of the constituents of the plasma are removed and excreted in the urine. The blood is thus "cleared" of particular solutes in the process of urine formation. These solutes may be removed from the blood by filtration through the glomerular capillaries or by secretion by the tubular cells into the filtrate.

LEARNING OUTCOMES

After studying this section, you should be able to:

9. Explain how renal plasma clearance is affected by reabsorption and secretion, and how it is used to measure GFR and total renal blood flow.

10. Define transport maximum and renal plasma threshold, and explain their significance.

One of the major functions of the kidneys is to eliminate excess ions and waste products from the blood. *Clearing* the blood of these substances is accomplished through their excretion in the urine. Because of renal clearance, the concentrations of these

substances in the blood leaving the kidneys (in the renal vein) is lower than their concentrations in the blood entering the kidneys (in the renal artery).

Transport Process Affecting Renal Clearance

Renal clearance refers to the ability of the kidneys to remove molecules from the blood plasma by excreting them in the urine. Molecules and ions dissolved in the plasma can be filtered through the glomerular capillaries and enter the glomerular capsules. Then, those that are not reabsorbed will be eliminated in the urine; they will be "cleared" from the blood.

The process of filtration, a type of bulk transport through capillaries, promotes renal clearance. The process of reabsorption—involving membrane transport by means of carrier proteins—moves particular molecules and ions from the filtrate into the blood, and thus reduces the renal clearance of these molecules from the blood.

There is another process that affects renal clearance, a membrane transport process called **secretion** (fig. 17.21). In terms of its direction of transport, secretion is the opposite of reabsorption—secreted molecules and ions move out of the peritubular capillaries into the interstitial fluid, and then are transported across the basolateral membrane of the tubular epithelial cells and into the lumen of the nephron tubule. Molecules that are both filtered and secreted are thus eliminated in the urine more rapidly (are cleared from the blood more rapidly) than molecules that are not secreted. In summary, the process of reabsorption decreases renal clearance, while the process of secretion increases renal clearance.

By examining figure 17.21, you can see that the rate at which a substance in the plasma is excreted in the urine is equal to the rate at which it enters the filtrate (by filtration and secretion) minus the rate at which it is reabsorbed from the filtrate. This is shown in the following equation:

$$\text{Excretion rate} = (\text{filtration rate} + \text{secretion rate}) - \text{reabsorption rate}$$

It follows that if a substance in the plasma is filtered (enters the filtrate in Bowman's capsule) but is neither reabsorbed nor secreted, its excretion rate must equal its filtration rate. This fact is used to measure the volume of blood plasma filtered per minute by the kidneys, called the **glomerular filtration rate (GFR).** Measurement of the GFR is very important in assessing the health of the kidneys.

Tubular Secretion of Drugs

Many molecules foreign to the body—known generally as *xenobiotics* and including toxins and drugs—are eliminated in the urine more rapidly than would be possible by just glomerular filtration. This implies that they are secreted by membrane carriers that somehow recognize them as foreign to the body. Considering that membrane carriers are specific and that there are so many possible xenobiotic molecules, how is this accomplished?

Scientists have discovered that there is a large number of transporters whose primary function is the elimination of xenobiotics. The major group of transport proteins involved in this elimination is the **organic anion transporter (OAT)** family. These carriers mediate a sodium-independent transport that secretes some endogenous compounds—such as steroids and bile acids—as well as numerous xenobiotics, including many therapeutic and abused drugs. Relatively small xenobiotic molecules (including penicillin and PAH, discussed shortly) are eliminated by the type of OAT in the kidneys. These transporters are located in the basolateral membrane of the proximal tubule and function to secrete their transported molecules into the filtrate of the proximal tubule. Larger xenobiotics are eliminated by the type of OATs produced in the liver that transport xenobiotics into the bile (chapter 18, section 18.5).

There are also **organic cation transporters (OCTs)** that secrete particular xenobiotics such as *metformin,* a drug used to treat type 2 diabetes mellitus (chapter 19, section 19.4). Genetic studies indicate that OCT carriers vary significantly between people, suggesting that these can contribute to individual variability in the elimination of this drug—and thereby cause differences in the responsiveness to the drug.

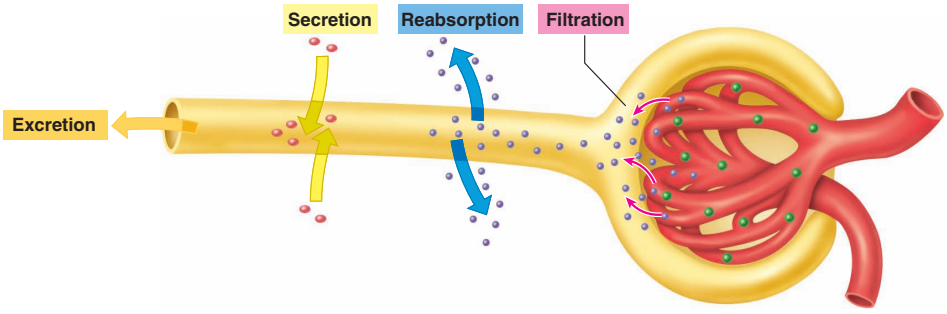


Figure 17.21 **Secretion is the reverse of reabsorption.** The term *secretion* refers to the active transport of substances from the peritubular capillaries into the tubular fluid. This transport is opposite in direction to that which occurs in reabsorption. In the actual nephron, most of the reabsorption and secretion occurs across the walls of the proximal tubule, although some important transport processes occur in later regions of the nephron tubule.

These carriers are each specific for a broad range of molecules; they are described as being *polyspecific*. The specificity of one type of carrier overlaps with the specificity of other carriers, so that they can transport a wide variety of exogenous ("originating outside") and endogenous ("originating inside") molecules across the nephron tubules. This allows the kidneys to rapidly eliminate potentially toxic molecules from the blood. however, tubular secretion of therapeutic drugs can interfere with the ability of those drugs to work.

CLINICAL APPLICATION

Probenecid is a drug used to treat *gout* by improving the ability of the kidneys to eliminate uric acid from the blood. It does this by inhibiting the uric acid transporters in the cells of the proximal tubule, reducing the *renal reabsorption* of uric acid and thereby promoting its excretion. During World War II, when **penicillin** was in short supply, probenecid was used to inhibit the *organic anion transporters* (*OATs*) in the proximal tubule, thereby reducing the *renal secretion* of penicillin. This reduces the rate at which penicillin is cleared from the blood, increasing its effectiveness and decreasing its *nephrotoxicity* (toxicity to the kidneys). Probenecid may still be used in severe infections to increase the effectiveness of penicillin and other antibiotics—including ampicillin and cephalosporin—that are secreted into the nephron by OATs.

Clinical Investigation CLUES

Lauren took probenecid to treat her gout.

- How does this drug act on the kidneys to help treat gout?
- How might this drug act on the kidneys to affect Lauren's response to certain antibiotics?

Renal Clearance of Inulin: Measurement of GFR

If a substance is neither reabsorbed nor secreted by the tubules, the amount excreted in the urine per minute will equal the amount that is filtered out of the glomeruli per minute. There does not seem to be a single substance produced by the body, however, that is not reabsorbed or secreted to some degree. Plants such as artichokes, dahlias, onions, and garlic, fortunately, do produce such a compound. This compound, a polymer of the monosaccharide fructose, is **inulin.** Once injected into the blood, inulin is filtered by the glomeruli and the amount of inulin excreted per minute is exactly equal to the amount that was filtered per minute (fig. 17.22).

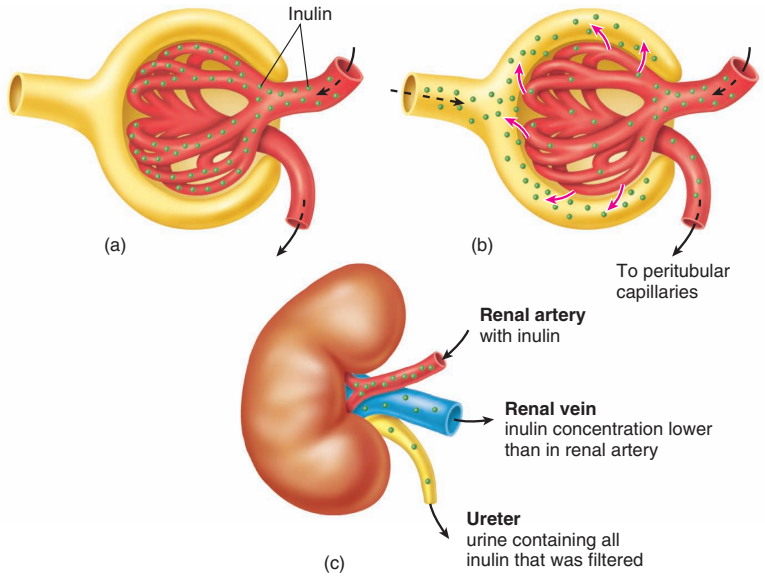


Figure 17.22 **The renal clearance of inulin.** (*a*) Inulin is present in the blood entering the glomeruli, and (*b*) some of this blood, together with its dissolved inulin, is filtered. All of this filtered inulin enters the urine, whereas most of the filtered water is returned to the vascular system (is reabsorbed). (*c*) The blood leaving the kidneys in the renal vein, therefore, contains less inulin than the blood that entered the kidneys in the renal artery. Because inulin is filtered but neither reabsorbed nor secreted, the inulin clearance rate equals the glomerular filtration rate (GFR).

See the ***Test Your Quantitative Ability*** section of the Review Activities at the end of this chapter.

If the concentration of inulin in urine is measured and the rate of urine formation is determined, the rate of inulin excretion can easily be calculated:

$$\underset{(\text{mg/min})}{\text{Quantity excreted per minute}} = \underset{\left(\frac{\text{ml}}{\text{min}}\right)}{V} \times \underset{\left(\frac{\text{mg}}{\text{ml}}\right)}{U}$$

where

V = rate of urine formation
U = inulin concentration in urine

The rate at which a substance is filtered by the glomeruli (in milligrams per minute) can be calculated by multiplying the milliliters of plasma filtered per minute (the *glomerular filtration rate,* or *GFR*) by the concentration of that substance in the plasma, as shown in this equation:

$$\underset{(\text{mg/min})}{\text{Quantity filtered per minute}} = \underset{\left(\frac{\text{ml}}{\text{min}}\right)}{GFR} \times \underset{\left(\frac{\text{mg}}{\text{ml}}\right)}{P}$$

where

P = inulin concentration in plasma

Because inulin is neither reabsorbed nor secreted, the amount filtered equals the amount excreted:

$$\underset{\text{(amount filtered)}}{GFR \times P} = \underset{\text{(amount excreted)}}{V \times U}$$

The preceding equation can now be solved for the glomerular filtration rate,

$$GFR_{(\text{ml/min})} = \frac{V_{(\text{ml/min})} \times U_{(\text{mg/ml})}}{P_{(\text{mg/ml})}}$$

Suppose, for example, that inulin is infused into a vein and its concentrations in the urine and plasma are found to be 30 mg per ml and 0.5 mg per ml, respectively. If the rate of urine formation is 2 ml per minute, the GFR can be calculated as:

$$GFR = \frac{2 \text{ ml/min} \times 30 \text{ mg/ml}}{0.5 \text{ mg/ml}} = 120 \text{ ml/min}$$

This equation states that 120 ml of plasma must have been filtered each minute in order to excrete the measured amount of inulin that appeared in the urine. The glomerular filtration rate is thus 120 ml per minute in this example.

CLINICAL APPLICATION

Creatinine is produced in muscles from creatine and released into the blood plasma, where its concentration is used to help assess kidney function. Creatinine is filtered by the kidneys and not reabsorbed; but it is slightly secreted by the tubules, giving it a renal plasma clearance a little greater than that of inulin (and thus a little greater than the true GFR). However, its plasma concentration, together with a person's age, sex, and weight, is frequently used in equations to calculate an **estimated GFR** (**eGFR**). Also, the ratio of the plasma concentrations of urea (called a *BUN—blood urea nitrogen*—test) to creatinine provides additional information about kidney health.

Clinical Investigation CLUES

Lauren's blood test results indicated that she has a normal eGFR.

- What is an eGFR and how is it obtained?
- What is the significance of an eGFR measurement?

Renal Clearance Measurements

The **renal plasma clearance** is the volume of plasma from which a substance is completely removed in one minute by excretion in the urine. Notice that the units for renal plasma clearance are ml/min. The simplest example is the renal plasma clearance of inulin, which is filtered but neither reabsorbed nor secreted. In that case the amount of inulin that enters the urine equals the amount that enters the glomerular filtrate. Because of this, the renal plasma clearance of inulin is equal to the glomerular filtration rate (giving a GFR of 120 ml/ min in the previous example). This volume of filtered plasma, however, also contains other solutes that may be reabsorbed to varying degrees. If a portion of a filtered solute is reabsorbed, the amount of it excreted in the urine is less than the amount of it contained in the 120 ml of plasma filtered. Thus, *the renal plasma clearance of a substance that is reabsorbed must be less than the GFR* (table 17.4).

Table 17.4 | Effects of Filtration, Reabsorption, and Secretion on Renal Plasma Clearance

Term	Definition	Effect on Renal Clearance
Filtration	A substance enters the glomerular ultrafiltrate.	Some or all of a filtered substance may enter the urine and be "cleared" from the blood.
Reabsorption	A substance is transported from the filtrate, through tubular cells, and into the blood.	Reabsorption decreases the rate at which a substance is cleared; clearance rate is less than the glomerular filtration rate (GFR).
Secretion	A substance is transported from peritubular blood, through tubular cells, and into the filtrate.	When a substance is secreted by the nephrons, its renal plasma clearance is greater than the GFR.

Table 17.5 | Renal "Handling" of Different Plasma Molecules

If Substance Is:	Example	Concentration in Renal Vein	Renal Clearance Rate
Not filtered	Proteins	Same as in renal artery	Zero
Filtered, not reabsorbed or secreted	Inulin	Less than in renal artery	Equal to GFR (115–125 ml/min)
Filtered, partially reabsorbed	Urea	Less than in renal artery	Less than GFR
Filtered, completely reabsorbed	Glucose	Same as in renal artery	Zero
Filtered and secreted	PAH	Less than in renal artery; approaches zero	Greater than GFR; up to total plasma flow rate (~625 ml/min)
Filtered, reabsorbed, and secreted	K^+	Variable	Variable

If a substance is not reabsorbed, all of the filtered amount will be cleared. If this substance is, in addition, secreted by active transport into the renal tubules from the peritubular blood, an additional amount of plasma can be cleared of that substance. Therefore, *the renal plasma clearance of a substance that is filtered and secreted is greater than the GFR* (table 17.5). In order to compare the renal "handling" of various substances in terms of their reabsorption or secretion, the renal plasma clearance is calculated using the same formula used for determining the GFR:

$$\text{Renal plasma clearance} = \frac{V \times U}{P}$$

where

V = urine volume per minute
U = concentration of substance in urine
P = concentration of substance in plasma

Clearance of Urea

Urea may be used as an example of how the clearance calculations can reveal the way the kidneys handle a molecule. Urea is a waste product of amino acid metabolism that is released by the liver into the blood and filtered into the glomerular capsules. Using the formula for renal clearance previously described and these sample values, the urea clearance can be obtained:

$V = 2$ ml/min
$U = 7.5$ mg/ml of urea
$P = 0.2$ mg/ml of urea

$$\text{Urea clearance} = \frac{(2 \text{ ml/min})(7.5 \text{ mg/ml})}{0.2 \text{ mg/ml}} = 75 \text{ ml/min}$$

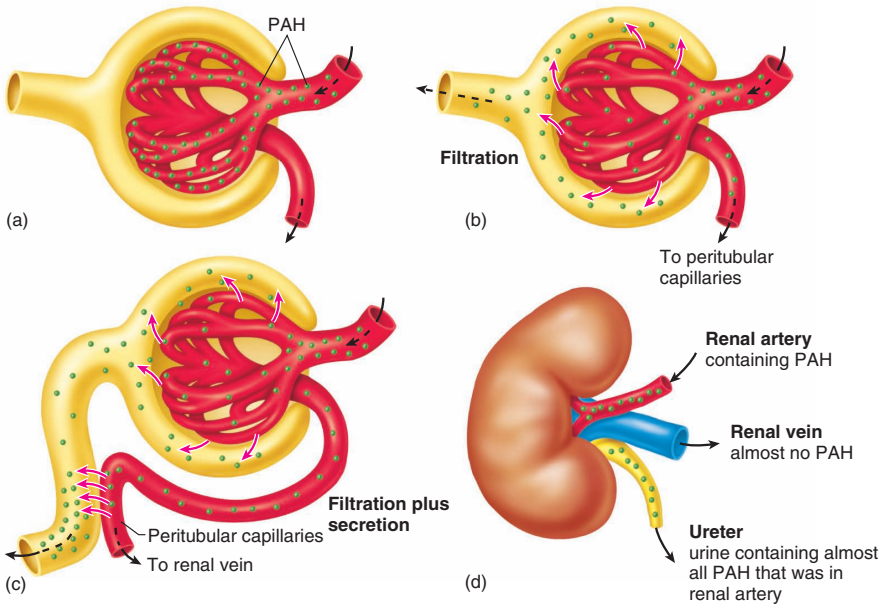


Figure 17.23 The renal clearance of PAH. Some of the para-aminohippuric acid (PAH) in glomerular blood (*a*) is filtered into the glomerular (Bowman's) capsules (*b*). The PAH present in the unfiltered blood is secreted from the peritubular capillaries into the nephron (*c*), so that all of the blood leaving the kidneys is free of PAH (*d*). The clearance of PAH therefore equals the total renal blood flow.

The clearance of urea in this example (75 ml/min) is less than the clearance of inulin (120 ml/min). Even though 120 ml of plasma filtrate entered the nephrons per minute, only the amount of urea contained in 75 ml of filtrate is excreted. We can conclude that the kidneys must have reaborbed some of the filtered urea. Although urea is a waste product of amino acid metabolism, a significant portion of the filtered urea (from 40% to 60%) is always reabsorbed by facilitated diffusion through the urea channels described in section 17.3. Urea diffuses out of the collecting duct and into the ascending limb, recycling in the interstitial fluid of the renal medulla and thereby contributing to its hypertonicity (see fig. 17.18).

Clearance of PAH: Measurement of Renal Blood Flow

Not all of the blood delivered to the glomeruli is filtered into the glomerular capsules; most of the glomerular blood passes through to the efferent arterioles and peritubular capillaries. The inulin and urea in this unfiltered blood are not excreted but instead return to the general circulation. Blood must therefore make many passes through the kidneys before it can be completely cleared of a given amount of inulin or urea.

For compounds in the unfiltered renal blood to be cleared, they must be secreted into the tubules by active transport from the peritubular capillaries. In this way, all of the blood going to the kidneys can potentially be cleared of a secreted compound in a single pass. This is the case for an exogenous molecule called **para-aminohippuric acid (PAH),** which can be infused into the blood. All of the PAH entering the peritubular capillaries is secreted by carriers of the organic anion transporter family (previously discussed) into the filtrate of the proximal tubule (fig. 17.23). Because of this, the clearance (in ml/min) of PAH can be used to measure the **total renal blood flow.** The normal PAH clearance has been found to average 625 ml/min. Since the glomerular filtration rate averages about 120 ml/min, this indicates that only about 120/625, or roughly 20%, of the renal plasma flow is filtered. The remaining 80% passes on to the efferent arterioles.

Reabsorption of Glucose

Glucose and amino acids in the blood are easily filtered by the glomeruli into the renal tubules. However, these molecules are not present (above trace amounts) in normal urine, indicating that they must be completely reabsorbed. This occurs in the proximal tubule by secondary active transport, which is mediated by membrane carriers that cotransport glucose and Na^+ (fig. 17.24), or amino acids and Na^+.

Carrier-mediated transport displays the property of *saturation.* This means that when the transported molecule (such as glucose) is present in sufficiently high concentrations, all of the carriers become occupied and the transport rate reaches a maximal value. This is known as the **transport maximum** (abbreviated T_m). When the plasma glucose concentration is in the normal range, the glucose carriers are not saturated and the filtered glucose can be completely reabsorbed. however, when the plasma concentration is sufficiently high the filtered glucose can saturate the carriers. Then, when the rate of glucose filtration is greater than the transport maximum of the carriers,

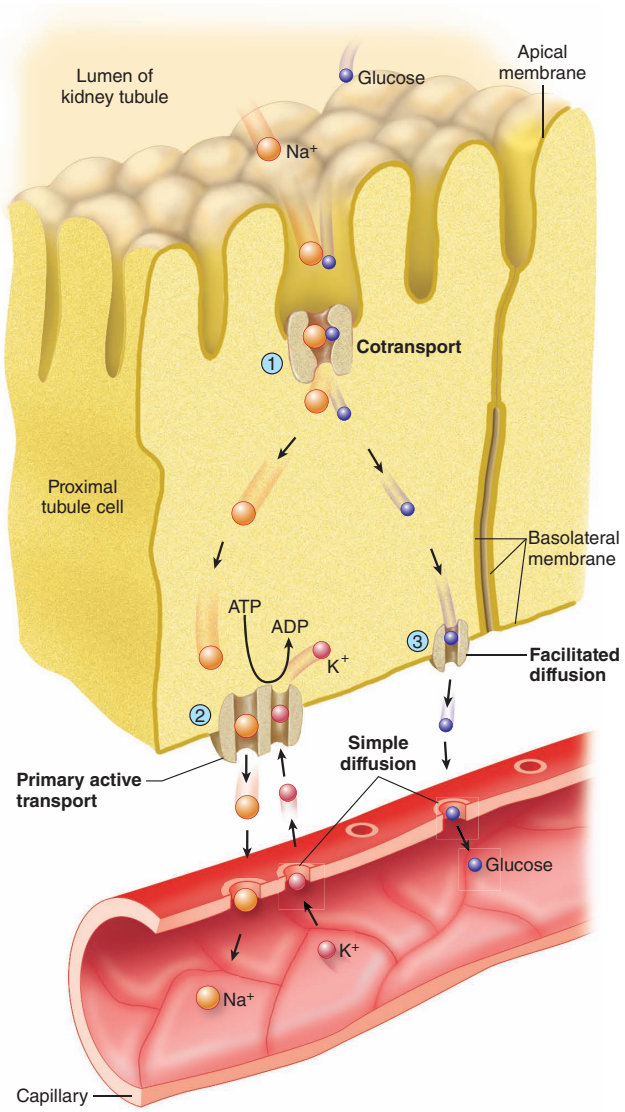


Figure 17.24 The mechanism of reabsorption in the proximal tubule. The appearance of proximal tubule cells in the electron microscope is illustrated. Molecules that are reabsorbed pass through the tubule cells from the apical membrane (*facing the filtrate*) to the basolateral membrane (*facing the blood*). (1) There is coupled transport (secondary active transport) of glucose and Na^+ into the cytoplasm, and (2) primary active transport of Na^+ across the basolateral membrane by the Na^+/K^+ pump. (3) Glucose is then transported out of the cell by facilitated diffusion and is reabsorbed into the blood.

the excess glucose will continue its journey through the renal tubules and "spill over" into the urine.

The average T_m for glucose is 375 mg per minute. This is much higher than the rate at which glucose is normally delivered to the tubules. The rate of glucose filtration equals the plasma glucose concentration multiplied by the glomerular filtration rate (GFR). Since the fasting plasma glucose concentration is about 1 mg per ml, and the GFR is about 125 ml per minute, the rate of glucose filtration is about 125 mg per minute. The carriers are not saturated until 375 mg per minute of glucose are filtered, so normally the carriers are not saturated and all of the glucose can be reabsorbed. The plasma glucose concentration would have to triple before the average transport maximum would be reached.

Glycosuria

Glucose appears in the urine—a condition called **glycosuria**—when more glucose passes through the tubules than can be reabsorbed. This occurs when the plasma glucose concentration reaches 180 to 200 mg per 100 ml. Because the rate of glucose delivery under these conditions is still below the average T_m for glucose, we must conclude that some nephrons have considerably lower T_m values than the average.

The **renal plasma threshold** is the minimum plasma concentration of a substance that results in the excretion of that substance in the urine. The renal plasma threshold for glucose, for example, is 180 to 200 mg per 100 ml. Glucose is normally absent from urine because plasma glucose concentrations normally remain below this threshold value. Fasting plasma glucose is about 100 mg per 100 ml, for example, and the plasma glucose concentration following meals does not usually exceed 150 mg per 100 ml. The appearance of glucose in the urine (glycosuria) occurs only when the plasma glucose concentration is abnormally high (*hyperglycemia*) and exceeds the renal plasma threshold.

Fasting hyperglycemia is caused by the inadequate secretion or action of insulin. When this hyperglycemia results in glycosuria, the disease is called **diabetes mellitus.** A person with uncontrolled diabetes mellitus also excretes a large volume of urine because the excreted glucose carries water with it as a result of the osmotic pressure it generates in the tubules. This condition should not be confused with diabetes insipidus (discussed previously), in which a large volume of dilute urine is excreted as a result of inadequate ADH secretion or action.

Clinical Investigation CLUES

Lauren's urine tested negative for glucose.

- What processes determine the presence of glucose in the urine?
- What would be the significance of a positive urine test for glucose?

CHECKPOINT

9a. Define *renal plasma clearance* and describe how this volume is measured. Explain why the glomerular filtration rate is equal to the clearance rate of inulin.

9b. Define the terms *reabsorption* and *secretion.* Using examples, describe how renal plasma clearance is affected by the processes of reabsorption and secretion.

9c. Explain why the total renal blood flow can be measured by the renal plasma clearance of PAH.

10. Define *transport maximum* and *renal plasma threshold.* Explain why people with diabetes mellitus have glycosuria.

17.5 RENAL CONTROL OF ELECTROLYTE AND ACID-BASE BALANCE

The kidneys regulate the blood concentrations of Na^+, K^+, HCO_3^- and H^+ and thereby are responsible for maintaining the homeostasis of plasma electrolytes and the acid-base balance. Renal reabsorption of Na^+ and secretion of K^+ and H^+ are stimulated by aldosterone.

LEARNING OUTCOMES

After studying this section, you should be able to:

11. Explain how the renal excretion and reabsorption of Na^+, K^+, and H^+, is regulated by the reninangiotensin-aldosterone system.

12. Explain how the kidneys reabsorb bicarbonate, and how the kidneys contribute to the regulation of acid-base balance.

The kidneys help regulate the concentrations of plasma electrolytes—sodium, potassium, chloride, bicarbonate, sulfate, and phosphate—by matching the urinary excretion of these compounds to the amounts ingested. For example, the reabsorption of sulfate and phosphate ions across the walls of the proximal tubules is the primary determinant of their plasma concentrations. Parathyroid hormone (PTH) secretion, stimulated by a fall in plasma Ca^{2+}, acts on the kidneys to decrease the reabsorption of phosphate (chapter 19; see fig. 19.22). The control of plasma Na^+ is important in the regulation of blood volume and pressure; the control of plasma K^+ is required to maintain proper function of cardiac and skeletal muscles.

Role of Aldosterone in Na^+/K^+ Balance

Approximately 90% of the filtered Na^+ and K^+ is reabsorbed in the early part of the nephron before the filtrate reaches the

distal tubule. This reabsorption occurs at a constant rate and is not subject to hormonal regulation. The final concentration of Na^+ and K^+ in the urine is varied according to the needs of the body by processes that occur in the late distal tubule and in the cortical region of the collecting duct (the portion of the collecting duct within the medulla does not participate in this regulation). Renal reabsorption of Na^+ and secretion of K^+ are regulated by **aldosterone,** the principal mineralocorticoid secreted by the adrenal cortex (chapter 11, section 11.4).

Sodium Reabsorption

Although about 90% of the filtered sodium is reabsorbed in the early region of the nephron, the amount left in the filtrate delivered to the distal convoluted tubule is still substantial. In the absence of aldosterone, 80% of this remaining amount is reabsorbed through the wall of the tubule into the peritubular blood; this represents 8% of the amount filtered. The amount of sodium excreted without aldosterone is thus 2% of the amount filtered. Although this percentage seems small, the actual amount it represents is an impressive 30 g of sodium excreted in the urine each day. When aldosterone is secreted in maximal amounts, by contrast, all of the Na^+ delivered to the distal tubule is reabsorbed. In this case urine contains no Na^+ at all.

Aldosterone stimulates Na^+ reabsorption to some degree in the *late distal convoluted tubule,* but the primary site of aldosterone action is in the **cortical collecting duct.** This is the initial portion of the collecting duct located in the renal cortex, which has different permeability properties than the terminal portion of the collecting duct in the renal medulla. Aldosterone stimulates the activity of Na^+/K^+ (ATPase) pumps in the basolateral membrane of cortical collecting duct cells. This increases the electrochemical gradient for the passive movement of Na^+ from the filtrate, through Na^+ channels in the apical membrane (facing the lumen), and into the cytoplasm. The active reabsorption of Na^+ creates a negative potential in the tubule lumen, which drives the passive reabsorption of Cl^-.

Potassium Secretion

About 90% of the filtered potassium is reabsorbed in the early regions of the nephron (mainly from the proximal tubule). In order for potassium to appear in the urine, it must be secreted into later regions of the nephron tubule. Secretion of potassium occurs in the parts of the nephron that are sensitive to aldosterone—that is, in the late distal tubule and cortical collecting duct (fig. 17.25).

The secretion of K^+ into the late distal tubule and cortical collecting duct matches the amount of K^+ ingested in the diet, so that the blood K^+ concentration remains in the normal range. When a person eats a K^+-rich meal, the rise in blood K^+ stimulates the adrenal cortex to secrete aldosterone. Aldosterone then stimulates an increase in the secretion of K^+ into the filtrate. In addition to this aldosterone-dependent K^+ secretion, there is also an aldosterone-independent K^+ secretion. In this process, the rise in blood K^+ directly causes additional K^+ channels to become inserted into the membrane of the cortical collecting duct. By contrast, when the blood K^+ falls, those K^+ channels are removed from the membrane by endocytosis and K^+ secretion is thereby reduced.

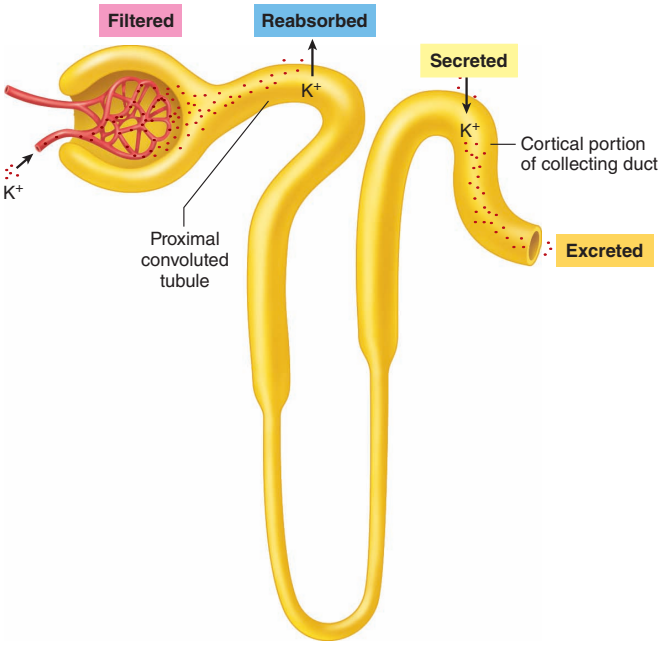


Figure 17.25 Potassium is reabsorbed and secreted. Potassium (K^+) is almost completely reabsorbed in the proximal tubule, but under aldosterone stimulation it is secreted into the cortical portion of the collecting duct. All of the K^+ in urine is derived from secretion rather than from filtration.

The secretion of K^+ involves the transport of K^+ across the basolateral membrane by means of the Na^+/K^+ ATPase pump, followed by the diffusion of K^+ into the filtrate through K^+ channels in the apical membrane. This diffusion of K^+ across the apical membrane is promoted by the reabsorption of Na^+, which creates a potential difference that favors the diffusion of K^+ into the filtrate. Because K^+ secretion is increased when there is an increased Na^+ reabsorption, a rise in the Na^+ content of the filtrate reaching the distal tubule will cause an increased K^+ secretion. At the same time, the increased Na^+ and water in the filtrate can stimulate the juxtaglomerular apparatus to secrete renin, activating the renin-angiotensin-aldosterone system (described shortly). The increased aldosterone secretion then also stimulates more Na^+ reabsorption and K^+ secretion.

There is yet another possible mechanism by which an increased delivery of Na^+, due to increased flow of filtrate to the distal tubule, can stimulate increased K^+ secretion. Distal tubule cells contain a primary cilium (discussed in the Clinical Application box on p. 586) that protrudes into the lumen. In the distal tubules of the nephrons, the bending of the primary cilium by increased flow rates could activate K^+ channels and lead to increased K^+ secretion into the filtrate.

These mechanisms help explain how certain diuretic drugs can produce hypokalemia (low blood potassium). *Diuretics* (drugs that increase urine volume; section 17.6) that act to inhibit Na^+ transport in the nephron loop increase the delivery of Na^+ to the distal tubule. This results in increased Na^+ reabsorption and K^+ secretion in the late distal tubule and cortical collecting duct. As a result, there can be excessive urinary excretion of K^+, which may require the person who is taking the diuretic to also take potassium supplements.

CLINICAL APPLICATION

Hyperkalemia is defined as a plasma K^+ concentration greater than the normal range of 3.5 to 5.0 mEq/L. Symptoms of moderate hyperkalemia include nausea, weakness, and changes in the ECG. Aldosterone is required for the adequate elimination of K^+ by stimulating the secretion of K^+ into the cortical collecting ducts, and so adrenal insufficiency (as may be produced by *Addison's disease;* chapter 11, section 11.4) can cause hyperkalemia as well as hyponatremia (low plasma Na^+). **Hypokalemia,** defined as a plasma K^+ concentration of less than 3.5 mEq/L, can produce heart arrhythmias and muscle weakness. It is most commonly caused by the use of certain diuretics (section 17.6) or vomiting and metabolic alkalosis (discussed shortly), but can also be caused by the excessive aldosterone secretion of *primary hyperaldosteronism* (*Conn syndrome*) or *Cushing syndrome.*

Clinical Investigation CLUES

Lauren experienced muscle weakness and her lab test revealed that she had hypokalemia. Her physician took her off hydrochlorothiazide and prescribed a different medicine.

- What is hypokalemia, and how might it have been produced in Lauren?
- What other symptoms might her hypokalemia produce?

Control of Aldosterone Secretion

Because aldosterone promotes Na^+ retention and K^+ loss, one might predict (on the basis of negative feedback) that aldosterone secretion would be increased when there was a low Na^+ or a high K^+ concentration in the blood. This indeed is the case. A rise in plasma K^+ concentration depolarizes the aldosterone-secreting cells of the adrenal cortex, directly stimulating aldosterone secretion. A decrease in plasma Na^+ also promotes aldosterone secretion, but it does this indirectly. This is because decreased plasma Na^+ is accompanied by a fall in blood volume, which activates the renin-angiotensin-aldosterone system (described next).

Juxtaglomerular Apparatus

The **juxtaglomerular apparatus** is the region in each nephron where the afferent arteriole comes into contact with the last portion of the thick ascending limb of the loop (fig. 17.26). Under the microscope, the afferent arteriole and tubule in this small region have a different appearance than in other regions. *Granular cells* within the afferent arteriole secrete the enzyme **renin** into the blood. The juxtaglomerular apparatus also contains the *macula densa,* to be described shortly.

Renin catalyzes the conversion of *angiotensinogen* (a protein in the blood plasma) into *angiotensin I* (a ten-amino-acid polypeptide). Angiotensin I is converted into **angiotensin II** (an eight-amino-acid polypeptide) by *angiotensin converting enzyme (ACE).* This conversion occurs primarily as blood passes through the capillaries of the lungs, where most of the ACE is present. The secretion of renin into the plasma by the granular cells of the juxtaglomerular apparatus thereby results in the increased production of angiotensin II.

Angiotensin II, in addition to its other effects (chapter 14, section 14.2), stimulates the adrenal cortex to secrete aldosterone. Thus, secretion of renin from the granular cells of the juxtaglomerular apparatus initiates the **renin-angiotensin-aldosterone system** (chapter 14; see fig. 14.12). conditions that result in increased renin secretion cause increased aldosterone secretion and, by this means, promote the reabsorption of Na^+ from cortical collecting duct into the blood (fig. 17.27).

Angiotensin II circulating through the body has long been known to raise systemic blood pressure as a result of its vasoconstrictor effects, and to stimulate aldosterone secretion. Additionally, angiotensin II is produced within the kidneys, where it: (1) stimulates sodium reabsorption by promoting the activity of sodium transporters in the renal tubules; and (2) stimulates vasoconstriction of afferent and efferent arterioles, leading to a decrease in GFR and sodium excretion. These renal effects contribute to the angiotensin II–induced rise in blood volume and blood pressure.

Regulation of Renin Secretion

An inadequate dietary intake of salt (NaCl) is always accompanied by a fall in blood volume. This is because the decreased plasma concentration (osmolality) inhibits ADH secretion. With less ADH, less water is reabsorbed through the collecting ducts and more is excreted in the urine. The fall in blood volume and the fall in renal blood flow that result cause increased renin secretion. Increased renin secretion is due in part to the direct effect of blood pressure on the granular cells, which function as baroreceptors in the afferent arterioles. Renin secretion is also stimulated by sympathetic nerve activation of β_1-adrenergic receptors in the granular cells of the juxtaglomerular apparatus. This happens during the baroreceptor reflex, which increases sympathetic nerve activity when there is a fall in blood volume and pressure (chapter 14, section 14.6).

An increased secretion of renin acts, via the increased production of angiotensin II, to stimulate aldosterone secretion.

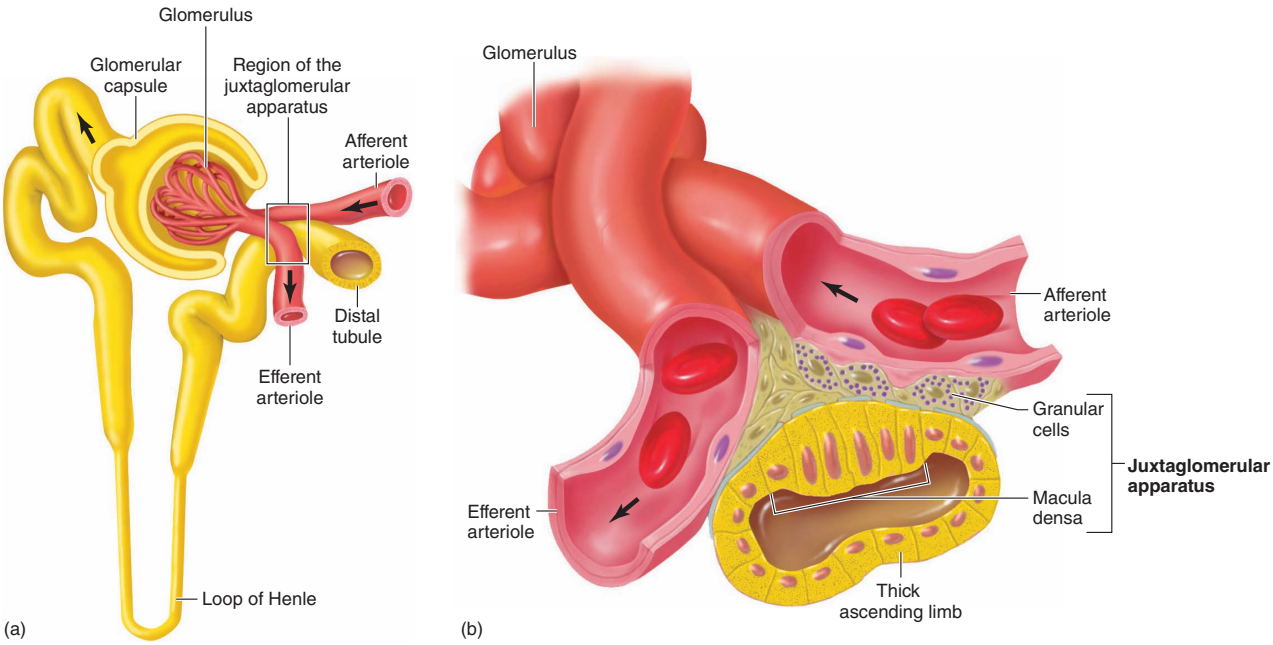


Figure 17.26 **The juxtaglomerular apparatus.** (*a*) The location of the juxtaglomerular apparatus. This structure includes the region where the afferent arteriole contacts the last portion of the thick ascending limb of the loop. The afferent arterioles in this region contain granular cells that secrete renin, and the tubule cells in contact with the granular cells form an area called the macula densa, seen in (*b*).

consequently, less sodium is excreted in the urine and more is retained in the blood. This negative feedback system is illustrated in figure 17.27.

Role of the Macula Densa

The region where the thick portion of the ascending limb makes contact with the granular cells of the afferent arteriole is called the *macula densa* (see fig. 17.26). When there is increased NaCl and H_2O in the filtrate, the macula densa senses this through its Na^+-K^+-$2Cl^-$ cotransporters (see fig. 17.15) and releases ATP. As described in section 17.2 on the autoregulation of the GFR, the ATP (or adenosine derived from it) stimulates the afferent arteriole to constrict. Constriction of the afferent arteriole lowers the GFR, reducing the flow of NaCl and H_2O in a negative feedback manner to complete the tubuloglomerular feedback loop.

When the plasma and filtrate concentrations of Na^+ increase, the macula densa also signals the granular cells to reduce their secretion of renin. There is thus less angiotensin II produced and less aldosterone secreted. With less aldosterone, less Na^+ is reabsorbed through the cortical collecting duct. As a result, more Na^+ (together with Cl^- and H_2O) is excreted in the urine to help restore homeostasis of blood volume. The regulation of renin and aldosterone secretion is summarized in table 17.6.

Natriuretic Peptides

Expansion of the blood volume causes increased salt and water excretion in the urine. This is partly due to an inhibition of aldosterone secretion, as previously described. However, it is also caused by increased secretion of a *natriuretic hormone,* a hormone that stimulates salt excretion (*natrium* is Latin for sodium)—an action opposite to that of aldosterone. The first natriuretic hormone to be identified is a polypeptide called **atrial natriuretic peptide (ANP),** also called *atrial natriuretic factor* (chapter 14, section 14.2). Atrial natriuretic peptide is

CLINICAL APPLICATIONS

In addition to atrial natriuretic peptide, scientists have discovered a natriuretic hormone released by the heart's ventricles called **B-type natriuretic peptide (BNP).** BNP is secreted in response to increased volume and pressure within the ventricles, and it acts like ANP to promote diuresis. Because the secretion of BNP increases in **congestive heart failure (CHF),** measurements of the blood level of BNP are used clinically to help diagnose CHF. This is especially useful in distinguishing cardiac versus pulmonary causes of a patient's *dyspnea* (difficulty breathing).

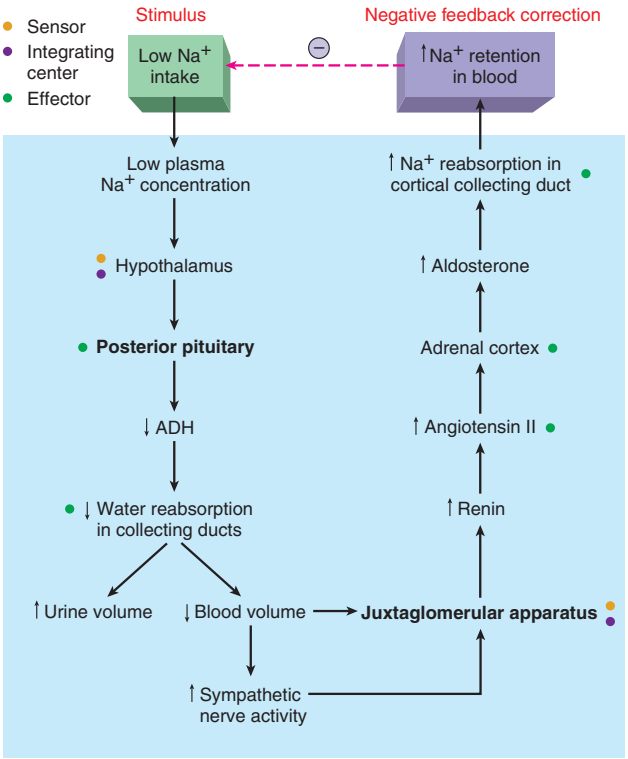


Figure 17.27 **Homeostasis of plasma Na^+.** This is the sequence of events by which a low sodium (salt) intake leads to increased sodium reabsorption by the kidneys. The dashed arrow and negative sign indicate the completion of the negative feedback loop.

produced by the atria of the heart and secreted in response to the stretching of the atrial walls by increased blood volume. In response to ANP action, the kidneys lower the blood volume by excreting more of the salt and water filtered out of the blood by the glomeruli. Atrial natriuretic peptide thus functions as an endogenous diuretic.

Relationship Between Na^+, K^+, and H^+

The plasma K^+ concentration indirectly affects the plasma H^+ concentration (pH). Changes in plasma pH likewise affect the K^+ concentration of the blood. When the extracellular H^+ concentration increases, for example, some of the H^+ moves into cells and causes cellular K^+ to diffuse outward into the extracellular fluid. The plasma concentration of H^+ is thus decreased while the K^+ increases, helping to reestablish the proper ratio of these ions in the extracellular fluid. A similar effect occurs in the cells of the distal region of the nephron.

In the cells of the late distal tubule and cortical collecting duct, positively charged ions (K^+ and H^+) are secreted in response to the negative polarity produced by reabsorption of Na^+ (fig. 17.28). Acidosis (increased plasma H^+ concentration) increases the secretion of H^+ and reduces the secretion of K^+ into the filtrate. Acidosis may thus be accompanied by a rise in blood K^+. By contrast, alkalosis (lowered plasma H^+ concentration) increases the renal secretion of K^+ into the filtrate, and thus the excretion of K^+ in the urine. If, on the other hand, hyperkalemia is the primary problem, there is an increased secretion of K^+ and thus a decreased secretion of H^+. Hyperkalemia can thus cause an increase in the blood concentration of H^+ and acidosis.

Because aldosterone promotes the secretion of both K^+ and H^+ into the filtrate, an abnormally high aldosterone secretion (as in primary hyperaldosteronism) causes both hypokalemia and metabolic alkalosis. Conversely, abnormally low aldosterone secretion (as in Addison's disease) can produce hyperkalemia accompanied by metabolic acidosis.

Renal Acid-Base Regulation

The kidneys help regulate the blood pH by excreting H^+ in the urine (mostly in buffered form, as described shortly) and by reabsorbing bicarbonate. Because the kidneys normally reabsorb almost all of the filtered bicarbonate and excrete H^+, normal urine contains little bicarbonate and is slightly acidic (with a pH range between 5 and 7). The mechanisms involved in the

Table 17.6 | Regulation of Renin and Aldosterone Secretion

Stimulus	Effect on Renin Secretion	Angiotensin II Production	Aldosterone Secretion	Mechanisms
↓Blood volume	Increased	Increased	Increased	Low blood volume stimulates renal baroreceptors; granular cells release renin.
↑Blood volume	Decreased	Decreased	Decreased	Increased blood volume inhibits baroreceptors; increased Na^+ in distal tubule acts via macula densa to inhibit release of renin from granular cells.
↑ K^+	None	Not changed	Increased	Direct stimulation of adrenal cortex
↑Sympathetic nerve activity	Increased	Increased	Increased	α-adrenergic effect stimulates constriction of afferent arterioles; β-adrenergic effect stimulates renin secretion directly.

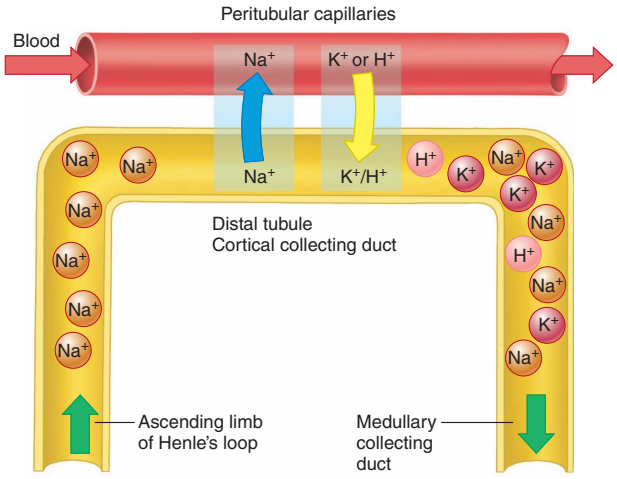


Figure 17.28 The reabsorption of Na^+ and secretion of K^+ and H^+. In the distal tubule, K^+ and H^+ are secreted in response to the potential difference produced by the reabsorption of Na^+. High concentrations of H^+ may therefore decrease K^+ secretion, and vice versa.

acidification of the urine and reabsorption of bicarbonate are summarized in figure 17.29.

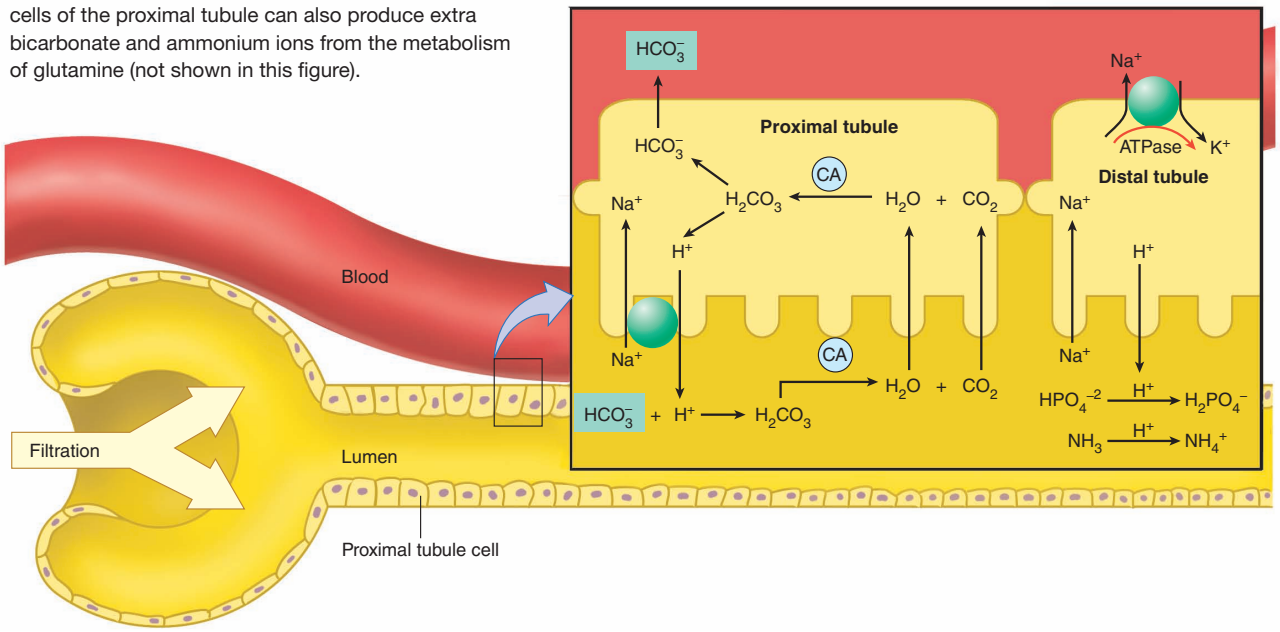
Reabsorption of Bicarbonate and Secretion of H^+

The cells of the proximal tubule use Na^+/H^+ pumps to transport H^+ into the filtrate in exchange for Na^+ from the filtrate (fig. 17.29). This exchange is "antiport" cotransport (chapter 6), because the Na^+ and H^+ move in opposite directions across the apical portion of the plasma membrane (facing the tubule lumen). Antiport cotransport is a form of secondary active transport, because Na^+ diffuses down the concentration gradient maintained by primary active transport Na^+/K^+ pumps in the basolateral portion of the plasma membrane. Most of the H^+ secreted into the filtrate from the proximal tubule is used for the reabsorption of bicarbonate.

The apical membranes of the tubule cells (facing the lumen) are impermeable to bicarbonate. The reabsorption of bicarbonate must therefore occur indirectly. When the urine is acidic, HCO_3^- combines with H^+ to form carbonic acid. Carbonic acid in the filtrate is then converted to CO_2 and H_2O in a reaction catalyzed by **carbonic anhydrase.** This enzyme is located in the apical plasma membrane of the proximal tubule in contact with the filtrate. Notice that the reaction that occurs in the filtrate is the same one that occurs within red blood cells in pulmonary capillaries (chapter 16, section 16.7).

The tubule cell cytoplasm also contains carbonic anhydrase. As CO_2 concentrations increase in the filtrate, the CO_2 diffuses

Figure 17.29 Acidification of the urine. This diagram summarizes how the urine becomes acidified and how bicarbonate is reabsorbed from the filtrate. It also depicts the buffering of the urine by phosphate and ammonium buffers. (CA = carbonic anhydrase.) The inset depicts an expanded view of proximal tubule cells. Note: The cells of the proximal tubule can also produce extra bicarbonate and ammonium ions from the metabolism of glutamine (not shown in this figure).



into the tubule cells. Within the tubule cell cytoplasm, carbonic anhydrase catalyzes the reaction in which CO_2 and H_2O form carbonic acid. The carbonic acid then dissociates to HCO_3^- and H^+ within the tubule cells. (These are the same events that occur in the red blood cells of tissue capillaries.) The bicarbonate within the tubule cell can then diffuse through the basolateral membrane and enter the blood (fig. 17.29).

Under normal condition, the proximal tubule reabsorbs 80% to 90% of the filtered bicarbonate. This process of HCO_3^- reabsorption in the proximal tubule leaves very little H^+ in the filtrate. Despite this, urine is usually more acidic than blood plasma. This is because the distal tubule secretes H^+ into the filtrate using primary active transport H^+ (ATPase) pumps (fig. 17.29), an activity that is primarily responsible for the acidification of the urine. The H^+ in the urine is mostly buffered by ammonium and phosphate buffers, as described shortly.

If a person has alkalosis, less H^+ is present in the filtrate, so that less HCO_3^- is reabsorbed; the resulting urinary excretion of HCO_3^- then helps to compensate for the alkalosis. If a person has acidosis, the proximal tubule cells can make *extra bicarbonate*—over that which is reabsorbed from the filtrate—that can enter the blood. This extra bicarbonate comes from the metabolism of the amino acid *glutamine,* derived from glutamic acid. The metabolism of one glutamine molecule yields two bicarbonate ions that are "extra" (because they were not reabsorbed from the filtrate) and two molecules of **ammonia (NH_3),** which is converted into **ammonium ion (NH_4^+)** in the filtrate. The extra bicarbonate produced by the kidneys helps compensate for acidosis, and the ammonia serves as a urinary buffer (discussed in the next section).

By these mechanisms, disturbances in acid-base balance caused by respiratory problems can be partially compensated for by changes in plasma bicarbonate concentrations. Metabolic acidosis or alkalosis—in which changes in bicarbonate concentrations occur as the primary disturbance—similarly can be partially compensated for by changes in ventilation. These interactions of the respiratory and metabolic components of acid-base balance are summarized in table 17.7.

CLINICAL APPLICATION

Acute mountain sickness (AMS; chapter 16, section 16.9) may occur when people go to high elevations and are not adequately acclimatized. Acclimatization involves the respiratory system (through hyperventilation) and the kidneys, which have a diuretic response to the high altitude. Diuresis produces *hypovolemia* (decreased blood volume), which helps mitigate the symptoms of AMS. The diuresis is a response to a decreased secretion of ADH and aldosterone, and to an increased secretion of natriuretic hormones. If necessary, these responses can be aided by **acetazolamide,** a drug that inhibits carbonic anhydrase. This decreases the renal reabsorption of bicarbonate (and thus water), thereby producing both a mild diuretic effect and metabolic acidosis. The acidosis then stimulates the central chemoreceptors, which promotes a hyperventilation that aids acclimatization.

Urinary Buffers

When a person has a blood pH of less than 7.35 (acidosis), the urine pH almost always falls below 5.5. The nephron, however, cannot produce a urine pH that is significantly less than 4.5. In order for more H^+ to be excreted, the acid must be buffered. (Actually, even in normal urine, most of the H^+ excreted is in a buffered form.) Bicarbonate cannot serve this buffering function because it is normally completely reabsorbed.

Instead, the buffering reactions of phosphates (mainly HPO_4^{2-}) and ammonia (NH_3) provide the means for excreting most of the H^+ in the urine. Phosphate enters the urine by filtration. Ammonia, which is evident in urine from its odor, is produced in the tubule cells by deamination of the amino acid glutamine. Metabolic acidosis causes increased production of ammonia, which occurs mostly in the proximal tubule. Ammonia travels through the nephron loop and, because of the way different segments of the tubule reabsorb or secrete ammonia, it becomes concentrated in the interstitial fluid of the medulla. This creates a gradient favoring the diffusion of ammonia into the collecting duct.

Phosphate and ammonia buffer H^+ in the urine as indicated by the following equations:

$$NH_3 + H^+ \rightarrow NH_4^+ \text{ (ammonium ion)}$$

$$HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$$

Table 17.7 | Categories of Disturbances in Acid-Base Balance

	Bicarbonate (mEq/L)*		
P_{CO_2} (mmHg)	*Less than 21*	*21–26*	*More than 26*
More than 45	Combined metabolic and respiratory acidosis	Respiratory acidosis	Metabolic alkalosis and respiratory acidosis
35–45	Metabolic acidosis	Normal	Metabolic alkalosis
Less than 35	Metabolic acidosis and respiratory alkalosis	Respiratory alkalosis	Combined metabolic and respiratory alkalosis

*mEq/L = milliequivalents per liter. This is the millimolar concentration of HCO_3^- multiplied by its valence (×1).

CHECKPOINT

11a. Describe the effects of aldosterone on the renal nephrons and explain how aldosterone secretion is regulated.

11b. Explain how changes in blood volume regulate renin secretion and how the secretion of renin helps to regulate the blood volume.

11c. Explain the mechanisms by which the cortical collecting duct secretes K^+ and H^+. How might hyperkalemia affect the blood pH?

12a. Explain how the kidneys reabsorb filtered bicarbonate and how this process is affected by acidosis and alkalosis.

12b. Suppose a person with diabetes mellitus had an arterial pH of 7.30, an abnormally low arterial P_{CO_2}, and an abnormally low bicarbonate concentration. What type of acid-base disturbance would this be? What might have caused the imbalances?

17.6 DIURETICS AND RENAL FUNCTION TESTS

Different types of diuretic drugs act on specific segments of the nephron tubule to indirectly inhibit the reabsorption of water and thus promote the lowering of blood volume. A knowledge of how diuretics exert their effects enhances our understanding of the physiology of the nephron.

LEARNING OUTCOMES

After studying this section, you should be able to:

13. Explain how the different classes of diuretics act on the nephron.

14. Describe renal insufficiency and uremia.

The importance of renal function in maintaining homeostasis, and the ease with which urine can be collected and used as a mirror of the plasma's chemical composition, make the clinical study of renal function and urine composition particularly useful. Further, the ability of the kidneys to regulate blood volume is exploited clinically in the management of high blood pressure.

Use of Diuretics

People who need to lower their blood volume because of hypertension, congestive heart failure, or edema take medications called **diuretics** that increase the volume of urine excreted. Diuretics directly lower blood volume (and hence blood pressure) by increasing the proportion of the glomerular filtrate that is excreted as urine. These drugs also decrease the interstitial fluid volume (and hence relieve edema) by a more indirect route. By lowering plasma volume, diuretic drugs increase the concentration, and thus the oncotic pressure, of the plasma within blood capillaries (see chapter 14, fig. 14.9). This promotes the osmosis of interstitial fluid into the capillary blood, helping to reduce the edema.

The various diuretic drugs act on the renal nephron in different ways (table 17.8; fig. 17.30). On the basis of their chemical structure or aspects of their actions, commonly used diuretics

Table 17.8 | Actions of Different Classes of Diuretics

Category of Diuretic	Example	Mechanism of Action	Major Site of Action
Loop diuretics	Furosemide	Inhibits sodium transport	Thick segments of ascending limbs
Thiazides	Hydrochlorothiazide	Inhibits sodium transport	Last part of ascending limb and first part of distal tubule
Carbonic anhydrase inhibitors	Acetazolamide	Inhibits reabsorption of bicarbonate	Proximal tubule
Osmotic diuretics	Mannitol	Reduces osmotic reabsorption of water by reducing osmotic gradient	Last part of distal tubule and cortical collecting duct
Potassium-sparing diuretics	Spironolactone	Inhibits action of aldosterone	Last part of distal tubule and cortical collecting duct
	Triamterene	Inhibits Na^+ reabsorption and K^+ secretion	Last part of distal tubule and cortical collecting duct

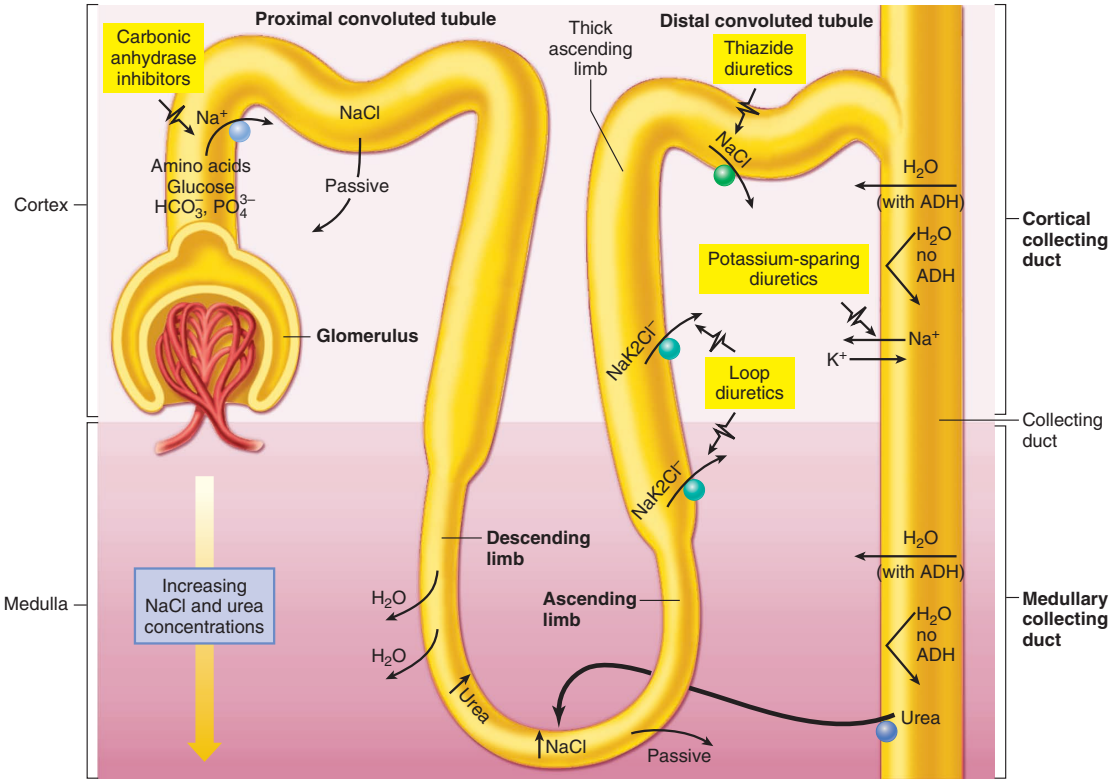


Figure 17.30 **Sites of action of clinical diuretics.** The different diuretic drugs act on the nephron tubules at various sites to inhibit the reabsorption of water. As a result of these actions, less water is reabsorbed into the blood and more is excreted in the urine. This lowers the blood volume and pressure.

are categorized as *loop diuretics, thiazides, carbonic anhydrase inhibitors, osmotic diuretics,* or *potassium-sparing diuretics.*

The most powerful diuretics, which inhibit salt and water reabsorption by as much as 25%, are the drugs that inhibit active salt transport out of the ascending limb of the nephron loop. Examples of these **loop diuretics** are *furosemide (Lasix)* and *ethacrynic acid.* The **thiazide diuretics** (e.g., *hydrochlorothiazide*) inhibit salt and water reabsorption by as much as 8% through inhibition of salt transport by the first segment of the distal convoluted tubule. The **carbonic anhydrase inhibitors** (e.g., *acetazolamide*) are much weaker diuretics; they act primarily in the proximal tubule to prevent the water reabsorption that occurs when bicarbonate is reabsorbed. Largely because it also promotes the urinary excretion of bicarbonate, acetazolamide is used to treat acute mountain sickness (as previously described).

When extra solutes are present in the filtrate, they increase the osmotic pressure of the filtrate and in this way decrease the reabsorption of water by osmosis. The extra solutes thus act as **osmotic diuretics.** *Mannitol* is sometimes used clinically for this purpose. Osmotic diuresis can occur in diabetes mellitus because glucose is present in the filtrate and urine; this extra solute causes the excretion of excessive amounts of water in the urine and can result in severe dehydration of a person with uncontrolled diabetes.

All of these diuretics cause increased delivery of Na^+ to the cortical collecting ducts, which directly and indirectly stimulates increased K^+ secretion as previously described. This may cause excessive elimination of K^+ in the urine, which can dangerously lower the plasma K^+ concentration (a condition called *hypokalemia*). Hypokalemia may produce neuromuscular disorders and ECG abnormalities. People who take diuretics are usually on a low-sodium diet and must often supplement their meals with potassium chloride (KCl) to offset their loss of K^+.

For this reason, **potassium-sparing diuretics** are sometimes used. *Spironolactones (Aldactone)* are aldosterone antagonists that compete with aldosterone for cytoplasmic receptor proteins in the cells of the cortical collecting duct. These drugs thus block the aldosterone stimulation of Na^+ reabsorption and K^+ secretion. *Triamterene (Dyrenium)* is a different type of potassium-sparing diuretic that acts on the tubule more directly to block Na^+ reabsorption and K+ secretion. Combinations of spironolactone or triamterene together with hydrochlorothiazide (*Aldactazide* and *Dyazide,* respectively) are sometimes prescribed for the diuretic treatment of hypertension.

Clinical Investigation CLUES

After Lauren experienced hypokalemia, her physician discontinued her hydrochlorothiazide and prescribed a different medicine.

- How does hydrochlorothiazide work as a diuretic, and how might it produce hypokalemia?
- What other type of diuretic might the physician prescribe, and how would it help Lauren's hypertension and hypokalemia?

Renal Function Tests and Kidney Disease

Renal function can be tested by techniques that include the renal plasma clearance of PAH, which measures total blood flow to the kidneys, and the measurement of the GFR by the inulin clearance. The plasma creatinine concentration (see p. 601) also provides an index of renal function. These tests aid the diagnosis of kidney diseases such as glomerulonephritis and renal insufficiency. The *urinary albumin excretion rate* is a commonly performed test that can detect an excretion rate of blood albumin that is slightly above normal. This condition, called **microalbuminuria** (30–300 mg protein per day), is often the first manifestation of renal damage that may be caused by diabetes or hypertension. **Proteinuria** is present when a person excretes more than 300 mg of protein per day, and an excretion of greater than 3.5 g per day occurs in the **nephrotic syndrome.**

Acute Renal Failure

In **acute renal failure,** the ability of the kidneys to excrete wastes and regulate the homeostasis of blood volume, pH, and electrolytes deteriorates over a relatively short period of time (hours to days). There is a rise in blood creatinine concentration and a decrease in the renal plasma clearance of creatinine. This may be due to a reduced blood flow through the kidneys, perhaps as a result of atherosclerosis or inflammation of the renal tubules. The compromised kidney function may be the result of ischemia (reduced blood flow), but it may also result from excessive use of certain drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as phenacetin.

Glomerulonephritis

Inflammation of the glomeruli, or **glomerulonephritis,** is believed to be an *autoimmune disease*—a disease that involves the person's own antibodies (chapter 15, section 15.6). These antibodies may have been raised against the basement membrane of the glomerular capillaries. More commonly, however, they appear to have been produced in response to streptococcus infections (such as strep throat). A variable number of glomeruli are destroyed in this condition, and the remaining glomeruli become more permeable to plasma proteins. Leakage of proteins into the urine results in decreased plasma colloid osmotic pressure and can therefore lead to edema.

Renal Insufficiency

When nephrons are destroyed—as in chronic glomerulonephritis, infection of the renal pelvis and nephrons (*pyelonephritis*), or loss of a kidney—or when kidney function is reduced by damage caused by diabetes mellitus, arteriosclerosis, or blockage by kidney stones, a condition of **renal insufficiency** may develop. This can cause hypertension, which is due primarily to the retention of salt and water, and **uremia** (high plasma urea concentrations). The inability to excrete urea is accompanied by an elevated plasma H^+ concentration (acidosis) and an elevated K^+ concentration, which are more immediately dangerous than the high levels of urea. Uremic coma appears to result from these associated changes.

Patients with uremia or the potential for developing uremia are often placed on a *dialysis* machine. The term *dialysis* refers to the separation of molecules on the basis of their ability to diffuse through an artificial selectively permeable membrane (chapter 6; see fig. 6.4). This principle is used in the "artificial kidney machine" for **hemodialysis.** Urea and other wastes in the patient's blood can easily pass through the membrane pores, whereas plasma proteins are left behind (just as occurs across glomerular capillaries). The plasma is thus cleansed of these wastes as they pass from the blood into the dialysis fluid. Unlike the tubules, however, the dialysis membrane cannot reabsorb Na^+, K^+, glucose, and other needed molecules. These substances are kept in the blood by including them in the dialysis fluid so that there is no concentration gradient that would favor their diffusion through the membrane. By contrast, the bicarbonate concentration in the dialysate is at first higher than in the blood, favoring its diffusion into the blood. Hemodialysis is commonly performed three times a week for several hours each session.

More recent techniques include the use of the patient's own peritoneal membranes (which line the abdominal cavity) for dialysis. Dialysis fluid is introduced into the peritoneal cavity, and then after a period of time when wastes have accumulated the fluid is discarded. This procedure, called **continuous ambulatory peritoneal dialysis (CAPD),** can be performed several times a day by the patients themselves on an outpatient basis. Although CAPD is more convenient and less expensive for patients than hemodialysis, it is less efficient in removing wastes and it is more often complicated by infection.

The many dangers presented by renal insufficiency and the difficulties encountered in attempting to compensate for this condition are stark reminders of the importance of renal function in maintaining homeostasis. The ability of the kidneys to regulate blood volume and chemical composition in accordance with the body's changing needs requires great complexity of function. Homeostasis is maintained in large part by coordination of renal functions with those of the cardiovascular and pulmonary systems, as described in the preceding chapters.