CHAPTER

23

Kidney Function

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CHAPTER OUTLINE

- **FUNCTIONAL RENAL ANATOMY**
- **AN OVERVIEW OF KIDNEY FUNCTION**
- **RENAL BLOOD FLOW**
- **GLOMERULAR FILTRATION**
- **TRANSPORT IN THE PROXIMAL TUBULE**

- **TUBULAR TRANSPORT IN THE LOOPS OF HENLE**
- **TUBULAR TRANSPORT IN THE DISTAL NEPHRON**
- **URINARY CONCENTRATION AND DILUTION**
- **INHERITED DEFECTS IN KIDNEY TUBULE EPITHELIAL CELLS**

KEY CONCEPTS

1. The formation of urine involves glomerular filtration, tubular reabsorption, and tubular secretion.
2. The renal clearance of a substance is equal to its rate of excretion divided by its plasma concentration.
3. Inulin clearance provides the most accurate measure of glomerular filtration rate (GFR).
4. The clearance of *p*-aminohippurate (PAH) is equal to the effective renal plasma flow.
5. The rate of net tubular reabsorption of a substance is equal to its filtered load minus its excretion rate. The rate of net tubular secretion of a substance is equal to its excretion rate minus its filtered load.
6. The kidneys, especially the cortex, have a high blood flow.
7. Kidney blood flow is autoregulated; it is also profoundly influenced by nerves and hormones.
8. The glomerular filtrate is an ultrafiltrate of plasma.
9. GFR is determined by the glomerular ultrafiltration coefficient, glomerular capillary hydrostatic pressure, hydrostatic pressure in the space of Bowman's capsule, and glomerular capillary colloid osmotic pressure.
10. The proximal convoluted tubule reabsorbs about 70% of filtered Na^+, K^+, and water and nearly all of the filtered glucose and amino acids. It also secretes a large variety of organic anions and organic cations.

11. The transport of water and most solutes across tubular epithelia is dependent upon active reabsorption of Na^+.
12. The thick ascending limb is a water-impermeable segment that reabsorbs Na^+ via a Na-K-2Cl cotransporter in the apical cell membrane and a vigorous Na^+/K^+-ATPase in the basolateral cell membrane.
13. The distal convoluted tubule epithelium is water-impermeable and reabsorbs Na^+ via a thiazide-sensitive apical membrane Na-Cl cotransporter.
14. Cortical collecting duct principal cells reabsorb Na^+ and secrete K^+.
15. The kidneys save water for the body by producing urine with a total solute concentration (i.e., osmolality) greater than plasma.
16. The loops of Henle are countercurrent multipliers; they set up an osmotic gradient in the kidney medulla. Vasa recta are countercurrent exchangers; they passively help maintain the medullary gradient. Collecting ducts are osmotic equilibrating devices; they have a low water permeability, which is increased by arginine vasopressin (AVP).
17. Genetic defects in kidney epithelial cells account for several disorders.

The kidneys play a dominant role in regulating the composition and volume of the extracellular fluid (ECF). They normally maintain a stable internal environment by excreting appropriate amounts of many substances in the urine. These substances include not only waste products and foreign compounds, but also many useful substances that are present in excess because of eating, drinking, or metabolism. This chapter considers the basic renal processes that determine the excretion of various substances.

The kidneys perform a variety of important functions:

1) They regulate the osmotic pressure (osmolality) of the body fluids by excreting osmotically dilute or concentrated urine.

2) They regulate the concentrations of numerous ions in blood plasma, including Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, bicarbonate (HCO_3^-), phosphate, and sulfate.

3) They play an essential role in acid-base balance by excreting H^+, when there is excess acid, or HCO_3^-, when there is excess base.

4) They regulate the volume of the ECF by controlling Na^+ and water excretion.

5) They help regulate arterial blood pressure by adjusting Na^+ excretion and producing various substances (e.g., renin) that can affect blood pressure.

6) They eliminate the waste products of metabolism, including urea (the main nitrogen-containing end-product of protein metabolism in humans), uric acid (an end-product of purine metabolism), and creatinine (an end-product of muscle metabolism).

7) They remove many drugs (e.g., penicillin) and foreign or toxic compounds.

8) They are the major production sites of certain hormones, including erythropoietin (see Chapter 11) and 1,25-dihydroxy vitamin D_3 (see Chapter 36).

9) They degrade several polypeptide hormones, including insulin, glucagon, and parathyroid hormone.

10) They synthesize ammonia, which plays a role in acid-base balance (see Chapter 25).

11) They synthesize substances that affect renal blood flow and Na^+ excretion, including arachidonic acid derivatives (prostaglandins, thromboxane A_2) and kallikrein (a proteolytic enzyme that results in the production of kinins).

When the kidneys fail, a host of problems ensue. Dialysis and kidney transplantation are commonly used treatments for advanced (end-stage) renal failure (see Clinical Focus Box 23.1).

CLINICAL FOCUS BOX 23.1

Dialysis and Transplantation

Chronic renal failure can result from a large variety of diseases but is most often due to inflammation of the glomeruli (glomerulonephritis) or urinary reflux and infections (pyelonephritis). Renal damage may occur over many years and may be undetected until a considerable loss of nephrons has occurred. When GFR has declined to 5% of normal or less, the internal environment becomes so disturbed that patients usually die within weeks or months if they are not dialyzed or provided with a functioning kidney transplant.

Most of the signs and symptoms of renal failure can be relieved by **dialysis,** the separation of smaller molecules from larger molecules in solution by diffusion of the small molecules through a selectively permeable membrane. Two methods of dialysis are commonly used to treat patients with severe, irreversible ("end-stage") renal failure.

In **continuous ambulatory peritoneal dialysis** (CAPD), the peritoneal membrane, which lines the abdominal cavity, acts as a dialyzing membrane. About 1 to 2 liters of a sterile glucose-salt solution are introduced into the abdominal cavity and small molecules (e.g., K^+ and urea) diffuse into the introduced solution, which is then drained and discarded. The procedure is usually done several times every day.

Hemodialysis is more efficient in terms of rapidly removing wastes. The patient's blood is pumped through an artificial kidney machine. The blood is separated from a balanced salt solution by a cellophane-like membrane, and small molecules can diffuse across this membrane. Excess fluid can be removed by applying pressure to the blood and filtering it. Hemodialysis is usually done 3 times a week (4 to 6 hours per session) in a medical facility or at home.

Dialysis can enable patients with otherwise fatal renal disease to live useful and productive lives. Several physiological and psychological problems persist, however, including bone disease, disorders of nerve function, hypertension, atherosclerotic vascular disease, and disturbances of sexual function. There is a constant risk of infection and, with hemodialysis, clotting and hemorrhage. Dialysis does not maintain normal growth and development in children. Anemia (primarily a result of deficient erythropoietin production by damaged kidneys) was once a problem but can now be treated with recombinant human erythropoietin.

Renal transplantation is the only real cure for patients with end-stage renal failure. It may restore complete health and function. In 1999, about 12,500 kidney transplant operations were performed in the United States. At present, 94% of kidneys grafted from living donors related to the recipient function for 1 year; about 90% of kidneys from unrelated donors (cadaver) function for 1 year.

Several problems complicate kidney transplantation. The immunological rejection of the kidney graft is a major challenge. The powerful drugs used to inhibit graft rejection compromise immune defensive mechanisms so that unusual and difficult-to-treat infections often develop. The limited supply of donor organs is also a major unsolved problem; there are many more patients who would benefit from a kidney transplant than there are donors. The median waiting time for a kidney transplant is currently more than 900 days. Finally, the cost of transplantation (or dialysis) is high. Fortunately for people in the United States, Medicare covers the cost of dialysis and transplantation, but these life-saving therapies are beyond the reach of most people in developing countries.
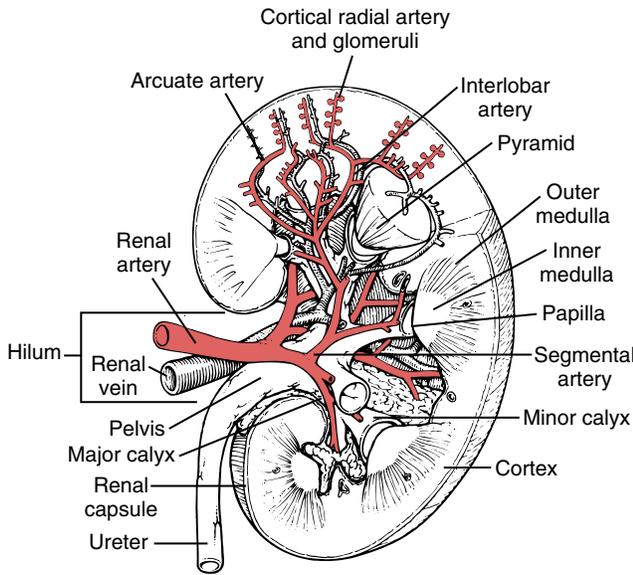
FUNCTIONAL RENAL ANATOMY

Each kidney in an adult weighs about 150 g and is roughly the size of one's fist. If the kidney is sectioned (Fig. 23.1), two regions are seen: an outer part, called the **cortex,** and an inner part, called the **medulla.** The cortex typically is reddish brown and has a granulated appearance. All of the glomeruli, convoluted tubules, and cortical collecting ducts are located in the cortex. The medulla is lighter in color and has a striated appearance that results from the parallel arrangement of the loops of Henle, medullary collecting ducts, and blood vessels of the medulla. The medulla can be further subdivided into an **outer medulla,** which is closer to the cortex, and an **inner medulla,** which is farther from the cortex.

The human kidney is organized into a series of **lobes,** usually 8 to 10. Each lobe consists of a pyramid of medullary tissue and the cortical tissue overlying its base and covering its sides. The tip of the **medullary pyramid** forms a **renal papilla.** Each renal papilla drains its urine into a **minor calyx.** The minor calices unite to form a **major calyx,** and the urine then flows into the **renal pelvis.** The urine is propelled by peristaltic movements down the **ureters** to the **urinary bladder,** which stores the urine until the bladder is emptied. The medial aspect of each kidney is indented in a region called the **hilum,** where the ureter, blood vessels, nerves, and lymphatic vessels enter or leave the kidney.

The Nephron Is the Basic Unit of Renal Structure and Function

Each human kidney contains about one million **nephrons** (Fig. 23.2), which consist of a **renal corpuscle** and a **renal tubule.** The renal corpuscle consists of a tuft of capillaries, the **glomerulus,** surrounded by **Bowman's capsule.** The renal tubule is divided into several segments. The part of the tubule nearest the glomerulus is the **proximal tubule.** This is subdivided into a **proximal convoluted tubule** and **proximal straight tubule.** The straight portion heads toward the
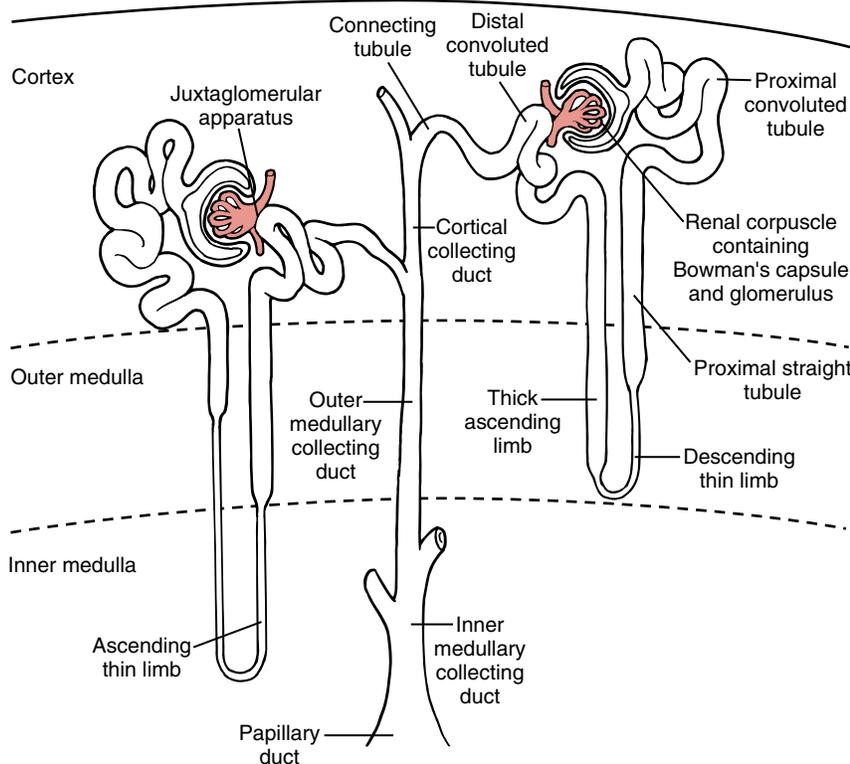

FIGURE 23.2 **Components of the nephron and the collecting duct system.** On the left is a long-looped juxtamedullary nephron; on the right is a superficial cortical nephron. (Modified from Kriz W, Bankir L. A standard nomenclature for structures of the kidney. Am J Physiol 1988;254:F1–F8.)

medulla, away from the surface of the kidney. The **loop of Henle** includes the proximal straight tubule, **thin limb,** and **thick ascending limb**. The next segment, the short **distal convoluted tubule,** is connected to the collecting duct system by **connecting tubules**. Several nephrons drain into a **cortical collecting duct,** which passes into an **outer medullary collecting duct**. In the inner medulla, **inner medullary collecting ducts** unite to form large **papillary ducts**.

The collecting ducts perform the same types of functions as the renal tubules, so they are often considered to be part of the nephron. The collecting ducts and nephrons differ, however, in embryological origin, and because the collecting ducts form a branching system, there are many more nephrons than collecting ducts. The entire renal tubule and collecting duct system consists of a single layer of epithelial cells surrounding fluid (urine) in the tubule or duct lumen. Cells in each segment have a characteristic histological appearance. Each segment has unique transport properties (discussed later).

Not All Nephrons Are Alike

Three groups of nephrons are distinguished, based on the location of their glomeruli in the cortex: **superficial, midcortical,** and **juxtamedullary nephrons**. The juxtamedullary nephrons, whose glomeruli lie in the cortex next to the medulla, comprise about one-eighth of the nephron population. They differ in several ways from the other nephron types: they have a longer loop of Henle, longer thin limb (both descending and ascending portions), larger glomerulus, lower renin content, different tubular permeability and transport properties, and a different type of postglomerular blood supply. Figure 23.2 shows superficial and juxtamedullary nephrons; note the long loop of the juxtamedullary nephron.

The Kidneys Have a Rich Blood Supply and Innervation

Each kidney is typically supplied by a single **renal artery** that branches into anterior and posterior divisions, which give rise to a total of five **segmental arteries**. The segmental arteries branch into **interlobar arteries**, which pass toward the cortex between the kidney lobes (see Fig. 23.1). At the junction of cortex and medulla, the interlobar arteries branch to form **arcuate arteries**. These, in turn, give rise to smaller **cortical radial arteries,** which pass through the cortex toward the surface of the kidney. Several short, wide, muscular **afferent arterioles** arise from the cortical radial arteries. Each afferent arteriole gives rise to a **glomerulus**. The glomerular capillaries are followed by an **efferent arteriole**. The efferent arteriole then divides into a second capillary network, the **peritubular capillaries**, that surrounds the kidney tubules. Venous vessels, in general, lie parallel to the arterial vessels and have similar names.

The blood supply to the medulla is derived from the efferent arterioles of juxtamedullary glomeruli. These vessels give rise to two patterns of capillaries: peritubular capillaries, which are similar to those in the cortex, and **vasa recta**, which are straight, long capillaries (Fig. 23.3).
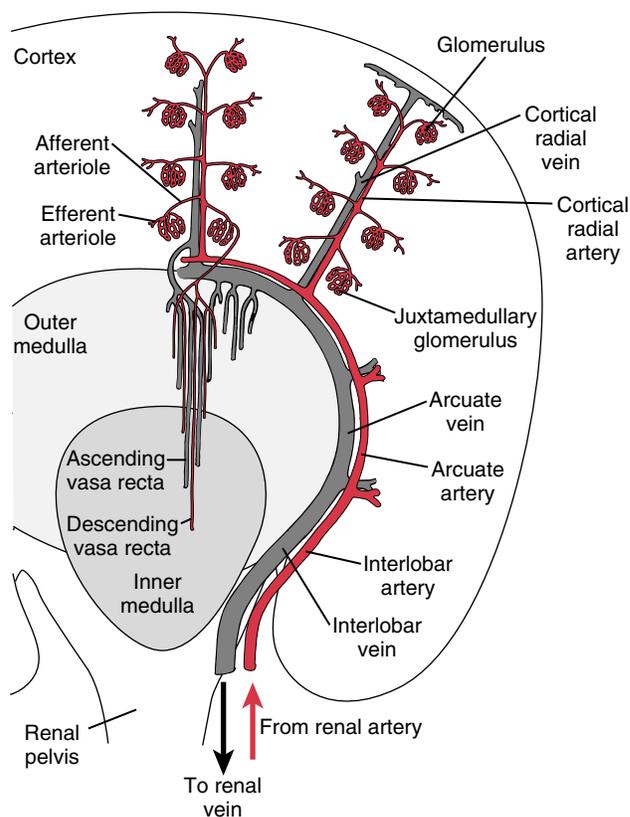

FIGURE 23.3 **The blood vessels in the kidney; peritubular capillaries are not shown.** (Modified from Kriz W, Bankir L. A standard nomenclature for structures of the kidney. Am J Physiol. 1988;254:F1–F8.)

Some vasa recta reach deep into the inner medulla. In the outer medulla, descending and ascending vasa recta are grouped in vascular bundles and are in close contact with each other. This arrangement greatly facilitates the exchange of substances between blood flowing in and out of the medulla.

The kidneys are richly innervated by **sympathetic nerve fibers**, which travel to the kidneys, mainly in thoracic spinal nerves T10, T11, and T12 and lumbar spinal nerve L1. Stimulation of sympathetic fibers causes constriction of renal blood vessels and a fall in renal blood flow. Sympathetic nerve fibers also innervate tubular cells and may cause an increase in Na^+ reabsorption by a direct action on these cells. In addition, stimulation of sympathetic nerves increases the release of renin by the kidneys. Afferent (sensory) renal nerves are stimulated by mechanical stretch or by various chemicals in the renal parenchyma.

Renal lymphatic vessels drain the kidneys, but little is known about their functions.

The Juxtaglomerular Apparatus Is the Site of Renin Production

Each nephron forms a loop, and the thick ascending limb touches the vascular pole of the glomerulus (see Fig. 23.2). At this site is the **juxtaglomerular apparatus**, a region com-
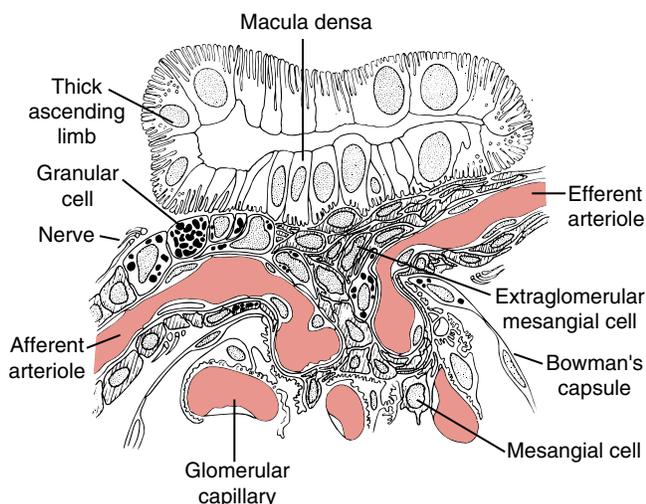
FIGURE 23.4 **Histological appearance of the juxta-glomerular apparatus.** A cross section through a thick ascending limb is on top and part of a glomerulus is below. The juxtaglomerular apparatus consists of the macula densa, extraglomerular mesangial cells, and granular cells. (From Taugner R, Hackenthal E. The Juxtaglomerular Apparatus: Structure and Function. Berlin: Springer, 1989.)

prised of the macula densa, extraglomerular mesangial cells, and granular cells (Fig. 23.4). The **macula densa** (dense spot) consists of densely crowded tubular epithelial cells on the side of the thick ascending limb that faces the glomerular tuft; these cells monitor the composition of the fluid in the tubule lumen at this point. The **extraglomerular mesangial cells** are continuous with mesangial cells of the glomerulus; they may transmit information from macula densa cells to the granular cells. The **granular cells** are modified vascular smooth muscle cells with an epithelioid appearance, located mainly in the afferent arterioles close to the glomerulus. These cells synthesize and release **renin,** a proteolytic enzyme that results in angiotensin formation (see Chapter 24).

AN OVERVIEW OF KIDNEY FUNCTION

Three processes are involved in forming urine: glomerular filtration, tubular reabsorption, and tubular secretion (Fig. 23.5). **Glomerular filtration** involves the ultrafiltration of plasma in the glomerulus. The filtrate collects in the urinary
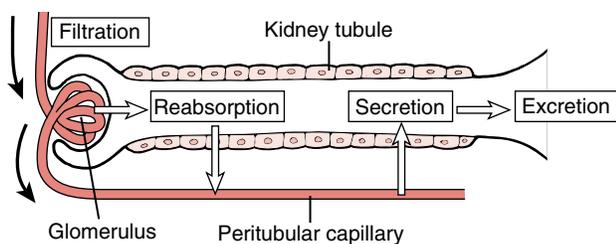

FIGURE 23.5 **Processes involved in urine formation.** This highly simplified drawing shows a nephron and its associated blood vessels.

space of Bowman's capsule and then flows downstream through the tubule lumen, where its composition and volume are altered by tubular activity. **Tubular reabsorption** involves the transport of substances out of tubular urine; these substances are then returned to the capillary blood, which surrounds the kidney tubules. Reabsorbed substances include many important ions (e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, phosphate), water, important metabolites (e.g., glucose, amino acids), and even some waste products (e.g., urea, uric acid). **Tubular secretion** involves the transport of substances into the tubular urine. For example, many organic anions and cations are taken up by the tubular epithelium from the blood surrounding the tubules and added to the tubular urine. Some substances (e.g., H^+, ammonia) are produced in the tubular cells and secreted into the tubular urine. The terms *reabsorption* and *secretion* indicate movement out of and into tubular urine, respectively. Tubular transport (reabsorption, secretion) may be active or passive, depending on the particular substance and other conditions.

Excretion refers to elimination via the urine. In general, the amount excreted is expressed by the following equation:

$$\text{Excreted} = \text{Filtered} - \text{Reabsorbed} + \text{Secreted} \quad (1)$$

The functional state of the kidneys can be evaluated using several tests based on the renal clearance concept. These tests measure the rates of glomerular filtration, renal blood flow, and tubular reabsorption or secretion of various substances. Some of these tests, such as the measurement of glomerular filtration rate, are routinely used to evaluate kidney function.

Renal Clearance Equals Urinary Excretion Rate Divided by Plasma Concentration

A useful way of looking at kidney function is to think of the kidneys as clearing substances from the blood plasma. When a substance is excreted in the urine, a certain volume of plasma is, in effect, freed (or cleared) of that substance. The **renal clearance** of a substance can be defined as the volume of plasma from which that substance is completely removed (cleared) per unit time. The clearance formula is:

$$C_x = U_x \times \frac{\dot{V}}{P_x} \quad (2)$$

where X is the substance of interest, C_X is the clearance of substance X, U_X is the urine concentration of substance, P_X is the plasma concentration of substance X, and $\dot{V}$ is the urine flow rate. The product $U_X \times \dot{V}$ equals the excretion rate per minute and has dimensions of amount per unit time (e.g., mg/min or mEq/day). The clearance of a substance can easily be determined by measuring the concentrations of a substance in urine and plasma and the urine flow rate (urine volume/time of collection) and substituting these values into the clearance formula.

Inulin Clearance Equals the Glomerular Filtration Rate

An important measurement in the evaluation of kidney function is the **glomerular filtration rate** (GFR), the rate at
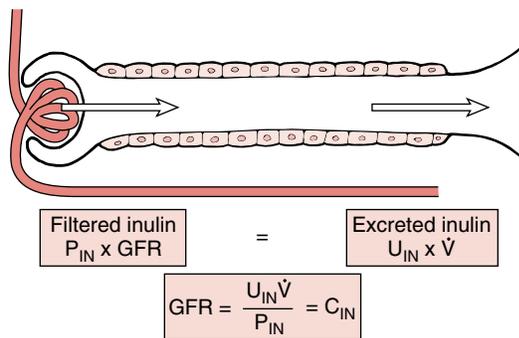
| Filtered inulin $P_{IN} \times GFR$ | = | Excreted inulin $U_{IN} \times \dot{V}$ |

$$GFR = \frac{U_{IN}\dot{V}}{P_{IN}} = C_{IN}$$

FIGURE 23.6 **The principle behind the measurement of glomerular filtration rate (GFR).** P_{IN} = plasma [inulin], U_{IN} = urine [inulin], V = urine flow rate, C_{IN} = inulin clearance.

which plasma is filtered by the kidney glomeruli. If we had a substance that was cleared from the plasma only by glomerular filtration, it could be used to measure GFR.

The ideal substance to measure GFR is **inulin,** a fructose polymer with a molecular weight of about 5,000. Inulin is suitable for measuring GFR for the following reasons:

- It is freely filterable by the glomeruli.
- It is not reabsorbed or secreted by the kidney tubules.
- It is not synthesized, destroyed, or stored in the kidneys.
- It is nontoxic.
- Its concentration in plasma and urine can be determined by simple analysis.

The principle behind the use of inulin is illustrated in Figure 23.6. The amount of inulin (IN) filtered per unit time, the **filtered load,** is equal to the product of the plasma [inulin] (P_{IN}) × GFR. The rate of inulin excretion is equal to U_{IN} × V. Since inulin is not reabsorbed, secreted, synthesized, destroyed, or stored by the kidney tubules, the filtered inulin load equals the rate of inulin excretion. The equation can be rearranged by dividing by the plasma [inulin]. The expression $U_{IN}\dot{V}/P_{IN}$ is defined as the **inulin clearance.** Therefore, inulin clearance equals GFR.

Normal values for inulin clearance or GFR (corrected to a body surface area of 1.73 m^2) are 110 ± 15 (SD) mL/min for young adult women and 125 ± 15 mL/min for young adult men. In newborns, even when corrected for body surface area, GFR is low, about 20 mL/min per 1.73 m^2 body surface area. Adult values (when corrected for body surface area) are attained by the end of the first year of life. After the age of 45 to 50 years, GFR declines, and is typically reduced by 30 to 40% by age 80.

If GFR is 125 mL plasma/min, then the volume of plasma filtered in a day is 180 L (125 mL/min × 1,440 min/day). Plasma volume in a 70-kg young adult man is only about 3 L, so the kidneys filter the plasma some 60 times in a day. The glomerular filtrate contains essential constituents (salts, water, metabolites), most of which are reabsorbed by the kidney tubules.

The Endogenous Creatinine Clearance Is Used Clinically to Estimate GFR

Inulin clearance is the highest standard for measuring GFR and is used whenever highly accurate measurements of GFR

are desired. The clearance of iothalamate, an iodinated organic compound, also provides a reliable measure of GFR. It is not common, however, to use these substances in the clinic. They must be infused intravenously, and because short urine collection periods are used, the bladder is usually catheterized; these procedures are inconvenient. It would be simpler to use an endogenous substance (i.e., one native to the body) that is only filtered, is excreted in the urine, and normally has a stable plasma value that can be accurately measured. There is no such known substance, but creatinine comes close.

Creatinine is an end-product of muscle metabolism, a derivative of muscle creatine phosphate. It is produced continuously in the body and is excreted in the urine. Long urine collection periods (e.g., a few hours) can be used because creatinine concentrations in the plasma are normally stable and creatinine does not have to be infused; consequently, there is no need to catheterize the bladder. Plasma and urine concentrations can be measured using a simple colorimetric method. The **endogenous creatinine clearance** is calculated from the formula:

$$C_{CREATININE} = \frac{U_{CREATININE} \times \dot{V}}{P_{CREATININE}} \qquad (3)$$

There are two potential drawbacks to using creatinine to measure GFR. First, creatinine is not only filtered but also secreted by the human kidney. This elevates urinary excretion of creatinine, normally causing a 20% increase in the numerator of the clearance formula. The second drawback is due to errors in measuring plasma [creatinine]. The colorimetric method usually used also measures other plasma substances, such as glucose, leading to a 20% increase in the denominator of the clearance formula. Because both numerator and denominator are 20% too high, the two errors cancel, so the endogenous creatinine clearance fortuitously affords a good approximation of GFR when it is about normal. When GFR in an adult has been reduced to about 20 mL/min because of renal disease, the endogenous creatinine clearance may overestimate the GFR by as much as 50%. This results from higher plasma creatinine levels and increased tubular secretion of creatinine. Drugs that inhibit tubular secretion of creatinine or elevated plasma concentrations of chromogenic (color-producing) substances other than creatinine may cause the endogenous creatinine clearance to underestimate GFR.

Plasma Creatinine Concentration Can Be Used as an Index of GFR

Because the kidneys continuously clear creatinine from the plasma by excreting it in the urine, the GFR and plasma [creatinine] are inversely related. Figure 23.7 shows the steady state relationship between these variables—that is, when creatinine production and excretion are equal. Halving the GFR from a normal value of 180 L/day to 90 L/day results in a doubling of plasma [creatinine] from a normal value of 1 mg/dL to 2 mg/dL after a few days. Reducing GFR from 90 L/day to 45 L/day results in a greater increase in plasma creatinine, from 2 to 4 mg/dL. Figure 23.7 shows that with low GFR values, small absolute changes in GFR
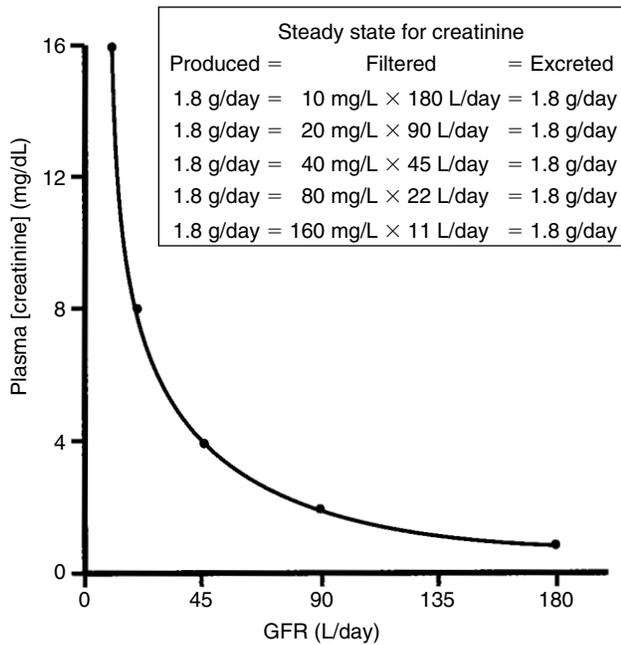
FIGURE 23.7 **The inverse relationship between plasma [creatinine] and GFR.** If GFR is decreased by half, plasma [creatinine] is doubled when the production and excretion of creatinine are in balance in a new steady state.

lead to much greater changes in plasma [creatinine] than occur at high GFR values.

The inverse relationship between GFR and plasma [creatinine] allows the use of plasma [creatinine] as an index of GFR, provided certain cautions are kept in mind:

1) It takes a certain amount of time for changes in GFR to produce detectable changes in plasma [creatinine].

2) Plasma [creatinine] is also influenced by muscle mass. A young, muscular man will have a higher plasma [creatinine] than an older woman with reduced muscle mass.

3) Some drugs inhibit tubular secretion of creatinine, leading to a raised plasma [creatinine] even though GFR may be unchanged.

The relationship between plasma [creatinine] and GFR is one example of how a substance's plasma concentration can depend on GFR. The same relationship is observed for several other substances whose excretion depends on GFR. For example, when GFR falls, the plasma [urea] (or blood urea nitrogen, BUN) rises in a similar fashion.

p-Aminohippurate Clearance Nearly Equals Renal Plasma Flow

Renal blood flow (RBF) can be determined from measurements of renal plasma flow (RPF) and blood hematocrit, using the following equation:

$$RBF = RPF/(1 - Hematocrit) \qquad (4)$$

The hematocrit is easily determined by centrifuging a blood sample. Renal plasma flow is estimated by measuring the clearance of the organic anion *p*-aminohippurate (PAH), infused intravenously. PAH is filtered and vigorously se-

creted, so it is nearly completely cleared from all of the plasma flowing through the kidneys. The renal clearance of PAH, at low plasma PAH levels, approximates the renal plasma flow.

The equation for calculating the true value of the renal plasma flow is:

$$RPF = C_{PAH}/E_{PAH} \qquad (5)$$

where C_{PAH} is the PAH clearance and E_{PAH} is the extraction ratio (see Chapter 16) for PAH—the arterial plasma [PAH] (P^a_{PAH}) minus renal venous plasma [PAH] (P^{rv}_{PAH}) divided by the arterial plasma [PAH]. The equation is derived as follows. In the steady state, the amounts of PAH per unit time entering and leaving the kidneys are equal. The PAH is supplied to the kidneys in the arterial plasma and leaves the kidneys in urine and renal venous plasma, or PAH entering kidneys is equal to PAH leaving kidneys:

$$RPF \times P^a_{PAH} = U_{PAH} \times \dot{V} + RPF \times P^{rv}_{PAH} \qquad (6)$$

Rearranging, we get:

$$RPF = U_{PAH} \times \dot{V}/(P^a_{PAH} - P^{rv}_{PAH}) \qquad (7)$$

If we divide the numerator and denominator of the right side of the equation by P^a_{PAH}, the numerator becomes C_{PAH} and the denominator becomes E_{PAH}.

If we assume extraction of PAH is 100% ($E_{PAH} = 1.00$), then the RPF equals the PAH clearance. When this assumption is made, the renal plasma flow is usually called the **effective renal plasma flow** and the blood flow calculated is called the **effective renal blood flow**. However, the extraction of PAH by healthy kidneys at suitably low plasma PAH concentrations is not 100% but averages about 91%. Assuming 100% extraction underestimates the true renal plasma flow by about 10%. To calculate the true renal plasma flow or blood flow, it is necessary to cannulate the renal vein to measure its plasma [PAH], a procedure not often done.

Net Tubular Reabsorption or Secretion of a Substance Can Be Calculated From Filtered and Excreted Amounts

The rate at which the kidney tubules reabsorb a substance can be calculated if we know how much is filtered and how much is excreted per unit time. If the filtered load of a substance exceeds the rate of excretion, the kidney tubules must have reabsorbed the substance. The equation is:

$$T_{reabsorbed} = P_x \times GFR - U_x \times \dot{V} \qquad (8)$$

where T is the tubular transport rate.

The rate at which the kidney tubules secrete a substance is calculated from this equation:

$$T_{secreted} = U_x \times \dot{V} - P_x \times GFR \qquad (9)$$

Note that the quantity excreted exceeds the filtered load because the tubules secrete X.

In equations 8 and 9, we assume that substance X is freely filterable. If, however, substance X is bound to the plasma proteins, which are not filtered, then it is necessary to correct the filtered load for this binding. For example, about 40% of plasma Ca^{2+} is bound to plasma proteins, so 60% of plasma Ca^{2+} is freely filterable.
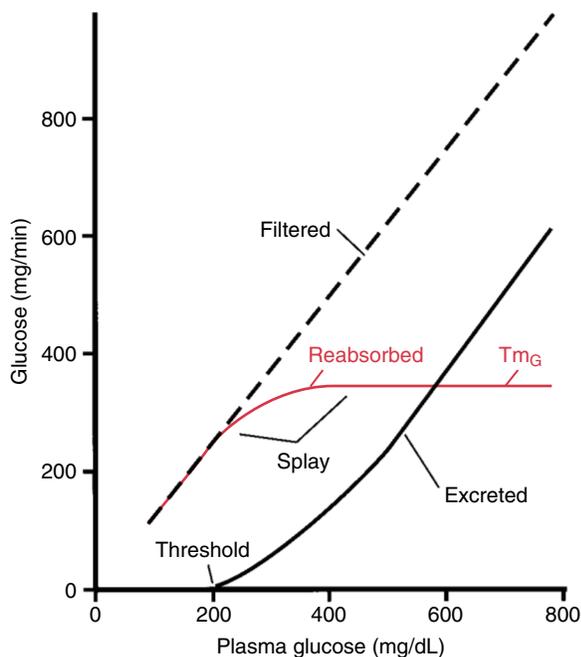
FIGURE 23.8 **Glucose titration study in a healthy man.** The plasma [glucose] was elevated by infusing glucose-containing solutions. The amount of glucose filtered per unit time (top line) is determined from the product of the plasma [glucose] and GFR (measured with inulin). Excreted glucose (bottom line) is determined by measuring the urine [glucose] and flow rate. Reabsorbed glucose is calculated from the difference between filtered and excreted glucose. Tm_G = tubular transport maximum for glucose.

Equations 8 and 9 for quantitating tubular transport rates yield the *net* rate of reabsorption or secretion of a substance. It is possible for a single substance to be both reabsorbed and secreted; the equations do not give unidirectional reabsorptive and secretory movements, but only the net transport.

The Glucose Titration Study Assesses Renal Glucose Reabsorption

Insights into the nature of glucose handling by the kidneys can be derived from a **glucose titration** study (Fig. 23.8). The plasma [glucose] is elevated to increasingly higher levels by the infusion of glucose-containing solutions. Inulin is infused to permit measurement of GFR and calculation of the filtered glucose load (plasma [glucose] $\times$ GFR). The rate of glucose reabsorption is determined from the difference between the filtered load and the rate of excretion. At normal plasma glucose levels (about 100 mg/dL), all of the filtered glucose is reabsorbed and none is excreted. When the plasma [glucose] exceeds a certain value (about 200 mg/dL, see Fig. 23.8), significant quantities of glucose appear in the urine; this plasma concentration is called the **glucose threshold.** Further elevations in plasma glucose lead to progressively more excreted glucose. Glucose appears in the urine because the filtered amount of glucose exceeds the capacity of the tubules to reabsorb it. At very high filtered glucose loads, the rate of glucose reabsorption reaches a constant maximal value, called the **tubular transport maximum** (Tm) for glucose (G). At Tm_G, the limited number of tubule glucose carriers are all saturated and transport glucose at the maximal rate.

The glucose threshold is not a fixed plasma concentration but depends on three factors: GFR, Tm_G, and amount of splay. A low GFR leads to an elevated threshold because the filtered glucose load is reduced and the kidney tubules can reabsorb all the filtered glucose despite an elevated plasma [glucose]. A reduced Tm_G lowers the threshold because the tubules have a diminished capacity to reabsorb glucose.

Splay is the rounding of the glucose reabsorption curve; Figure 23.8 shows that tubular glucose reabsorption does not abruptly attain Tm_G when plasma glucose is progressively elevated. One reason for splay is that not all nephrons have the same filtering and reabsorbing capacities. Thus, nephrons with relatively high filtration rates and low glucose reabsorptive rates excrete glucose at a lower plasma concentration than nephrons with relatively low filtration rates and high reabsorptive rates. A second reason for splay is that the glucose carrier does not have an infinitely high affinity for glucose, so glucose escapes in the urine even before the carrier is fully saturated. An increase in splay results in a decrease in glucose threshold.

In uncontrolled **diabetes mellitus**, plasma glucose levels are abnormally elevated, and more glucose is filtered than can be reabsorbed. Urinary excretion of glucose, **glucosuria**, produces an osmotic diuresis. A diuresis is an increase in urine output; in osmotic diuresis, the increased urine flow results from the excretion of osmotically active solute. Diabetes (from the Greek for "syphon") gets its name from this increased urine output.

The Tubular Transport Maximum for PAH Provides a Measure of Functional Proximal Secretory Tissue

p-Aminohippurate is secreted only by proximal tubules in the kidneys. At low plasma PAH concentrations, the rate of secretion increases linearly with the plasma [PAH]. At high plasma PAH concentrations, the secretory carriers are saturated and the rate of PAH secretion stabilizes at a constant maximal value, called the **tubular transport maximum for PAH** (Tm_{PAH}). The Tm_{PAH} is directly related to the number of functioning proximal tubules and, therefore, provides a measure of the mass of proximal secretory tissue. Figure 23.9 illustrates the pattern of filtration, secretion, and excretion of PAH observed when the plasma [PAH] is progressively elevated by intravenous infusion.

RENAL BLOOD FLOW

The kidneys have a very high blood flow. This allows them to filter the blood plasma at a high rate. Many factors, both intrinsic (autoregulation, local hormones) and extrinsic (nerves, bloodborne hormones), affect the rate of renal blood flow.

The Kidneys Have a High Blood Flow

In resting, healthy, young adult men, renal blood flow averages about 1.2 L/min. This is about 20% of the cardiac output (5 to 6 L/min). Both kidneys together weigh about
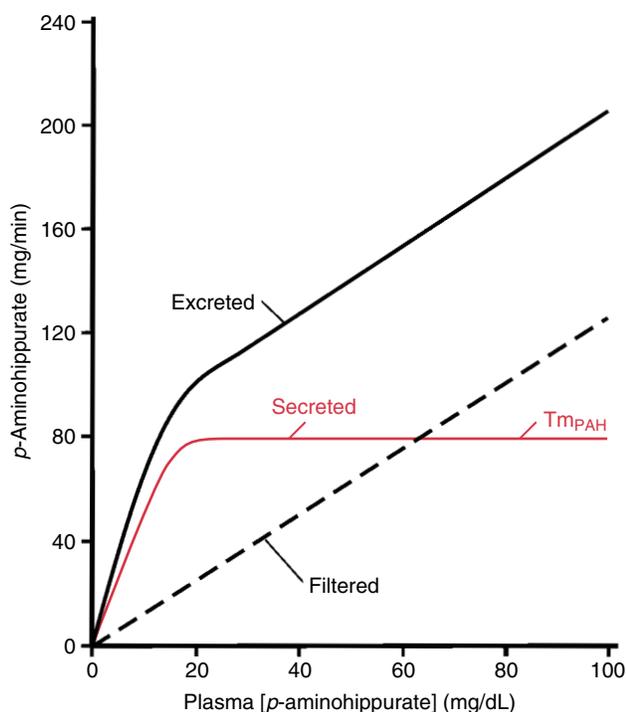
FIGURE 23.10 **Blood flow rates (in mL/min per gram of tissue) in different parts of the kidney.** (Modified from Brobeck JR, ed. Best & Taylor's Physiological Basis of Medical Practice. 10th Ed. Baltimore: Williams & Wilkins, 1979.)

300 g, so blood flow per gram of tissue averages about 4 mL/min. This rate of perfusion exceeds that of all other organs in the body, except the neurohypophysis and carotid bodies. The high blood flow to the kidneys is necessary for a high GFR and is not due to excessive metabolic demands.

The kidneys use about 8% of total resting oxygen consumption, but they receive much more oxygen than they need. Consequently, renal extraction of oxygen is low, and renal venous blood has a bright red color (because of a high oxyhemoglobin content). The anatomical arrangement of the vessels in the kidney permits a large fraction of the arterial oxygen to be shunted to the veins before the blood enters the capillaries. Therefore, the oxygen tension in the tissue is not as high as one might think, and the kidneys are certainly sensitive to ischemic damage.

Blood Flow Is Higher in the Renal Cortex and Lower in the Renal Medulla

Blood flow rates differ in different parts of the kidney (Fig. 23.10). Blood flow is highest in the cortex, averaging 4 to 5 mL/min per gram of tissue. The high cortical blood flow permits a high rate of filtration in the glomeruli. Blood flow (per gram of tissue) is about 0.7 to 1 mL/min in the outer medulla and 0.20 to 0.25 mL/min in the inner medulla. The relatively low blood flow in the medulla helps maintain a hyperosmolar environment in this region of the kidney.
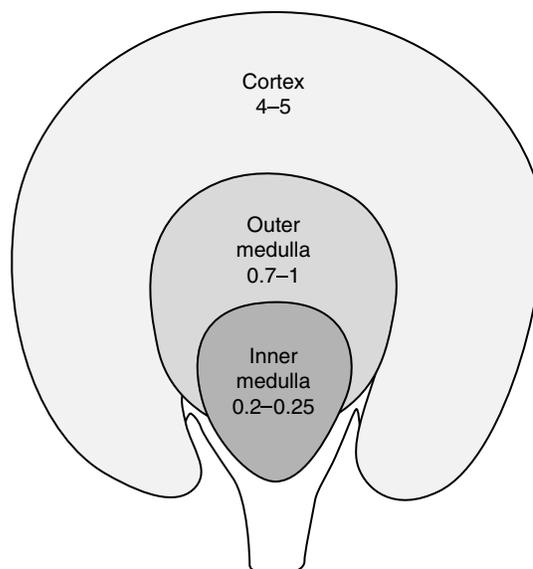
The Kidneys Autoregulate Their Blood Flow

Despite changes in mean arterial blood pressure (from 80 to 180 mm Hg), renal blood flow is kept at a relatively constant level, a process known as **autoregulation** (see Chapter 16). Autoregulation is an intrinsic property of the kidneys and is observed even in an isolated, denervated, perfused kidney. GFR is also autoregulated (Fig. 23.11). When the blood pressure is raised or lowered, vessels upstream of the glomerulus (cortical radial arteries and afferent arterioles) constrict or dilate, respectively, maintaining relatively constant glomerular blood flow and capillary pressure. Below or above the autoregulatory range of pressures, blood flow and GFR change appreciably with arterial blood pressure.

Two mechanisms account for renal autoregulation: the myogenic mechanism and the tubuloglomerular feedback mechanism. In the **myogenic mechanism,** an increase in pressure stretches blood vessel walls and opens stretch-activated cation channels in smooth muscle cells. The ensuing membrane depolarization opens voltage-dependent Ca^{2+} channels and intracellular $[Ca^{2+}]$ rises, causing smooth muscle contraction. Vessel lumen diameter decreases and vascular resistance increases. Decreased blood pressure causes the opposite changes.

In the **tubuloglomerular feedback mechanism**, the transient increase in GFR resulting from an increase in blood pressure leads to increased solute delivery to the macula densa (Fig. 23.12). This produces an increase in the tubular fluid [NaCl] at this site and increased NaCl reabsorption by macula densa cells. By mechanisms that are still uncertain, constriction of the nearby afferent arteriole results. The vasoconstrictor agent may be adenosine or ATP; it does not appear to be angiotensin II, although feedback sensitivity varies directly with the local concentration of angiotensin II. Blood flow and GFR are lowered to a more normal value. The tubuloglomerular feedback
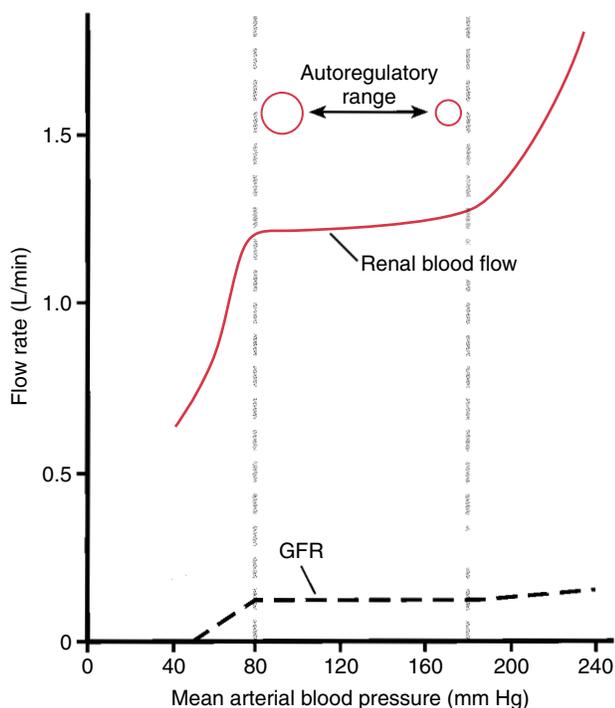
FIGURE 23.11 **Renal autoregulation, based on measurements in isolated, denervated, and perfused kidneys.** In the autoregulatory range, renal blood flow and GFR stay relatively constant despite changes in arterial blood pressure. This is accomplished by changes in the resistance (caliber) of preglomerular blood vessels. The circles indicate that vessel radius (r) is smaller when blood pressure is high and larger when blood pressure is low. Since resistance to blood flow varies as r^4, changes in vessel caliber are greatly exaggerated in this figure.
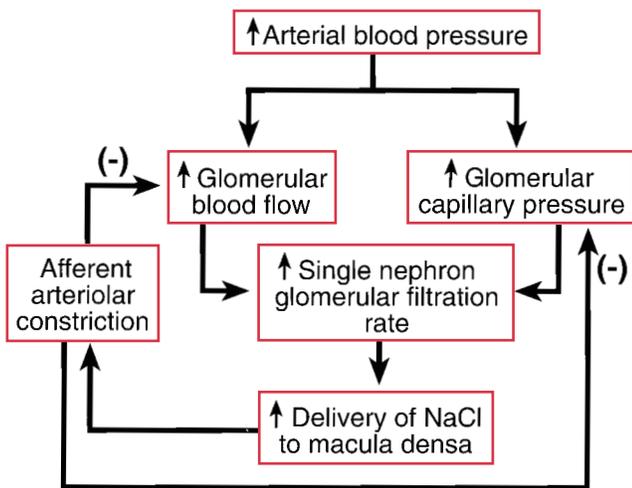

FIGURE 23.12 **The tubuloglomerular feedback mechanism.** When single nephron GFR is increased—for example, as a result of an increase in arterial blood pressure—more NaCl is delivered to and reabsorbed by the macula densa, leading to constriction of the nearby afferent arteriole. This negative-feedback system plays a role in renal blood flow and GFR autoregulation.

mechanism is a negative-feedback system that stabilizes renal blood flow and GFR.

If NaCl delivery to the macula densa is increased experimentally by perfusing the lumen of the loop of Henle, filtration rate in the perfused nephron decreases. This suggests that the purpose of tubuloglomerular feedback may be to control the amount of Na^+ presented to distal nephron segments. Regulation of Na^+ delivery to distal parts of the nephron is important because these segments have a limited capacity to reabsorb Na^+.

Renal autoregulation minimizes the impact of changes in arterial blood pressure on Na^+ excretion. Without renal autoregulation, increases in arterial blood pressure would lead to dramatic increases in GFR and potentially serious losses of NaCl and water from the ECF.

Renal Sympathetic Nerves and Various Hormones Change Renal Blood Flow

Renal blood flow may be changed by the stimulation of renal sympathetic nerves or by the release of various hormones. Sympathetic nerve stimulation causes renal vasoconstriction and a consequent decrease in renal blood flow. Renal sympathetic nerves are activated under stressful conditions, including cold temperatures, deep anesthesia, fearful situations, hemorrhage, pain, and strenuous exercise. In these conditions, the decrease in renal blood flow may be viewed as an emergency mechanism that makes more of the cardiac output available to perfuse other organs, such as the brain and heart, which are more important for short-term survival.

Several substances cause vasoconstriction in the kidneys, including adenosine, angiotensin II, endothelin, epinephrine, norepinephrine, thromboxane A_2, and vasopressin. Other substances cause vasodilation in the kidneys, including atrial natriuretic peptide, dopamine, histamine, kinins, nitric oxide, and prostaglandins E_2 and I_2. Some of these substances (e.g., prostaglandins E_2 and I_2) are produced locally in the kidneys. An increase in sympathetic nerve activity or plasma angiotensin II concentration stimulates the production of renal vasodilator prostaglandins. These prostaglandins then oppose the pure constrictor effect of sympathetic nerve stimulation or angiotensin II, reducing the fall in renal blood flow, preventing renal damage.

GLOMERULAR FILTRATION

Glomerular filtration involves the **ultrafiltration** of plasma. This term reflects the fact that the glomerular filtration barrier is an extremely fine molecular sieve that allows the filtration of small molecules but restricts the passage of macromolecules (e.g., the plasma proteins).

The Glomerular Filtration Barrier Has Three Layers

An ultrafiltrate of plasma passes from glomerular capillary blood into the space of Bowman's capsule through the **glomerular filtration barrier** (Fig. 23.13). This barrier consists of three layers. The first, the capillary **endothelium**, is called the lamina fenestra because it contains pores or win-
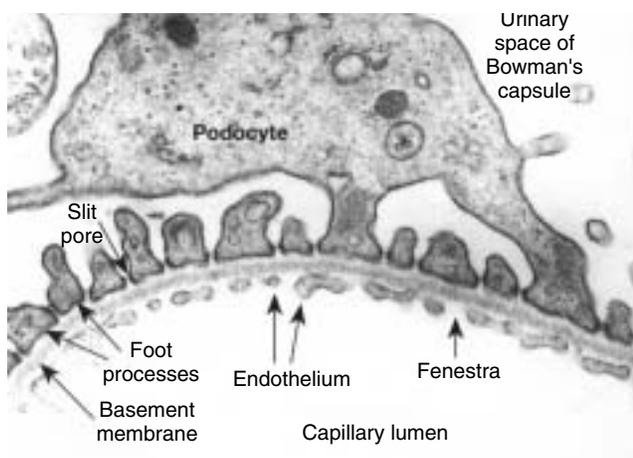
FIGURE 23.13 Electron micrograph showing the three layers of the glomerular filtration barrier: endothelium, basement membrane, and podocytes. (Courtesy of Dr. Andrew P. Evan, Indiana University.)

TABLE 23.1   Restrictions to the Glomerular Filtration of Molecules

Substance	Molecular Weight	Molecular Radius (nm)	[Filtrate]/ [Plasma Water]
Water	18	0.10	1.00
Glucose	180	0.36	1.00
Inulin	5,000	1.4	1.00
Myoglobin	17,000	2.0	0.75
Hemoglobin	68,000	3.3	0.03
Cationic dextran[a]		3.6	0.42
Neutral dextran		3.6	0.15
Anionic dextran		3.6	0.01
Serum albumin	69,000	3.6	0.001

[a]Dextrans are high-molecular-weight glucose polymers available in cationic (amine), neutral (uncharged), or anionic (sulfated) forms. (Adapted from Pitts RF. Physiology of the Kidney and Body Fluids. 3rd Ed. Chicago: Year Book, 1974; and Brenner BM, Bohrer MP, Baylis C, Deen WM. Determinants of glomerular permselectivity: Insights derived from observations *in vivo*. Kidney Int 1977;12:229–237.)

dows (fenestrae). At about 50 to 100 nm in diameter, these pores are too large to restrict the passage of plasma proteins. The second layer, the **basement membrane,** consists of a meshwork of fine fibrils embedded in a gel-like matrix. The third layer is composed of **podocytes,** which constitute the visceral layer of Bowman's capsule. Podocytes ("foot cells") are epithelial cells with extensions that terminate in foot processes, which rest on the outer layer of the basement membrane (see Fig. 23.13). The space between adjacent foot processes, called a **slit pore,** is about 20 nm wide and is bridged by a **filtration slit diaphragm.** A key component of the diaphragm is a molecule called **nephron,** which forms a zipper-like structure; between the prongs of the zipper are rectangular pores. The nephron is mutated in **congenital nephrotic syndrome,** a rare, inherited condition characterized by excessive filtration of plasma proteins. The glomerular filtrate normally takes an extracellular route, through holes in the endothelial cell layer, the basement membrane, and the pores between adjacent nephron molecules.

Size, Shape, and Electrical Charge Affect the Filterability of Macromolecules

The permeability properties of the glomerular filtration barrier have been studied by determining how well molecules of different sizes pass through it. Table 23.1 lists several molecules that have been tested. Molecular radii were calculated from diffusion coefficients. The concentration of the molecule in the glomerular filtrate (fluid collected from Bowman's capsule) is compared to its concentration in plasma water. A ratio of 1 indicates complete filterability, and a ratio of zero indicates complete exclusion by the glomerular filtration barrier.

Molecular size is an important factor affecting filterability. All molecules with weights less than 10,000 are freely filterable, provided they are not bound to plasma proteins. Molecules with weights greater than 10,000 experience more restriction to passage through the glomerular filtra-

tion barrier. Very large molecules (e.g., molecular weight, 100,000) cannot get through at all. Most plasma proteins are large molecules, so they are not appreciably filtered. From studies with molecules of different sizes, it has been calculated that the glomerular filtration barrier behaves as though it were penetrated by cylindric pores of about 7.5 to 10 nm in diameter. However, no one has ever seen pores of this size in electron micrographs of the glomerular filtration barrier.

Molecular shape influences the filterability of macromolecules. For a given molecular weight, a slender and flexible molecule will pass through the glomerular filtration barrier more easily than a spherical, nondeformable molecule.

Electrical charge influences the passage of macromolecules through the glomerular filtration barrier because the barrier bears fixed negative charges. Glomerular endothelial cells and podocytes have a negatively charged surface coat (glycocalyx), and the glomerular basement membrane contains negatively charged sialic acid, sialoproteins, and heparan sulfate. These negative charges impede the passage of negatively charged macromolecules by electrostatic repulsion and favor the passage of positively charged macromolecules by electrostatic attraction. This is supported by the finding that the filterability of dextran is lowest for anionic dextran, intermediate for neutral dextran, and highest for cationic dextran (see Table 23.1).

In addition to its large molecular size, the net negative charge on serum albumin at physiological pH is an important factor that reduces its filterability. In some glomerular diseases, a loss of fixed negative charges from the glomerular filtration barrier causes increased filtration of serum albumin. **Proteinuria,** abnormal amounts of protein in the urine, results. Proteinuria is the hallmark of glomerular disease (see Clinical Focus Box 23.2 and the Case Study).

The layer of the glomerular filtration barrier primarily responsible for limiting the filtration of macromolecules is a matter of debate. The basement membrane is probably the principal size-selective barrier, and the filtration slit diaphragm forms a second barrier. The major electrostatic

CLINICAL FOCUS BOX 23.2

Glomerular Disease

The kidney glomeruli may be injured by several immunological, toxic, hemodynamic, and metabolic disorders. Glomerular injury impairs filtration barrier function and, consequently, increases the filtration and excretion of plasma proteins (proteinuria). Red cells may appear in the urine, and sometimes GFR is reduced. Three general syndromes are encountered: nephritic diseases, nephrotic diseases (nephrotic syndrome), and chronic glomerulonephritis.

In the **nephritic diseases**, the urine contains red blood cells, red cell casts, and mild to modest amounts of protein. A red cell cast is a mold of the tubule lumen formed when red cells and proteins clump together; the presence of such casts in the final urine indicates that bleeding had occurred in the kidneys (usually in the glomeruli), not in the lower urinary tract. Nephritic diseases are usually associated with a fall in GFR, accumulation of nitrogenous wastes (urea, creatinine) in the blood, and hypervolemia (hypertension, edema). Most nephritic diseases are due to immunological damage. The glomerular capillaries may be injured by antibodies directed against the glomerular basement membrane, by deposition of circulating immune complexes along the endothelium or in the mesangium, or by cell-mediated injury (infiltration with lymphocytes and macrophages). A renal biopsy and tissue examination by light and electron microscopy and immunostaining are often helpful in determining the nature and severity of the disease and in predicting its most likely course.

Poststreptococcal glomerulonephritis is an example of a nephritic condition that may follow a sore throat caused by certain strains of streptococci. Immune complexes of antibody and bacterial antigen are deposited in the glomeruli, complement is activated, and polymorphonuclear leukocytes and macrophages infiltrate the glomeruli. Endothelial cell damage, accumulation of leukocytes, and the release of vasoconstrictor substances reduce the glomerular surface area and fluid permeability and lower glomerular blood flow, causing a fall in GFR.

Nephrotic syndrome is a clinical state that can develop as a consequence of many different diseases causing glomerular injury. It is characterized by heavy proteinuria (>3.5 g/day per 1.73 m^2 body surface area), hypoalbuminemia (<3 g/dL), generalized edema, and hyperlipidemia. Abnormal glomerular leakiness to plasma proteins leads to increased catabolism of the reabsorbed proteins in the kidney proximal tubules and increased protein excretion in the urine. The loss of protein (mainly serum albumin) leads to a fall in plasma [protein] (and colloid osmotic pressure). The edema results from the hypoalbuminemia and renal Na^+ retention. Also, a generalized increase in capillary permeability to proteins (not just in the glomeruli) may lead to a decrease in the effective colloid osmotic pressure of the plasma proteins and may contribute to the edema. The hyperlipidemia (elevated serum cholesterol and, in severe cases, elevated triglycerides) is probably a result of increased hepatic synthesis of lipoproteins and decreased lipoprotein catabolism. Most often, nephrotic syndrome in young children cannot be ascribed to a specific cause; this is called idiopathic nephrotic syndrome. Nephrotic syndrome in children or adults can be caused by infectious diseases, neoplasia, certain drugs, various autoimmune disorders (such as lupus), allergic reactions, metabolic disease (such as diabetes mellitus), or congenital disorders.

The distinctions between nephritic and nephrotic diseases are sometimes blurred, and both may result in **chronic glomerulonephritis**. This disease is characterized by proteinuria and/or hematuria (blood in the urine), hypertension, and renal insufficiency that progresses over years. Renal biopsy shows glomerular scarring and increased numbers of cells in the glomeruli and scarring and inflammation in the interstitial space. The disease is accompanied by a progressive loss of functioning nephrons and proceeds relentlessly even though the initiating insult may no longer be present. The exact reasons for disease progression are not known, but an important factor may be that surviving nephrons hypertrophy when nephrons are lost. This leads to an increase in blood flow and pressure in the remaining nephrons, a situation that further injures the glomeruli. Also, increased filtration of proteins causes increased tubular reabsorption of proteins, and the latter results in production of vasoactive and inflammatory substances that cause ischemia, interstitial inflammation, and renal scarring. Dietary manipulations (such as a reduced protein intake) or antihypertensive drugs (such as angiotensin-converting enzyme inhibitors) may slow the progression of chronic glomerulonephritis. Glomerulonephritis in its various forms is the major cause of renal failure in people.

Reference

Falk RJ, Jennette JC, Nachman PH. Primary glomerular diseases. In: Brenner BM, ed. Brenner & Rector's The Kidney. 6th Ed. Philadelphia: WB Saunders, 2000;1263–1349.

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barriers are probably the layers closest to the capillary lumen, the lamina fenestra and the innermost part of the basement membrane.

GFR Is Determined by Starling Forces

Glomerular filtration rate depends on the balance of hydrostatic and colloid osmotic pressures acting across the glomerular filtration barrier, the Starling forces (see Chapter 16); therefore, it is determined by the same factors that affect fluid movement across capillaries in general. In the glomerulus, the driving force for fluid filtration is the glomerular capillary hydrostatic pressure (P_{GC}). This pressure ultimately depends on the pumping of blood by the heart, an action that raises the blood pressure on the arterial side of the circulation. Filtration is opposed by the hydrostatic pressure in the space of Bowman's capsule (P_{BS}) and by the colloid osmotic pressure (COP) exerted by plasma proteins in glomerular capillary blood. Because the glomerular filtrate is virtually protein-free, we neglect the colloid osmotic pressure of fluid in Bowman's capsule. The **net ultrafiltration pressure gradi-**

ent (UP) is equal to the difference between the pressures favoring and opposing filtration:

$$GFR = K_f \times UP = K_f \times (P_{GC} - P_{BS} - COP) \quad (10)$$

where K_f is the glomerular ultrafiltration coefficient. Estimates of average, normal values for pressures in the human kidney are: P_{GC}, 55 mm Hg; P_{BS}, 15 mm Hg; and COP, 30 mm Hg. From these values, we calculate a net ultrafiltration pressure gradient of +10 mm Hg.

The Pressure Profile Along a Glomerular Capillary Is Unusual

Figure 23.14 shows how pressures change along the length of a glomerular capillary, in contrast to those seen in a capillary in other vascular beds (in this case, skeletal muscle). Note that average capillary hydrostatic pressure in the glomerulus is much higher (55 vs. 25 mm Hg) than in a skeletal muscle capillary. Also, capillary hydrostatic pressure declines little (perhaps 1 to 2 mm Hg) along the length of the glomerular capillary because the glomerulus contains many (30 to 50) capillary loops in parallel, making the resistance to blood flow in the glomerulus very low. In the skeletal muscle capillary, there is a much higher resistance

to blood flow, resulting in an appreciable fall in capillary hydrostatic pressure with distance. Finally, note that in the glomerulus, the colloid osmotic pressure increases substantially along the length of the capillary because a large volume of filtrate (about 20% of the entering plasma flow) is pushed out of the capillary and the proteins remain in the circulation. The increase in colloid osmotic pressure opposes the outward movement of fluid.

In the skeletal muscle capillary, the colloid osmotic pressure hardly changes with distance, since little fluid moves across the capillary wall. In the "average" skeletal muscle capillary, outward filtration occurs at the arterial end and absorption occurs at the venous end. At some point along the skeletal muscle capillary, there is no net fluid movement; this is the point of so-called **filtration pressure equilibrium**. Filtration pressure equilibrium probably is not attained in the normal human glomerulus; in other words, the outward filtration of fluid probably occurs all along the glomerular capillaries.

Several Factors Can Affect GFR

The GFR depends on the magnitudes of the different terms in equation 10. Therefore, GFR varies with changes in K_f, hydrostatic pressures in the glomerular capillaries and Bow-
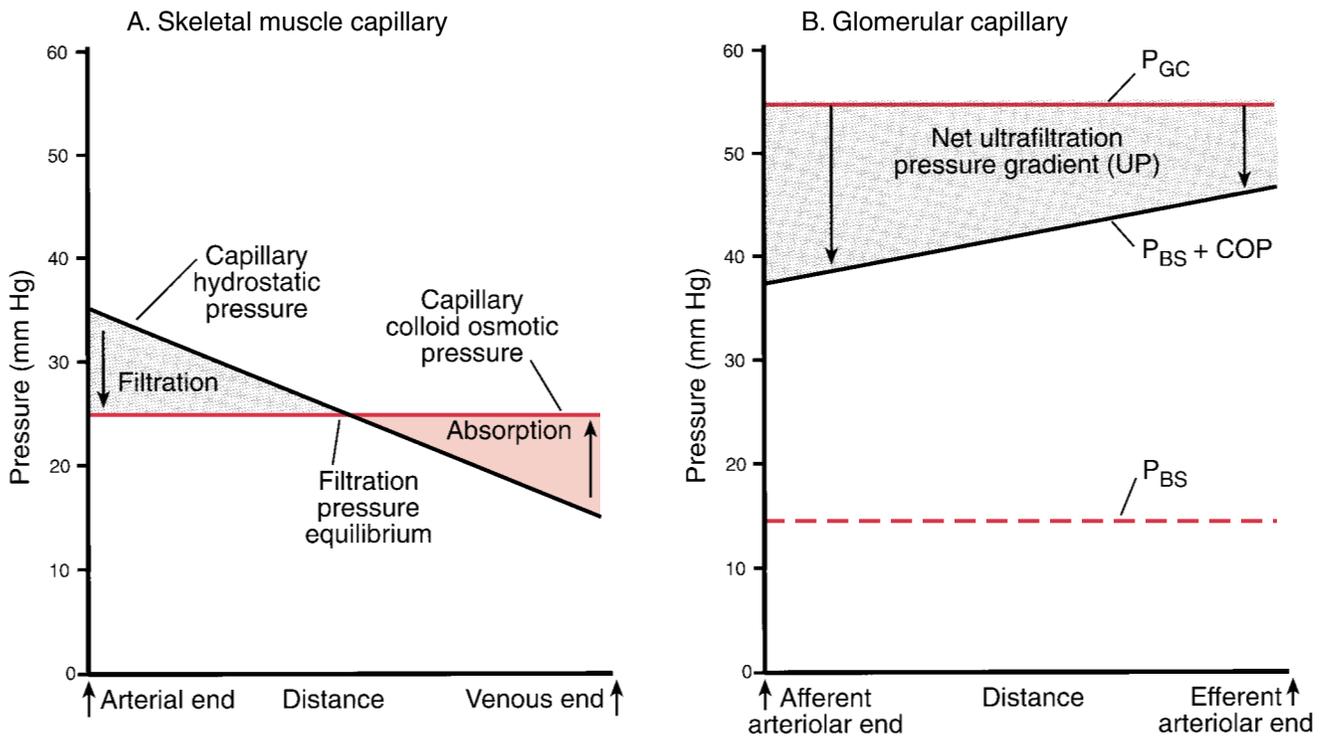

FIGURE 23.14 **Pressure profiles along a skeletal muscle capillary and a glomerular capillary. A,** In the typical skeletal muscle capillary, filtration occurs at the arterial end and absorption at the venous end of the capillary. Interstitial fluid hydrostatic and colloid osmotic pressures are neglected here because they are about equal and counterbalance each other. **B,** In the glomerular capillary, glomerular hydrostatic pressure (P_{GC}) (top line) is high and declines only slightly with distance. The bottom line represents the hydrostatic pressure in Bowman's capsule (P_{BS}). The middle line is the sum of P_{BS} and the glomerular capillary colloid osmotic pressure (COP). The difference between P_{GC} and P_{BS} + COP is equal to the net ultrafiltration pressure gradient (UP). In the normal human glomerulus, filtration probably occurs along the entire capillary. Assuming that K_f is uniform along the length of the capillary, filtration rate would be highest at the afferent arteriolar end and lowest at the efferent arteriolar end of the glomerulus.

man's capsule, and the glomerular capillary colloid osmotic pressure. These factors are discussed next.

The Glomerular Ultrafiltration Coefficient.   The **glomerular ultrafiltration coefficient** (K_f) is the glomerular equivalent of the capillary filtration coefficient encountered in Chapter 16. It depends on both the hydraulic conductivity (fluid permeability) and surface area of the glomerular filtration barrier. In chronic renal disease, functioning glomeruli are lost, leading to a reduction in surface area available for filtration and a fall in GFR. Acutely, a variety of drugs and hormones appear to change glomerular K_f and, thus, alter GFR, but the mechanisms are not completely understood.

Glomerular Capillary Hydrostatic Pressure.   Glomerular capillary hydrostatic pressure (P_{GC}) is the driving force for filtration; it depends on the arterial blood pressure and the resistances of upstream and downstream blood vessels. Because of autoregulation, P_{GC} and GFR are maintained at relatively constant values when arterial blood pressure is varied from 80 to 180 mm Hg. Below a pressure of 80 mm Hg, however, P_{GC} and GFR decrease, and GFR ceases at a blood pressure of about 40 to 50 mm Hg. One of the classic signs of hemorrhagic or cardiogenic shock is an absence of urine output, which is due to an inadequate P_{GC} and GFR.

The caliber of afferent and efferent arterioles can be altered by a variety of hormones and by sympathetic nerve stimulation, leading to changes in P_{GC}, glomerular blood flow, and GFR. Some hormones act preferentially on afferent or efferent arterioles. Afferent arteriolar dilation increases glomerular blood flow and P_{GC} and, therefore, produces an increase in GFR. Afferent arteriolar constriction produces the exact opposite effects. Efferent arteriolar dilation increases glomerular blood flow but leads to a fall in GFR because P_{GC} is decreased. Constriction of efferent arterioles increases P_{GC} and decreases glomerular blood flow. With modest efferent arteriolar constriction, GFR increases because of the increased P_{GC}. With extreme efferent arteriolar constriction, however, GFR decreases because of the marked decrease in glomerular blood flow.

Hydrostatic Pressure in Bowman's Capsule.   Hydrostatic pressure in Bowman's capsule (P_{BS}) depends on the input of glomerular filtrate and the rate of removal of this fluid by the tubule. This pressure opposes filtration. It also provides the driving force for fluid movement down the tubule lumen. If there is obstruction anywhere along the urinary tract—for example, stones, ureteral obstruction, or prostate enlargement—then pressure upstream to the block is increased, and GFR consequently falls. If tubular reabsorption of water is inhibited, pressure in the tubular system is increased because an increased pressure head is needed to force a large volume flow through the loops of Henle and collecting ducts. Consequently, a large increase in urine output caused by a diuretic drug may be associated with a tendency for GFR to fall.

Glomerular Capillary Colloid Osmotic Pressure.   The COP opposes glomerular filtration. Dilution of the plasma proteins (e.g., by intravenous infusion of a large volume of isotonic saline) lowers the plasma COP and leads to an increase in GFR. Part of the reason glomerular blood flow has important effects on GFR is that the COP profile is changed along the length of a glomerular capillary. Consider, for example, what would happen if glomerular blood flow were low. Filtering a small volume out of the glomerular capillary would lead to a sharp rise in COP early along the length of the glomerulus. As a consequence, filtration would soon cease and GFR would be low. On the other hand, a high blood flow would allow a high rate of filtrate formation with a minimal rise in COP. In general, renal blood flow and GFR change hand in hand, but the exact relation between GFR and renal blood flow depends on the magnitude of the other factors that affect GFR.

Several Factors Contribute to the High GFR in the Human Kidney

The rate of plasma ultrafiltration in the kidney glomeruli (180 L/day) far exceeds that in all other capillary beds, for several reasons:

1) The filtration coefficient is unusually high in the glomeruli. Compared with most other capillaries, the glomerular capillaries behave as though they had more pores per unit surface area; consequently, they have an unusually high hydraulic conductivity. The total glomerular filtration barrier area is large, about 2 m^2.

2) Capillary hydrostatic pressure is higher in the glomeruli than in any other capillaries.

3) The high rate of renal blood flow helps sustain a high GFR by limiting the rise in colloid osmotic pressure, favoring filtration along the entire length of the glomerular capillaries.

In summary, glomerular filtration is high because the glomerular capillary blood is exposed to a large porous surface and there is a high transmural pressure gradient.

TRANSPORT IN THE PROXIMAL TUBULE

Glomerular filtration is a rather nonselective process, since both useful and waste substances are filtered. By contrast, tubular transport is selective; different substances are transported by different mechanisms. Some substances are reabsorbed, others are secreted, and still others are both reabsorbed and secreted. For most, the amount excreted in the urine depends in large measure on the magnitude of tubular transport. Transport of various solutes and water differs in the various nephron segments. Here we describe transport along the nephron and collecting duct system, starting with the proximal convoluted tubule.

The proximal convoluted tubule comprises the first 60% of the length of the proximal tubule. Because the proximal straight tubule is inaccessible to study *in vivo*, most quantitative information about function in the living animal is confined to the convoluted portion. Studies on isolated tubules *in vitro* indicate that both segments of the proximal tubule are functionally similar. The proximal tubule is responsible for reabsorbing all of the filtered glucose and amino acids; reabsorbing the largest fraction of the filtered Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-, and water and secreting various organic anions and organic cations.
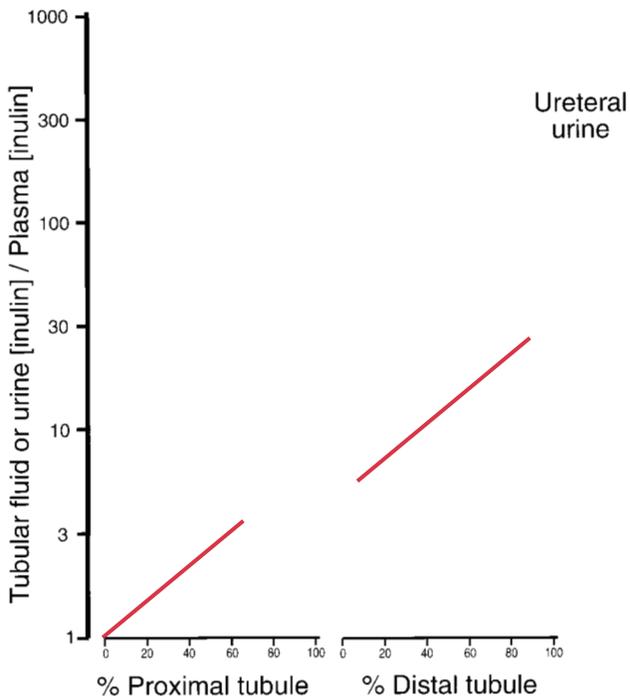
FIGURE 23.15 **Tubular fluid (or urine) [inulin]/plasma [inulin] ratio as a function of collection site (data from micropuncture experiments in rats).** The increase in this ratio depends on the extent of tubular water reabsorption. The distal tubule is defined in these studies as beginning at the macula densa and ending at the junction of the tubule and a collecting duct and it includes distal convoluted tubule, connecting tubule, and initial part of the collecting duct. (Modified from Giebisch G, Windhager E. Renal tubular transfer of sodium, chloride, and potassium. Am J Med 1964;36:643–669.)

The Proximal Convoluted Tubule Reabsorbs About 70% of the Filtered Water

The percentage of filtered water reabsorbed along the nephron has been determined by measuring the degree to which inulin is concentrated in tubular fluid, using the **kidney micropuncture** technique in laboratory animals. Samples of tubular fluid from surface nephrons are collected and analyzed, and the site of collection is identified by nephron microdissection. Because inulin is filtered but not reabsorbed by the kidney tubules, as water is reabsorbed, the inulin becomes increasingly concentrated. For example, if 50% of the filtered water is reabsorbed by a certain point along the tubule, the [inulin] in tubular fluid (TF_{IN}) will be twice the plasma [inulin] (P_{IN}). The percentage of filtered water reabsorbed by the tubules is equal to $100 \times (SNGFR - \dot{V}_{TF})/SNGFR$, where SN (single nephron) GFR gives the rate of filtration of water and $\dot{V}_{TF}$ is the rate of tubular fluid flow at a particular point. The SNGFR can be measured from the single nephron inulin clearance and is equal to $TF_{IN} \times \dot{V}_{TF}/P_{IN}$. From these relations:

$$\text{% of filtered water} = [1 - 1/(TF_{IN}/P_{IN})] \times 100 \quad (11)$$

Figure 23.15 shows how the TF_{IN}/P_{IN} ratio changes along the nephron in normal rats. In fluid collected from Bowman's capsule, the [inulin] is identical to that in plasma (inulin is freely filterable), so the concentration ratio starts at 1. By the end of the proximal convoluted tubule, the ratio is a

little higher than 3, indicating that about 70% of the filtered water was reabsorbed in the proximal convoluted tubule. The ratio is about 5 at the beginning of the distal tubule, indicating that 80% of the filtered water was reabsorbed up to this point. From these measurements, we can conclude that the loop of Henle reabsorbed 10% of the filtered water. The urine/plasma inulin concentration ratio in the ureter is greater than 100, indicating that more than 99% of the filtered water was reabsorbed. These percentages are not fixed; they can vary widely, depending on conditions.

Proximal Tubular Fluid Is Essentially Isosmotic to Plasma

Samples of fluid collected from the proximal convoluted tubule are always essentially isosmotic to plasma, a consequence of the high water permeability of this segment (Fig. 23.16). Overall, 70% of filtered solutes and water are reabsorbed along the proximal convoluted tubule.

Na^+ salts are the major osmotically active solutes in the plasma and glomerular filtrate. Since osmolality does not change appreciably with proximal tubule length, it is
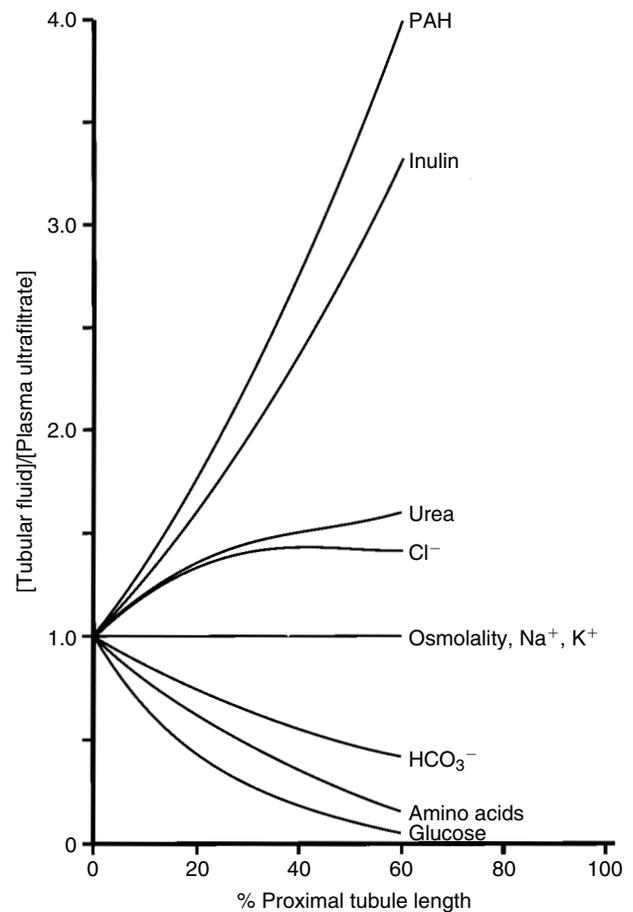

FIGURE 23.16 **Tubular fluid-plasma ultrafiltrate concentration ratios for various solutes as a function of proximal tubule length.** All values start at a ratio of 1, since the fluid in Bowman's capsule (0% proximal tubule length) is a plasma ultrafiltrate.

not surprising that $[Na^+]$ also does not change under ordinary conditions.

If an appreciable quantity of nonreabsorbed solute is present (e.g., the sugar alcohol mannitol), proximal tubular fluid $[Na^+]$ falls to values below the plasma concentration. This is evidence that Na^+ can be reabsorbed against a concentration gradient and is an active process. The fall in proximal tubular fluid $[Na^+]$ increases diffusion of Na^+ into the tubule lumen and results in reduced net Na^+ and water reabsorption, leading to increased excretion of Na^+ and water, an osmotic diuresis.

Two major anions, Cl^- and HCO_3^-, accompany Na^+ in plasma and glomerular filtrate. HCO_3^- is preferentially reabsorbed along the proximal convoluted tubule, leading to a fall in tubular fluid $[HCO_3^-]$, mainly because of H^+ secretion (see Chapter 25). The Cl^- lags behind; as water is reabsorbed, $[Cl^-]$ rises (see Fig. 23.16). The result is a tubular fluid-to-plasma concentration gradient that favors Cl^- diffusion out of the tubule lumen. Outward movement of Cl^- in the late proximal convoluted tubule creates a small (1–2 mV), lumen-positive transepithelial potential difference that favors the passive reabsorption of Na^+.

Figure 23.16 shows that the $[K^+]$ hardly changes along the proximal convoluted tubule. If K^+ were not reabsorbed, its concentration would increase as much as that of inulin. The fact that the concentration ratio for K^+ remains about 1 in this nephron segment indicates that 70% of filtered K^+ is reabsorbed along with 70% of the filtered water.

The concentrations of glucose and amino acids fall steeply in the proximal convoluted tubule. This nephron segment and the proximal straight tubule are responsible for complete reabsorption of these substances. Separate, specific mechanisms reabsorb glucose and various amino acids.

The concentration ratio for urea rises along the proximal tubule, but not as much as the inulin concentration ratio because about 50% of the filtered urea is reabsorbed. The concentration ratio for PAH in proximal tubular fluid increases more steeply than the inulin concentration ratio because of PAH secretion.

In summary, though the osmolality (total solute concentration) does not detectably change along the proximal convoluted tubule, it is clear that the concentrations of individual solutes vary widely. The concentrations of some substances fall (glucose, amino acids, HCO_3^-), others rise (inulin, urea, Cl^-, PAH), and still others do not change (Na^+, K^+). By the end of the proximal convoluted tubule, only about one-third of the filtered Na^+, water, and K^+ remain; almost all of the filtered glucose, amino acids, and HCO_3^- have been reabsorbed, and several solutes destined for excretion (PAH, inulin, urea) have been concentrated in the tubular fluid.

Na$^+$ Reabsorption Is the Major Driving Force for Reabsorption of Solutes and Water in the Proximal Tubule

Figure 23.17 is a model of a proximal tubule cell. Na^+ enters the cell from the lumen across the apical cell membrane and is pumped out across the basolateral cell membrane by Na^+/K^+-ATPase. The Na^+ and accompanying anions and water are then taken up by the blood sur-
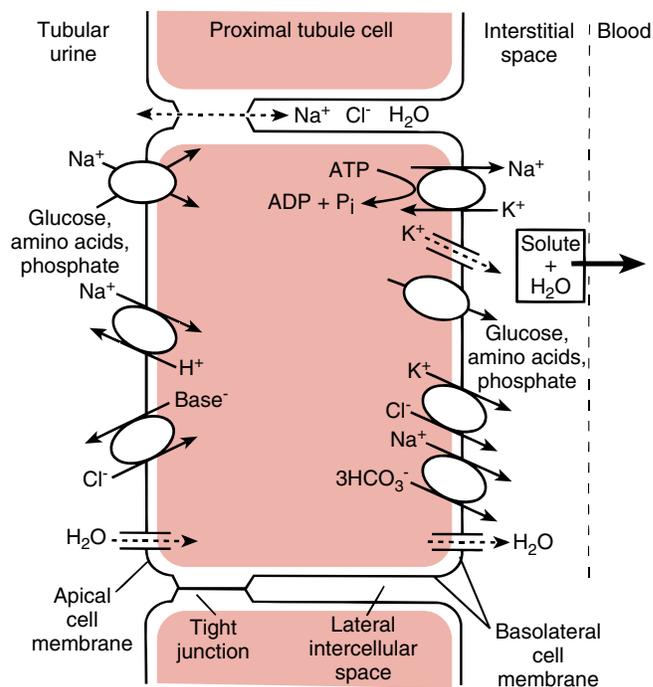

FIGURE 23.17 **A cell model for transport in the proximal tubule.** The luminal (apical) cell membrane in this nephron segment has a large surface area for transport because of the numerous microvilli that form the brush border (not shown). Glucose, amino acids, phosphate, and numerous other substances are transported by separate carriers.

rounding the tubules, and filtered Na^+ salts and water are returned to the circulation.

At the luminal cell membrane (brush border) of the proximal tubule cell, Na^+ enters the cell down combined electrical and chemical potential gradients. The inside of the cell is about -70 mV compared to tubular fluid, and intracellular $[Na^+]$ is about 30 to 40 mEq/L compared with a tubular fluid concentration of about 140 mEq/L. Na^+ entry into the cell occurs via several cotransporter and antiport mechanisms. Na^+ is reabsorbed together with glucose, amino acids, phosphate, and other solutes by way of separate, specific cotransporters. The downhill (energetically speaking) movement of Na^+ into the cell drives the uphill transport of these solutes. In other words, glucose, amino acids, phosphate, and so on are reabsorbed by secondary active transport. Na^+ is also reabsorbed across the luminal cell membrane in exchange for H^+. The Na^+/H^+ exchanger, an antiporter, is also a secondary active transport mechanism; the downhill movement of Na^+ into the cell energizes the uphill secretion of H^+ into the lumen. This mechanism is important in the acidification of urine (see Chapter 25). Cl^- may enter the cells by way of a luminal cell membrane Cl^--base (formate or oxalate) exchanger.

Once inside the cell, Na^+ is pumped out the basolateral side by a vigorous Na^+/K^+-ATPase that keeps intracellular $[Na^+]$ low. This membrane ATPase pumps three Na^+ out of the cell and two K^+ into the cell and splits one ATP molecule for each cycle of the pump. K^+ pumped into the cell diffuses out the basolateral cell membrane mostly through a K^+ channel. Glucose, amino acids, and phosphate, accu-

mulated in the cell because of active transport across the luminal cell membrane, exit across the basolateral cell membrane by way of separate, Na^+-independent facilitated diffusion mechanisms. HCO_3^- exits together with Na^+ by an electrogenic mechanism; the carrier transports three HCO_3^- for each Na^+. Cl^- may leave the cell by way of an electrically neutral K-Cl cotransporter.

The reabsorption of Na^+ and accompanying solutes establishes an osmotic gradient across the proximal tubule epithelium that is the driving force for water reabsorption. Because the water permeability of the proximal tubule epithelium is extremely high, only a small gradient (a few mOsm/kg H_2O) is needed to account for the observed rate of water reabsorption. Some experimental evidence indicates that proximal tubular fluid is slightly hypoosmotic to plasma; since the osmolality difference is so small, it is still proper to consider the fluid as essentially isosmotic to plasma. Water crosses the proximal tubule epithelium through the cells via water channels (aquaporin-1) in the cell membranes and between the cells (tight junctions and lateral intercellular spaces).

The final step in the overall reabsorption of solutes and water is uptake by the peritubular capillaries. This mechanism involves the usual Starling forces that operate across capillary walls. Recall that blood in the peritubular capillar-ies was previously filtered in the glomeruli. Because a protein-free filtrate was filtered out of the glomeruli, the [protein] (hence, colloid osmotic pressure) of blood in the peritubular capillaries is high, providing an important driving force for the uptake of reabsorbed fluid. The hydrostatic pressure in the peritubular capillaries (a pressure that opposes the capillary uptake of fluid) is low because the blood has passed through upstream resistance vessels. The balance of pressures acting across peritubular capillaries favors the uptake of reabsorbed fluid from the interstitial spaces surrounding the tubules.

The Proximal Tubule Secretes Organic Ions

The proximal tubule, both convoluted and straight portions, secretes a large variety of organic anions and organic cations (Table 23.2). Many of these substances are endogenous compounds, drugs, or toxins. The organic anions are mainly carboxylates and sulfonates (carboxylic and sulfonic acids in their protonated forms). A negative charge on the molecule appears to be important for secretion of these compounds. Examples of organic anions actively secreted in the proximal tubule include penicillin and PAH. Organic anion transport becomes saturated at high plasma organic anion concentrations (see Fig. 23.9), and the organic anions compete with each other for secretion.

Figure 23.18 shows a cell model for active secretion. Proximal tubule cells actively take up PAH from the blood

TABLE 23.2	Some Organic Compounds Secreted by Proximal Tubules[a]
Compound	**Use**
Organic anions	
Phenol red (phenolsulfonphthalein)	pH indicator dye
p-Aminohippurate (PAH)	Measurement of renal plasma flow and proximal tubule secretory mass
Penicillin	Antibiotic
Probenecid (Benemid)	Inhibitor of penicillin secretion and uric acid reabsorption
Furosemide (Lasix)	Loop diuretic drug
Acetazolamide (Diamox)	Carbonic anhydrase inhibitor
Creatinine[b]	Normal end-product of muscle metabolism
Organic cations	
Histamine	Vasodilator, stimulator of gastric acid secretion
Cimetidine	Drug for treatment of gastric and duodenal ulcers
Cisplatin	Cancer chemotherapeutic agent
Norepinephrine	Neurotransmitter
Quinine	Antimalarial drug
Tetraethylammonium (TEA)	Ganglion blocking drug
Creatinine[b]	Normal end-product of muscle metabolism

[a]This list includes only a few of the large variety of organic anions and cations secreted by kidney proximal tubules.
[b]Creatinine is an unusual compound because it is secreted by both organic anion and cation mechanisms. The creatinine molecule bears negatively charged and positively charged groups at physiological pH (it is a zwitterion), and this property may enable it to interact with both secretory mechanisms.
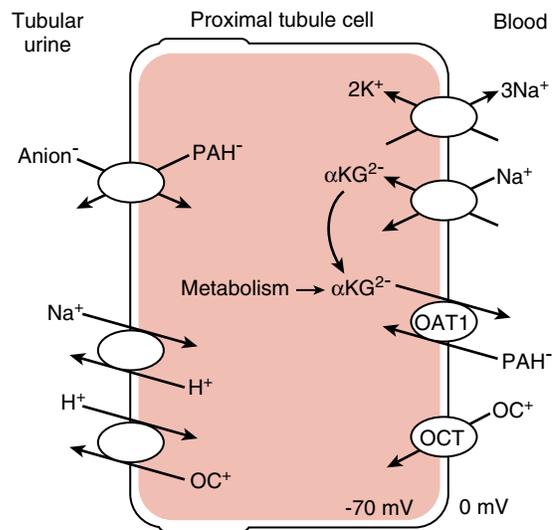

FIGURE 23.18 **A cell model for the secretion of organic anions (PAH) and organic cations in the proximal tubule.** Upward pointing arrows indicate transport against an electrochemical gradient (energetically uphill transport) and downward pointing arrows indicate downhill transport. There are two steps in the transcellular secretion of an organic anion or organic cation (OC^+): the active (uphill) transport step occurs in the basolateral membrane for PAH and in the luminal (brush border) membrane for the OC^+. There are actually more transporters for these molecules than are depicted in this figure. α-KG^{2-}, α-ketoglutarate; OAT1, organic anion transporter 1; OCT, organic cation transporter.

side by exchange for cell α-ketoglutarate. This exchange is mediated by an organic anion transporter (OAT) called OAT1. The cells accumulate α-ketoglutarate from metabolism and because of cell membrane Na^+-dependent dicarboxylate transporters. PAH accumulates in the cells at a high concentration and then moves downhill into the tubular urine in an electrically neutral fashion, by exchanging for an inorganic anion (e.g., Cl^-) or an organic anion.

The organic cations are mainly amine and ammonium compounds and are secreted by other transporters. Entry into the cell across the basolateral membrane is favored by the inside negative membrane potential and occurs via facilitated diffusion, mediated by an organic cation transporter (OCT). The exit of organic cations across the luminal membrane is accomplished by an organic cation/H^+ antiporter (exchanger) and is driven by the lumen-to-cell $[H^+]$ gradient established by Na^+/H^+ exchange. The transporters for organic anions and organic cations show broad substrate specificity and accomplish the secretion of a large variety of chemically diverse compounds.

In addition to being actively secreted, some organic compounds passively diffuse across the tubular epithelium. Organic anions can accept H^+ and organic cations can release H^+, so their charge is influenced by pH. The nonionized (uncharged) form, if it is lipid-soluble, can diffuse through the lipid bilayer of cell membranes down concentration gradients. The ionized (charged) form passively penetrates cell membranes with difficulty.

Consider, for example, the carboxylic acid probenecid ($pK_a = 3.4$). This compound is filtered by the glomeruli and secreted by the proximal tubule. When H^+ is secreted into the tubular urine (see Chapter 25), the anionic form (A^-) is converted to the nonionized acid (HA). The concentration of nonionized acid is also increased because of water reabsorption. A concentration gradient for passive reabsorption across the tubule wall is created, and appreciable quantities of probenecid are passively reabsorbed. This occurs in most parts of the nephron, but particularly in those where pH gradients are largest and where water reabsorption has resulted in the greatest concentration (i.e., the collecting ducts). The excretion of probenecid is enhanced by making the urine more alkaline (by administering $NaHCO_3$) and by increasing urine output (by drinking water).

Finally, a few organic anions and cations are also actively reabsorbed. For example, uric acid is both secreted and reabsorbed in the proximal tubule. Normally, the amount of uric acid excreted is equal to about 10% of the filtered uric acid, so reabsorption predominates. In **gout**, plasma levels of uric acid are increased. One treatment for gout is to promote urinary excretion of uric acid by administering drugs that inhibit its tubular reabsorption.

TUBULAR TRANSPORT IN THE LOOP OF HENLE

The loop of Henle includes several distinct segments with different structural and functional properties. As noted earlier, the proximal straight tubule has transport properties similar to those of the proximal convoluted tubule. The thin descending, thin ascending, and thick ascending limbs of the loop of Henle all display different permeability and transport properties.

Descending and Ascending Limbs Differ in Water Permeability

Tubular fluid entering the loop of Henle is isosmotic to plasma, but fluid leaving the loop is distinctly hypoosmotic. Fluid collected from the earliest part of the distal convoluted tubule has an osmolality of about 100 mOsm/kg H_2O, compared with 285 mOsm/kg H_2O in plasma because more solute than water is reabsorbed by the loop of Henle. The loop of Henle reabsorbs about 20% of filtered Na^+, 25% of filtered K^+, 30% of filtered Ca^{2+}, 65% of filtered Mg^{2+}, and 10% of filtered water. The descending limb of the loop of Henle (except for its terminal portion) is highly water-permeable. The ascending limb is water-impermeable. Because solutes are reabsorbed along the ascending limb and water cannot follow, fluid along the ascending limb becomes more and more dilute. Deposition of these solutes (mainly Na^+ salts) in the interstitial space of the kidney medulla is critical in the operation of the urinary concentrating mechanism.

The Luminal Cell Membrane of the Thick Ascending Limb Contains a Na-K-2Cl Cotransporter

Figure 23.19 is a model of a thick ascending limb cell. Na^+ enters the cell across the luminal cell membrane by an electrically neutral Na-K-2Cl cotransporter that is specifically inhibited by the "loop" diuretic drugs bumetanide and furosemide. The downhill movement of Na^+ into the cell results in secondary active transport of one K^+ and two Cl^-. Na^+ is pumped out the basolateral cell membrane by a vigorous Na^+/K^+-ATPase. K^+ recycles back into the lumen via a luminal cell membrane K^+ channel. Cl^- leaves through the basolateral side by a K-Cl cotransporter or Cl^- channel. The luminal cell membrane is predominantly permeable to K^+, and the basolateral cell membrane is pre-
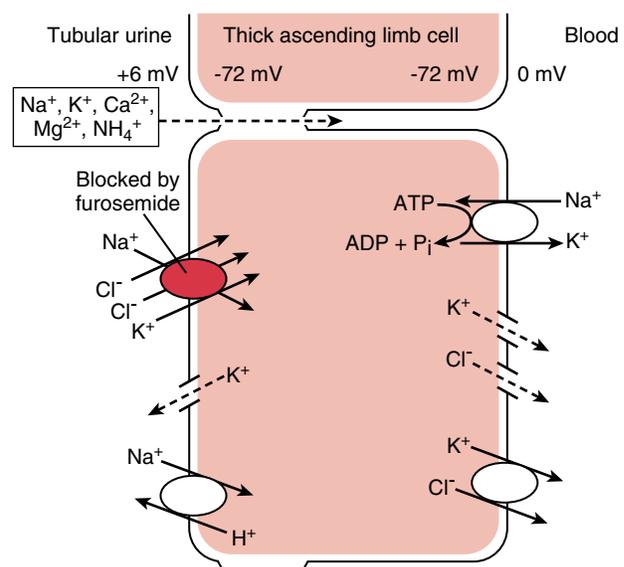

FIGURE 23.19 A cell model for ion transport in the thick ascending limb.

dominantly permeable to Cl⁻. Diffusion of these ions out of the cell produces a transepithelial potential difference, with the lumen about +6 mV compared with interstitial space around the tubules. This potential difference drives small cations (Na^+, K^+, Ca^{2+}, Mg^{2+}, and NH_4^+) out of the lumen, between the cells. The tubular epithelium is extremely impermeable to water; there is no measurable water reabsorption along the ascending limb despite a large transepithelial gradient of osmotic pressure.

TUBULAR TRANSPORT IN THE DISTAL NEPHRON

The so-called **distal nephron** includes several distinct segments: distal convoluted tubule; connecting tubule; and cortical, outer medullary, and inner medullary collecting ducts (see Fig. 23.2). Note that the distal nephron includes the collecting duct system, which, strictly speaking, is not part of the nephron, but from a functional perspective, this is justified. Transport in the distal nephron differs from that in the proximal tubule in several ways:

1) The distal nephron reabsorbs much smaller amounts of salt and water. Typically, the distal nephron reabsorbs 9% of the filtered Na^+ and 19% of the filtered water, compared with 70% for both substances in the proximal convoluted tubule.

2) The distal nephron can establish steep gradients for salt and water. For example, the $[Na^+]$ in the final urine may be as low as 1 mEq/L (versus 140 mEq/L in plasma) and the urine osmolality can be almost one-tenth that of plasma. By contrast, the proximal tubule reabsorbs Na^+ and water along small gradients, and the $[Na^+]$ and osmolality of its tubule fluid are normally close to that of plasma.

3) The distal nephron has a "tight" epithelium, whereas the proximal tubule has a "leaky" epithelium (see Chapter 2). This explains why the distal nephron can establish steep gradients for small ions and water, whereas the proximal tubule cannot.

4) Na^+ and water reabsorption in the proximal tubule are normally closely coupled because epithelial water permeability is always high. By contrast, Na^+ and water reabsorption can be uncoupled in the distal nephron because water permeability may be low and variable.

Proximal reabsorption overall can be characterized as a coarse operation that reabsorbs large quantities of salt and water along small gradients. By contrast, distal reabsorption is a finer process.

The collecting ducts are at the end of the nephron system, and what happens there largely determines the excretion of Na^+, K^+, H^+, and water. Transport in the collecting ducts is finely tuned by hormones. Specifically, aldosterone increases Na^+ reabsorption and K^+ and H^+ secretion, and arginine vasopressin increases water reabsorption at this site.

The Luminal Cell Membrane of the Distal Convoluted Tubule Contains a Na-Cl Cotransporter

Figure 23.20 is a model of a distal convoluted tubule cell. In this nephron segment, Na^+ and Cl^- are transported from
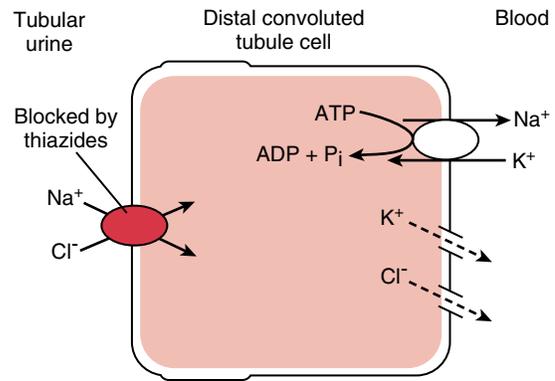

FIGURE 23.20   A cell model for ion transport in the distal convoluted tubule.

the lumen into the cell by a Na-Cl cotransporter that is inhibited by thiazide diuretics. Na^+ is pumped out the basolateral side by the Na^+/K^+-ATPase. Water permeability of the distal convoluted tubule is low and is not changed by arginine vasopressin.

The Cortical Collecting Duct Is an Important Site Regulating K^+ Excretion

Under normal circumstances, most of the excreted K^+ comes from K^+ secreted by the cortical collecting ducts. With great K^+ excess (e.g., a high-K^+ diet), the cortical collecting ducts may secrete so much K^+ that more K^+ is excreted than was filtered. With severe K^+ depletion, the cortical collecting ducts reabsorb K^+.

K^+ secretion appears to be a function primarily of the collecting duct principal cell (Fig. 23.21). K^+ secretion involves active uptake by a Na^+/K^+-ATPase in the basolateral cell membrane, followed by diffusion of K^+ through luminal membrane K^+ channels. Outward diffusion of K^+ from the cell is favored by concentration gradients and opposed by electrical gradients. Note that the electrical gradient opposing exit from the cell is smaller across the luminal cell membrane than across the basolateral cell membrane, favoring movement of K^+ into the lumen rather than back into the blood. The luminal cell membrane potential difference is low (e.g., 20 mV, cell inside negative) because this membrane has a high Na^+ permeability and is depolarized by Na^+ diffusing into the cell. Recall that the entry of Na^+ into a cell causes membrane depolarization (see Chapter 3).

The magnitude of K^+ secretion is affected by several factors (see Fig. 23.21):

1) The activity of the basolateral membrane Na^+/K^+-ATPase is a key factor affecting secretion; the greater the pump activity, the higher the rate of secretion. A high plasma $[K^+]$ promotes K^+ secretion. Increased amounts of Na^+ in the collecting duct lumen (e.g., a result of inhibition of Na^+ reabsorption by a loop diuretic drug) result in increased entry of Na^+ into principal cells, increased activity of the Na^+/K^+-ATPase, and increased K^+ secretion.

2) The lumen-negative transepithelial electrical potential promotes K^+ secretion.
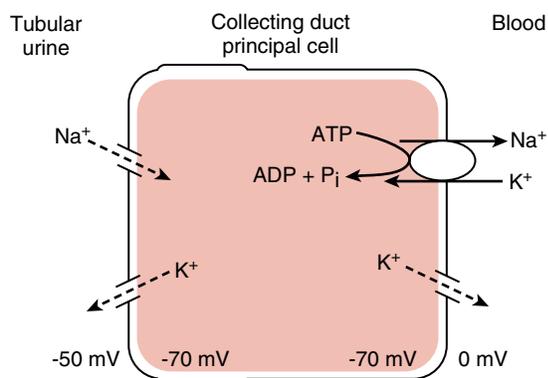
FIGURE 23.21 A model for ion transport by a collecting duct principal cell.

3) An increase in permeability of the luminal cell membrane to K^+ favors secretion.

4) A high fluid flow rate through the collecting duct lumen maintains the cell-to-lumen concentration gradient, which favors K^+ secretion.

The hormone aldosterone promotes K^+ secretion by several actions (see Chapter 24).

Na^+ entry into the collecting duct cell is by diffusion through a Na^+ channel (see Fig. 23.21). This channel has been cloned and sequenced and is known as **ENaC**, for **epithelial sodium (Na) channel**. The entry of Na^+ through this channel is rate-limiting for overall Na^+ reabsorption and is increased by aldosterone.

Intercalated cells are scattered among collecting duct principal cells; they are important in acid-base transport (see Chapter 25). A H^+/K^+-ATPase is present in the luminal cell membrane of α-intercalated cells and contributes to renal K^+ conservation when dietary intake of K^+ is deficient.

URINARY CONCENTRATION AND DILUTION

The human kidney can form urine with a total solute concentration greater or lower than that of plasma. Maximum and minimum urine osmolalities in humans are about 1,200 to 1,400 mOsm/kg H_2O and 30 to 40 mOsm/kg H_2O. We next consider the mechanisms involved in producing osmotically concentrated or dilute urine.

The Ability to Concentrate Urine Osmotically Is an Important Adaptation to Life on Land

When the kidneys form osmotically concentrated urine, they save water for the body. The kidneys have the task of getting rid of excess solutes (e.g., urea, various salts), which requires the excretion of solvent (water). Suppose, for example, we excrete 600 mOsm of solutes per day. If we were only capable of excreting urine that is isosmotic to plasma (approximately 300 mOsm/kg H_2O), we would need to excrete 2.0 L H_2O/day. If we can excrete the solutes in urine that is 4 times more concentrated than plasma (1,200 mOsm/kg H_2O), only 0.5 L H_2O/day would be required. By excreting solutes in osmotically concentrated urine, the kidneys, in effect, saved 2.0 − 0.5 = 1.5 L H_2O for the

body. The ability to concentrate the urine decreases the amount of water we are obliged to find and drink each day.

Arginine Vasopressin Promotes the Excretion of an Osmotically Concentrated Urine

Changes in urine osmolality are normally brought about largely by changes in plasma levels of **arginine vasopressin** (AVP), also known as **antidiuretic hormone** (ADH) (see Chapter 32). In the absence of AVP, the kidney collecting ducts are relatively water-impermeable. Reabsorption of solute across a water-impermeable epithelium leads to osmotically dilute urine. In the presence of AVP, collecting duct water permeability is increased. Because the medullary interstitial fluid is hyperosmotic, water reabsorption in the medullary collecting ducts can lead to the production of an osmotically concentrated urine.

A model for the action of AVP on cells of the collecting duct is shown in Figure 23.22. When plasma osmolality is increased, plasma AVP levels increase. The hormone binds to a specific vasopressin (V_2) receptor in the basolateral cell membrane. By way of a guanine nucleotide stimulatory protein (G_s), the membrane-bound enzyme adenylyl cyclase is activated. This enzyme catalyzes the formation of cyclic AMP (cAMP) from ATP. Cyclic AMP then activates a cAMP-dependent protein kinase (protein kinase A [PKA]) that phosphorylates other proteins. This leads to the insertion, by exocytosis, of intracellular vesicles that contain water channels (aquaporin-2) into the luminal cell membrane. The resulting increase in number of luminal membrane water channels leads to an increase in water permeability. Water can then move out of the duct lumen through the cells, and the urinary solutes become concentrated. This response to AVP occurs in minutes. AVP also has delayed effects on collecting ducts; it increases the transcription of aquaporin-
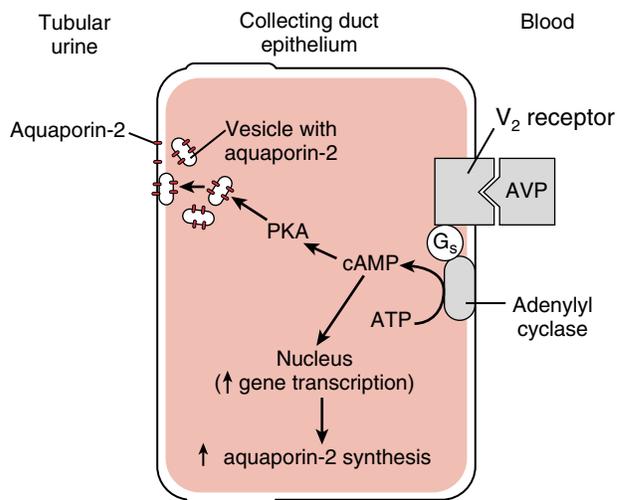

FIGURE 23.22 A model for the action of AVP on the epithelium of the collecting duct. The second messenger for AVP is cyclic AMP (cAMP). AVP has both prompt effects on luminal membrane water permeability (the movement of aquaporin-2-containing vesicles to the luminal cell membrane) and delayed effects (increased aquaporin-2 synthesis).

2 genes and produces an increase in the total number of aquaporin-2 molecules per cell.

The Loops of Henle Are Countercurrent Multipliers, and the Vasa Recta Are Countercurrent Exchangers

It has been known for longer than 50 years that there is a gradient of osmolality in the kidney medulla, with the highest osmolality present at the tips of the renal papillae. This gradient is explained by the **countercurrent hypothesis**. Two countercurrent processes occur in the kidney medulla—countercurrent multiplication and countercurrent exchange. The term *countercurrent* indicates a flow of fluid in opposite directions in adjacent structures (Fig. 23.23). The loops of Henle are **countercurrent multipliers.** Fluid flows toward the tip of the papilla along the descending limb of the loop and toward the cortex along the ascending limb of the loop. The loops of Henle set up the osmotic gradient in the medulla. Establishing a gradient requires work; the energy source is metabolism, which powers the active transport of Na^+ out of the thick ascending limb. The vasa recta are **countercurrent exchangers.** Blood flows in opposite directions along juxtaposed descending (arterial) and ascending (venous) vasa recta, and solutes and water are exchanged passively between these capillary blood vessels. The vasa
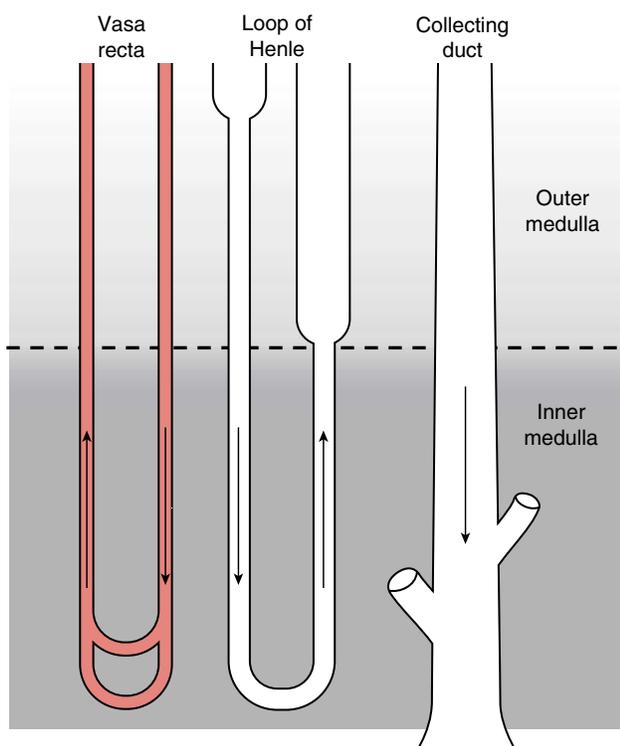
FIGURE 23.23 **Elements of the urinary concentrating mechanism.** The vasa recta are countercurrent exchangers, the loops of Henle are countercurrent multipliers, and the collecting ducts are osmotic equilibrating devices. Note that most loops of Henle and vasa recta do not reach the tip of the papilla, but turn at higher levels in the outer and inner medulla. Also, there are no thick ascending limbs in the inner medulla.

recta help maintain the gradient in the medulla. The collecting ducts act as **osmotic equilibrating devices;** depending on the plasma level of AVP, the collecting duct urine is allowed to equilibrate more or less with the hyperosmotic medullary interstitial fluid.

Countercurrent multiplication is the process in which a small gradient established at any level of the loop of Henle is increased (multiplied) into a much larger gradient along the axis of the loop. The osmotic gradient established at any level is called the **single effect.** The single effect involves movement of solute out of the water-impermeable ascending limb, solute deposition in the medullary interstitial fluid, and withdrawal of water from the descending limb. Because the fluid entering the next, deeper level of the loop is now more concentrated, repetition of the same process leads to an **axial gradient** of osmolality along the loop. The extent to which countercurrent multiplication can establish a large gradient along the axis of the loop depends on several factors, including the magnitude of the single effect, the rate of fluid flow, and the length of the loop of Henle. The larger the single effect, the larger the axial gradient. Impaired solute removal, as from the inhibition of active transport by thick ascending limb cells, leads to a reduced axial gradient. If flow rate through the loop is too high, not enough time is allowed for establishing a significant single effect, and consequently, the axial gradient is reduced. Finally, if the loops are long, there is more opportunity for multiplication and a larger axial gradient can be established.

Countercurrent exchange is a common process in the vascular system. In many vascular beds, arterial and venous vessels lie close to each other, and exchanges of heat or materials can occur between these vessels. For example, because of the countercurrent exchange of heat between blood flowing toward and away from its feet, a penguin can stand on ice and yet maintain a warm body (core) temperature. Countercurrent exchange between descending and ascending vasa recta in the kidney reduces dissipation of the solute gradient in the medulla. The descending vasa recta tend to give up water to the more concentrated interstitial fluid; this water is taken up by the ascending vasa recta, which come from more concentrated regions of the medulla. In effect, much of the water in the blood short-circuits across the tops of the vasa recta and does not flow deep into the medulla, where it would tend to dilute the accumulated solute. The ascending vasa recta tend to give up solute as the blood moves toward the cortex. Solute enters the descending vasa recta and, therefore, tends to be trapped in the medulla. Countercurrent exchange is a purely passive process; it helps maintain a gradient established by some other means.

Operation of the Urinary Concentrating Mechanism Requires an Integrated Functioning of the Loops of Henle, Vasa Recta, and Collecting Ducts

Figure 23.24 summarizes the mechanisms involved in producing osmotically concentrated urine. Maximally concentrated urine, with an osmolality of 1,200 mOsm/kg H_2O and a low urine volume (1% of the original filtered water), is being excreted.
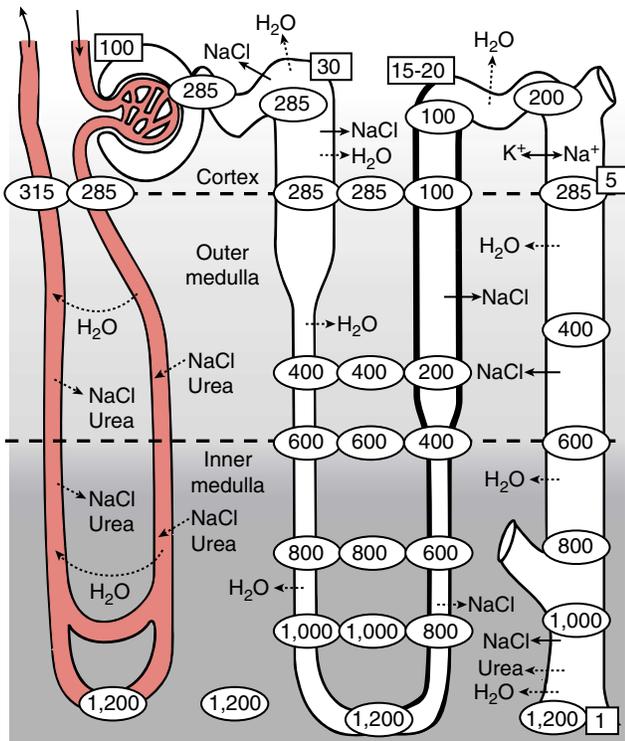
FIGURE 23.24 **Osmotically concentrated urine.** This diagram summarizes movements of ions, urea, and water in the kidney during production of maximally concentrated urine (1,200 mOsm/kg H_2O). Numbers in ovals represent osmolality in mOsm/kg H_2O. Numbers in boxes represent relative amounts of water present at each level of the nephron. Solid arrows indicate active transport; dashed arrows indicate passive transport. The heavy outlining along the ascending limb of the loop of Henle indicates relative water-impermeability.

About 70% of filtered water is reabsorbed along the proximal convoluted tubule, so 30% of the original filtered volume enters the loop of Henle. As discussed earlier, proximal reabsorption of water is essentially an isosmotic process, so fluid entering the loop is isosmotic. As the fluid moves along the descending limb of the loop Henle in the medulla, it becomes increasingly concentrated. This rise in osmolality, in principle, could be due to one of two processes:

1) The movement of water out of the descending limb because of the hyperosmolality of the medullary interstitial fluid.

2) The entry of solute from the medullary interstitial fluid.

The relative importance of these processes may depend on the species of animal. For most efficient operation of the concentrating mechanism, water removal should be predominant, so only this process is depicted in Figure 23.24. The removal of water along the descending limb leads to a rise in [NaCl] in the loop fluid to a value higher than in the interstitial fluid.

When the fluid enters the ascending limb, it enters water-impermeable segments. NaCl is transported out of the ascending limb and deposited in the medullary interstitial fluid. In the thick ascending limb, Na^+ transport is active and is powered by a vigorous Na^+/K^+-ATPase. In the thin ascending limb, NaCl reabsorption appears to be mainly

passive. It occurs because the [NaCl] in the tubular fluid is higher than in the interstitial fluid and because the passive permeability of the thin ascending limb to Na^+ is high. There is also some evidence for a weak active Na^+ pump in the thin ascending limb. The net addition of solute to the medulla by the loops is essential for the osmotic concentration of urine in the collecting ducts.

Fluid entering the distal convoluted tubule is hypoosmotic compared to plasma (see Fig. 23.24) because of the removal of solute along the ascending limb. In the presence of AVP, the cortical collecting ducts become water-permeable and water is passively reabsorbed into the cortical interstitial fluid. The high blood flow to the cortex rapidly carries away this water, so there is no detectable dilution of cortical tissue osmolality. Before the tubular fluid reenters the medulla, it is isosmotic and reduced to about 5% of the original filtered volume. The reabsorption of water in the cortical collecting ducts is important for the overall operation of the urinary concentrating mechanism. If this water were not reabsorbed in the cortex, an excessive amount would enter the medulla. It would tend to wash out the gra-
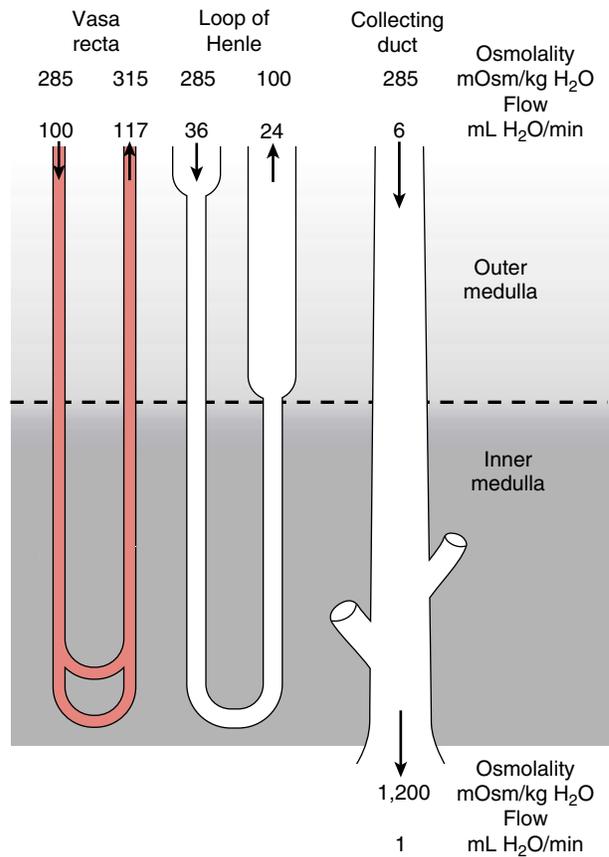

FIGURE 23.25 **Mass balance considerations for the medulla as a whole.** In the steady state, the inputs of water and solutes must equal their respective outputs. Water input into the medulla from the cortex (100 + 36 + 6 = 142 mL/min) equals water output from the medulla (117 + 24 + 1 = 142 mL/min). Solute input (28.5 + 10.3 + 1.7 = 40.5 mOsm/min) is likewise equal to solute output (36.9 + 2.4 + 1.2 = 40.5 mOsm/min).

dient in the medulla, leading to an impaired ability to concentrate the urine maximally.

All nephrons drain into collecting ducts that pass through the medulla. In the presence of AVP, the medullary collecting ducts are permeable to water. Water moves out of the collecting ducts into the more concentrated interstitial fluid. In high levels of AVP, the fluid equilibrates with the interstitial fluid, and the final urine becomes as concentrated as the tissue fluid at the tip of the papilla.

Many different models for the countercurrent mechanism have been proposed; each must take into account the principle of conservation of matter (mass balance). In the steady state, the inputs of water and every nonmetabolized solute must equal their respective outputs. This principle must be obeyed at every level of the medulla. Figure 23.25 presents a simplified scheme that applies the mass balance principle to the medulla as a whole. It provides some additional insight into the countercurrent mechanism. Notice that fluids entering the medulla (from the proximal tubule, descending vasa recta, and cortical collecting ducts) are isosmotic; they all have an osmolality of about 285 mOsm/kg H_2O. Fluid leaving the medulla in the urine is hyperosmotic. It follows from mass balance considerations that somewhere a hypoosmotic fluid has to leave the medulla; this occurs in the ascending limb of the loop of Henle.

The input of water into the medulla must equal its output. Because water is added to the medulla along the descending limbs of the loops of Henle and the collecting ducts, this water must be removed at an equal rate. The ascending limbs of the loops of Henle cannot remove the added water, since they are water-impermeable. The water is removed by the vasa recta; this is why ascending exceeds descending vasa recta blood flow (see Fig. 23.25). The blood leaving the medulla is hyperosmotic because it drains a region of high osmolality and does not instantaneously equilibrate with the medullary interstitial fluid.

Urea Plays a Special Role in the Concentrating Mechanism

It has long been known that animals or humans on low-protein diets have an impaired ability to maximally concentrate the urine. A low-protein diet is associated with a decreased [urea] in the kidney medulla.

Figure 23.26 shows how urea is handled along the nephron. The proximal convoluted tubule is fairly permeable to urea and reabsorbs about 50% of the filtered urea. Fluid collected from the distal convoluted tubule, however, has as much urea as the amount filtered. Therefore, urea is secreted in the loop of Henle.

The thick ascending limb, distal convoluted tubule, connecting tubule, cortical collecting duct, and outer medullary collecting duct are relatively urea-impermeable. As water is reabsorbed along cortical and outer medullary collecting ducts, the [urea] rises. The result is the delivery to the inner medulla of a concentrated urea solution. A concentrated solution has chemical potential energy and can do work.

The inner medullary collecting duct has a facilitated urea transporter, which is activated by AVP and favors urea diffusion into the interstitial fluid of the inner medulla. Urea
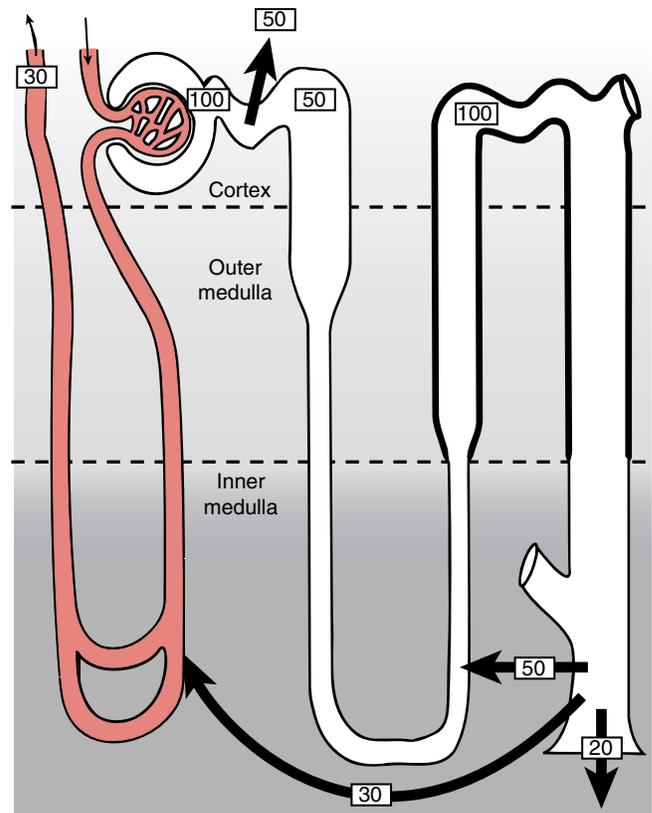

FIGURE 23.26 **Movements of urea along the nephron.** The numbers indicate relative amounts (100 = filtered urea), not concentrations. The heavy outline from the thick ascending limb to the outer medullary collecting duct indicates relatively urea-impermeable segments. Urea is added to the inner medulla by its collecting ducts; most of this urea reenters the loop of Henle, and some is removed by the vasa recta.

may reenter the loop of Henle and be recycled (see Fig. 23.26), building up its concentration in the inner medulla. Urea is also added to the inner medulla by diffusion from the urine surrounding the papillae (calyceal urine). Urea accounts for about half of the osmolality in the inner medulla. The urea in the interstitial fluid of the inner medulla counterbalances urea in the collecting duct urine, allowing the other solutes (e.g., NaCl) in the interstitial fluid to counterbalance osmotically the other solutes (e.g., creatinine, various salts) that need to be concentrated in the urine.

A Dilute Urine Is Excreted When Plasma AVP Levels Are Low

Figure 23.27 depicts kidney osmolalities during excretion of a dilute urine, as occurs when plasma AVP levels are low. Tubular fluid is diluted along the ascending limb and becomes more dilute as solute is reabsorbed across the relatively water-impermeable distal portions of the nephron and collecting ducts. Since as much as 15% of filtered water is not reabsorbed, a high urine flow rate results. In these circumstances, the osmotic gradient in the medulla is reduced but not abolished. The decreased gradient results from several factors, including an increased medullary blood flow,
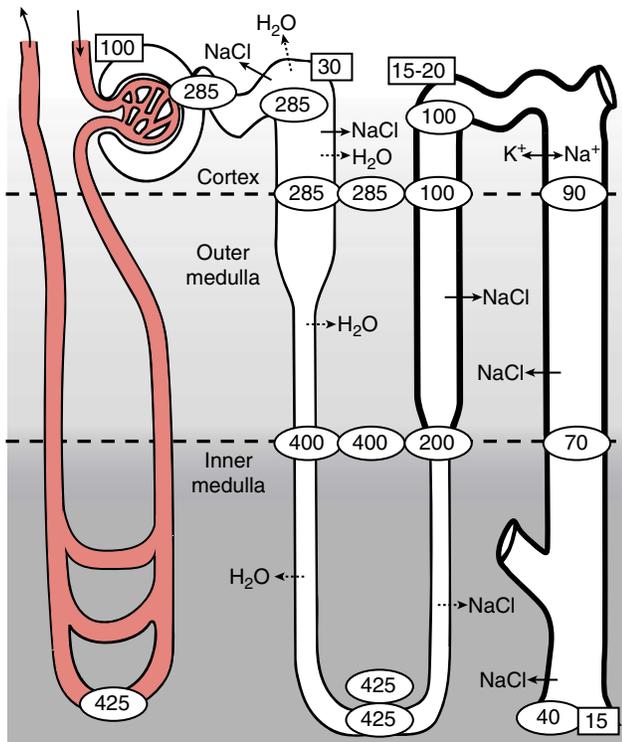
FIGURE 23.27 **Osmotic gradients during excretion of osmotically very dilute urine.** The collecting ducts are relatively water-impermeable (heavy outlining) because AVP is absent. Note that the medulla is still hyperosmotic, but less so than in a kidney producing osmotically concentrated urine.

TABLE 23.3 Inherited Defects in Kidney Tubule Epithelial Cells

Condition	Molecular Defect	Clinical Features
Renal glucosuria	Na^+-dependent glucose cotransporter	Glucosuria, polyuria, polydipsia, polyphagia
Cystinuria	Amino acid transporter	Kidney stone disease
Bartter's syndrome	Na-K-2Cl cotransporter, K channel or Cl channel in thick ascending limb	Salt wasting, hypokalemic metabolic alkalosis
Gitelman's syndrome	Thiazide-sensitive Na-Cl cotransporter in distal convoluted tubule	Salt wasting, hypokalemic metabolic alkalosis, hypocalciuria
Liddle's syndrome (pseudohyperaldosteronism)	Increased open time and number of principal cell epithelial sodium channels	Hypertension, hypokalemic metabolic alkalosis
Pseudohypoaldosteronism type 1	Decreased activity of epithelial sodium channels	Salt wasting, hyperkalemic metabolic
Distal renal tubular acidosis type 1	α-Intercalated cell Cl^-/HCO_3^- exchanger, H^+-ATPase	Metabolic acidosis, osteomalacia
Nephrogenic diabetes insipidus	Vasopressin-2 (V_2) receptor or aquaporin-2	Polyuria, polydipsia

reduced addition of urea, and the addition of too much water to the inner medulla by the collecting ducts.

INHERITED DEFECTS IN KIDNEY TUBULE EPITHELIAL CELLS

Recent studies have elucidated the molecular basis of several inherited kidney disorders. In many cases, the normal and mutated molecules have been cloned and sequenced. It appears that inherited defects in kidney tubule receptors (e.g., the vasopressin-2 receptor), ion channels, or carriers may explain the disturbed physiological processes of these conditions.

Table 23.3 lists some of these inherited disorders. Specific molecular defects have been identified in the proximal tubule (renal glucosuria, cystinuria), thick ascending limb (Bartter's syndrome), distal convoluted tubule (Gitelman's syndrome), and collecting duct (Liddle's syndrome, pseudohypoaldosteronism type 1, distal renal tubular acidosis, nephrogenic diabetes insipidus). Although these disorders are rare, they shed light on the pathophysiology of disease in general. For example, the finding that increased epithelial Na^+ channel activity in Liddle's syndrome leads to hypertension strengthens the view that excessive dietary salt leads to high blood pressure.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items of incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. The dimensions of renal clearance are
   (A) mg/mL
   (B) mg/min
   (C) mL plasma/min
   (D) mL urine/min
   (E) mL urine/mL plasma
2. A luminal cell membrane Na^+ channel is the main pathway for Na^+ reabsorption in
   (A) Proximal tubule cells
   (B) Thick ascending limb cells
   (C) Distal convoluted tubule cells
   (D) Collecting duct principal cells
   (E) Collecting duct intercalated cells
3. A man needs to excrete 570 mOsm of solute per day in his urine and his maximum urine osmolality is 1,140 mOsm/kg H2O. What is the minimum urine volume per day that he needs to excrete in order to stay in solute balance?
   (A) 0.25 L/day
   (B) 0.5 L/day

(C) 2.0 L/day
(D) 4.0 L/day
(E) 180 L/day

4. Which of the following results in an increased osmotic gradient in the medulla of the kidney?
(A) Administration of a diuretic drug that inhibits Na^+ reabsorption by thick ascending limb cells
(B) A low GFR (e.g., 20 mL/min in an adult)
(C) Drinking a liter of water
(D) Long loops of Henle
(E) Low dietary protein intake

5. Dilation of efferent arterioles results in an increase in
(A) Glomerular blood flow
(B) Glomerular capillary pressure
(C) GFR
(D) Filtration fraction
(E) Hydrostatic pressure in the space of Bowman's capsule

6. The main driving force for water reabsorption by the proximal tubule epithelium is
(A) Active reabsorption of amino acids and glucose
(B) Active reabsorption of Na^+
(C) Active reabsorption of water
(D) Pinocytosis
(E) The high colloid osmotic pressure in the peritubular capillaries

7. The following clearance measurements were made in a man after he took a diuretic drug. What percentage of filtered Na^+ did he excrete?
Plasma [inulin]   1 mg/mL
Urine [inulin]   10 mg/mL
Plasma [Na^+]   140 mEq/L
Urine [Na^+]   70 mEq/L
Urine flow rate   10 mL/min
(A) 1%
(B) 5%
(C) 10%
(D) 50%
(E) 99%

8. Renal autoregulation
(A) Is associated with increased renal vascular resistance when arterial blood pressure is lowered from 100 to 80 mm Hg
(B) Mainly involves changes in the caliber of efferent arterioles
(C) Maintains a normal renal blood flow during severe hypotension (blood pressure, 50 mm Hg)
(D) Minimizes the impact of changes in arterial blood pressure on renal Na^+ excretion
(E) Requires intact renal nerves

9. In a kidney producing urine with an osmolality of 1,200 mOsm/kg H_2O, the osmolality of fluid collected from the end of the cortical collecting duct is about
(A) 100 mOsm/kg H_2O
(B) 300 mOsm/kg H_2O
(C) 600 mOsm/kg H_2O
(D) 900 mOsm/kg H_2O
(E) 1,200 mOsm/kg H_2O

10. An older woman with diabetes arrives at the hospital in a severely dehydrated condition, and she is breathing rapidly. Blood plasma [glucose] is 500 mg/dL (normal, ~100 mg/dL) and the urine [glucose] is zero (dipstick test). What is the most likely explanation for the absence of glucose in the urine?
(A) The amount of splay in the glucose reabsorption curve is abnormally increased
(B) GFR is abnormally low
(C) The glucose Tm is abnormally high
(D) The glucose Tm is abnormally low
(E) The renal plasma glucose threshold is abnormally low

11. In a suicide attempt, a nurse took an overdose of the sedative phenobarbital. This substance is a weak, lipid-soluble organic acid that is reabsorbed by nonionic diffusion in the kidneys. Which of the following would promote urinary excretion of this substance?
(A) Abstain from all fluids
(B) Acidify the urine by ingesting NH_4Cl tablets
(C) Administer a drug that inhibits tubular secretion of organic anions
(D) Alkalinize the urine by infusing a $NaHCO_3$ solution intravenously

12. Which of the following provides the most accurate measure of GFR?
(A) Blood urea nitrogen (BUN)
(B) Endogenous creatinine clearance
(C) Inulin clearance
(D) PAH clearance
(E) Plasma (creatinine)

13. Hypertension was observed in a young boy since birth. Which of the following disorders may be present?
(A) Bartter's syndrome
(B) Gitelman's syndrome
(C) Liddle's syndrome
(D) Nephrogenic diabetes insipidus
(E) Renal glucosuria

14. In a person with severe central diabetes insipidus (deficient production or release of AVP), urine osmolality and flow rate is typically about
(A) 50 mOsm/kg H_2O, 18 L/day
(B) 50 mOsm/kg H_2O, 1.5 L/day
(C) 300 mOsm/kg H_2O, 1.5 L/day
(D) 300 mOsm/kg H_2O, 18 L/day
(E) 1,200 mOsm/kg H_2O, 0.5 L/day

15. Which of the following substances has the highest renal clearance?
(A) Creatinine
(B) Inulin
(C) PAH
(D) Na^+
(E) Urea

16. If the plasma concentration of a freely filterable substance is 2 mg/mL, GFR is 100 mL/min, urine concentration of the substance is 10 mg/mL, and urine flow rate is 5 mL/min, we can conclude that the kidney tubules
(A) reabsorbed 150 mg/min
(B) reabsorbed 200 mg/min
(C) secreted 50 mg/min
(D) secreted 150 mg/min
(E) secreted 200 mg/min

17. A clearance study was done on a young woman with suspected renal disease:
Arterial [PAH]   0.02 mg/mL
Renal vein [PAH]   0.01 mg/mL
Urine [PAH]   0.60 mg/mL
Urine flow rate   5.0 mL/min
Hematocrit, % cells 40
What is her true renal blood flow?
(A) 150 mL/min
(B) 300 mL/min
(C) 500 mL/min
(D) 750 mL/min
(E) 1,200 mL/min

18. A man has progressive, chronic kidney disease. Which of the following indicates the greatest absolute decrease in GFR?
(A) A fall in plasma creatinine from 4 mg/dL to 2 mg/dL
(B) A fall in plasma creatinine from 2 mg/dL to 1 mg/dL
(C) A rise in plasma creatinine from 1 mg/dL to 2 mg/dL
(D) A rise in plasma creatinine from 2 mg/dL to 4 mg/dL
(E) A rise in plasma creatinine from 4 mg/dL to 8 mg/dL

19. Renin in synthesized by
(A) Granular cells
(B) Intercalated cells
(C) Interstitial cells
(D) Macula densa cells
(E) Mesangial cells

20. The following determinations were made on a single glomerulus of a rat kidney: GFR, 42 nL/min; glomerular capillary hydrostatic pressure, 50 mm Hg; hydrostatic pressure in Bowman's space, 12 mm Hg; average glomerular capillary colloid osmotic pressure, 24 mm Hg. What is the glomerular ultrafiltration coefficient?
(A) 0.33 mm Hg per nL/min
(B) 0.49 nL/min per mm Hg
(C) 0.68 nL/min per mm Hg
(D) 1.48 mm Hg per nL/min
(E) 3.0 nL/min per mm Hg

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