The Kidneys and Regulation of Water and Inorganic Ions

SECTION A
BASIC PRINCIPLES OF RENAL PHYSIOLOGY
Renal Functions
Structure of the Kidneys and Urinary System
Basic Renal Processes
Glomerular Filtration
Tubular Reabsorption
Tubular Secretion
Metabolism by the Tubules
Regulation of Membrane Channels and Transporters
“Division of Labor” in the Tubules
The Concept of Renal Clearance
Micturition

SECTION B
REGULATION OF SODIUM, WATER, AND POTASSIUM BALANCE
Total-Body Balance of Sodium and Water
Basic Renal Processes for Sodium and Water
Primary Active Sodium Reabsorption
Coupling of Water Reabsorption to Sodium Reabsorption
Urine Concentration: The Countercurrent Multiplier System
Renal Sodium Regulation
Control of GFR
Control of Sodium Reabsorption
Renal Water Regulation
Baroreceptor Control of Vasopressin Secretion
Osmoreceptor Control of Vasopressin Secretion
A Summary Example: The Response to Sweating
Thirst and Salt Appetite
Potassium Regulation
Renal Regulation of Potassium

SECTION C
CALCIUM REGULATION
Effector Sites for Calcium Homeostasis
Bone
Kidneys
Gastrointestinal Tract
Hormonal Controls
Parathyroid Hormone
1,25-Dihydroxyvitamin D₃
Calcitonin
Metabolic Bone Diseases

SECTION D
HYDROGEN-ION REGULATION
Sources of Hydrogen-ion Gain or Loss
Buffering of Hydrogen Ions in the Body
Integration of Homeostatic Controls
Renal Mechanisms
Bicarbonate Handling
Addition of New Bicarbonate to the Plasma
Renal Responses to Acidosis and Alkalosis
Classification of Acidosis and Alkalosis

SECTION E
DIURETICS AND KIDNEY DISEASE
Diuretics
Kidney Disease
Hemodialysis, Peritoneal Dialysis, and Transplantation

CHAPTER 16 CLINICAL TERMS
CHAPTER 16 THOUGHT QUESTIONS
This chapter deals with how the water and inorganic-ion composition of the internal environment is homeostatically regulated. The kidneys play the central role in these processes.

Regulation of the total-body balance of any substance can be studied in terms of the balance concept described in Chapter 7. Theoretically, a substance can appear in the body either as a result of ingestion or as a product of metabolism. On the loss side of the balance, a substance can be excreted from the body or can be metabolized. Therefore, if the quantity of any substance in the body is to be maintained at a nearly constant level over a period of time, the total amounts ingested and produced must equal the total amounts excreted and metabolized.

Reflexes that alter excretion, specifically excretion via the urine, constitute the major mechanisms that regulate the body balances of water and many of the inorganic ions that determine the properties of the extracellular fluid. The extracellular concentrations of these ions were given in Table 6–1. We will first describe how the kidneys work in general and then apply this information to how they process specific substances—sodium, water, potassium, and so on—and participate in reflexes that regulate these substances.

SECTION A

BASIC PRINCIPLES OF RENAL PHYSIOLOGY

Renal Functions

The adjective renal means “pertaining to the kidneys”; thus, for example, we refer to “renal physiology” and “renal functions.”

The kidneys process the plasma portion of blood by removing substances from it and, in a few cases, by adding substances to it. In so doing, they perform a variety of functions, as summarized in Table 16–1.

First, and very importantly, the kidneys play the central role in regulating the water concentration, inorganic-ion composition, and volume of the internal environment. They do so by excreting just enough water and inorganic ions to keep the amounts of these substances in the body relatively constant. For example, if you start eating a lot of salt (sodium chloride), the kidneys will increase the amount of the salt they excrete to match the intake. Alternatively, if there is not enough salt in the body, the kidneys will excrete very little salt or virtually none at all.

Second, the kidneys excrete metabolic waste products into the urine as fast as they are produced. This keeps waste products, which can be toxic, from accumulating in the body. These metabolic wastes include urea from the catabolism of protein, uric acid from nucleic acids, creatinine from muscle creatine, the end products of hemoglobin breakdown (which give urine much of its color), and many others.

A third function of the kidneys is the excretion, in the urine, of some foreign chemicals, such as drugs, pesticides, and food additives, and their metabolites.

A fourth function is gluconeogenesis. During prolonged fasting, the kidneys synthesize glucose from amino acids and other precursors and release it into the blood. The kidneys can supply approximately 20 percent as much glucose as the liver does at such times (Chapter 18).

Finally, the kidneys act as endocrine glands, secreting at least three hormones: erythropoietin (described in Chapter 14), renin, and 1,25-dihydroxyvitamin D3. These last two hormones are described in this chapter. (Note that renin is part of a hormonal system called the renin-angiotensin system; although renin functions as an enzyme in this system, it is customary to refer to it as a “hormone.”)
Structure of the Kidneys and Urinary System

The two kidneys lie in the back of the abdominal wall but not actually in the abdominal cavity. They are retroperitoneal, meaning they are just behind the peritoneum, the lining of this cavity. The urine flows from the kidneys through the ureters into the bladder, from which it is eliminated via the urethra (Figure 16–1).

TABLE 16–1 Functions of the Kidneys

| 1. Regulation of water and inorganic-ion balance |
| 2. Removal of metabolic waste products from the blood and their excretion in the urine |
| 3. Removal of foreign chemicals from the blood and their excretion in the urine |
| 4. Gluconeogenesis |
| 5. Secretion of hormones: |
| a. Erythropoietin, which controls erythrocyte production (Chapter 14) |
| b. Renin, which controls formation of angiotensin, which influences blood pressure and sodium balance (this chapter) |
| c. 1,25-dihydroxyvitamin D3, which influences calcium balance (this chapter) |

Each kidney contains approximately 1 million similar subunits called nephrons. Each nephron (Figure 16–2) consists of (1) an initial filtering component called the renal corpuscle, and (2) a tubule that extends out from the renal corpuscle. The renal corpuscle forms a filtrate from blood that is free of cells and proteins. This filtrate then leaves the renal corpuscle and enters the tubule. As it flows through the tubule, substances are added to it or removed from it. Ultimately the fluid from all the nephrons exits the kidneys as urine.

Let us look first at the anatomy of the renal corpuscles—the filters. Each renal corpuscle contains a compact tuft of interconnected capillary loops called the glomerulus (plural, glomeruli), or glomerular capillaries (Figures 16–2 and 16–3). Each glomerulus is supplied with blood by an arteriole called an afferent arteriole. The glomerulus protrudes into a fluid-filled capsule called Bowman’s capsule. The combination of a glomerulus and a Bowman’s capsule constitutes a renal corpuscle. As blood flows through the glomerulus, a portion of the plasma filters into Bowman’s capsule. The remaining blood then leaves the glomerulus by another arteriole, the efferent arteriole.

One way of visualizing the relationships within the renal corpuscle is to imagine a loosely clenched fist—the glomerulus—punched into a balloon—the Bowman’s capsule. The part of Bowman’s capsule in contact with the glomerulus becomes pushed inward but does not make contact with the opposite side of the capsule. Accordingly, a fluid-filled space—Bowman’s space—exists within the capsule, and it is into this space that protein-free fluid filters from the glomerulus.

Blood in the glomerulus is separated from the fluid in Bowman’s space by a filtration barrier consisting of three layers (Figure 16–3b): (1) the single-celled capillary endothelium, (2) a noncellular proteinaceous layer of basement membrane (also termed basal lamina) between the endothelium and the next layer, which is (3) the single-celled epithelial lining of Bowman’s capsule. The epithelial cells in this region are quite different from the simple flattened cells that line the rest of Bowman’s capsule (the part of the “balloon” not in contact with the “fist”) and are called podocytes. They have an octopus-like structure in that they possess a large number of extensions, or foot processes. Fluid filters first across the endothelial cells, then through the basement membrane, and finally between the foot processes of the podocytes.

In addition to the capillary endothelial cells and the podocytes, there is a third cell type, mesangial cells, which are modified smooth-muscle cells that surround the glomerular capillary loops but are not part of the filtration pathway. Their function will be described later.
The renal tubule is continuous with a Bowman’s capsule. It is a very narrow hollow cylinder made up of a single layer of epithelial cells (resting on a basement membrane). The epithelial cells differ in structure and function along the tubule’s length, and 10 to 12 distinct segments are presently recognized (see Figure 16–2). It is customary, however, to group two or more contiguous tubular segments when discussing function, and we shall follow this practice. Accordingly, the segment of the tubule that drains Bowman’s capsule is the proximal tubule (comprising the proximal convoluted tubule and the proximal straight tubule of Figure 16–2). The next portion of the tubule is the loop of Henle, which is a sharp hairpin-like loop
consisting of a descending limb coming from the proximal tubule and an ascending limb leading to the next tubular segment, the distal convoluted tubule. Fluid flows from the distal convoluted tubule into the collecting duct system, the first portion of which is the connecting tubule, followed by the cortical collecting duct and then the medullary collecting duct (the reasons for the terms “cortical” and “medullary” will be apparent shortly). The connecting tubule is so similar in function to the cortical collecting duct that, in subsequent discussions, we will not describe its function separately.

From Bowman’s capsule to the collecting-duct system, each nephron is completely separate from the others. This separation ends when multiple cortical collecting ducts merge. The result of additional mergings from this point on is that the completed urine drains into the kidney’s central cavity, the renal pelvis, via only several hundred large medullary collecting ducts. The renal pelvis is continuous with the ureter draining that kidney (Figure 16–4).

There are important regional differences in the kidney (Figures 16–2 and 16–4). The outer portion is the renal cortex, and the inner portion the renal medulla. The cortex contains all the renal corpuscles. The loops of Henle extend from the cortex for varying distances down into the medulla. The medullary collecting ducts pass through the medulla on their way to the renal pelvis.

All along its length, each tubule is surrounded by capillaries, called the peritubular capillaries. Note that we have now mentioned two sets of capillaries in the

**FIGURE 16–3**
(a) Anatomy of the renal corpuscle. Brown lines in the capillary loops indicate space between adjoining podocytes. (b) Cross section of the three corpuscular membranes—capillary endothelium, basement membrane, and epithelium (podocytes) of Bowman’s capsule. For simplicity, glomerular mesangial cells are not shown in this figure.
kidneys—the glomerular capillaries (glomeruli) and the peritubular capillaries. Within each nephron, the two sets of capillaries are connected to each other by an efferent arteriole, the vessel by which blood leaves the glomerulus (see Figures 16–2 and 16–3). Thus the renal circulation is very unusual in that it includes two sets of arterioles and two sets of capillaries. After supplying the tubules with blood, the peritubular capillaries then join together to form the veins by which blood leaves the kidney.

One additional anatomical detail involving both the tubule and the arterioles must be mentioned. Near its end, the ascending limb of each loop of Henle passes between the afferent and efferent arterioles of that loop’s own nephron (see Figure 16–2). At this point there is a patch of cells in the wall of the ascending limb called the macula densa, and the wall of the afferent arteriole contains secretory cells known as juxtaglomerular (JG) cells. The combination of macula densa and juxtaglomerular cells is known as the juxtaglomerular apparatus (JGA) (Figure 16–5). The juxtaglomerular cells secrete the hormone renin.

Basic Renal Processes

As we have said, urine formation begins with the filtration of plasma from the glomerular capillaries into Bowman’s space. This process is termed glomerular filtration, and the filtrate is called the glomerular filtrate. It is cell-free and except for proteins, contains all the substances in plasma in virtually the same concentrations as in plasma; this type of filtrate is also termed an ultrafiltrate.

During its passage through the tubules, the filtrate’s composition is altered by movements of substances from the tubules to the peritubular capillaries and vice versa (Figure 16–6). When the direction of movement is from tubular lumen to peritubular capillary plasma, the process is called tubular reabsorption, or simply reabsorption. (A more accurate term for this process is absorption, but reabsorption persists, for historical reasons, as the term more commonly used by renal physiologists.) Movement in the opposite direction—that is, from peritubular plasma to tubular lumen—is called tubular secretion, or simply secretion. Tubular secretion is also used to denote the movement of a solute from the cell interior to the lumen in the cases in which the kidney tubular cells themselves generate the substance.

To summarize: A substance can gain entry to the tubule and be excreted in the urine by glomerular filtration or tubular secretion. Once in the tubule, however, the substance need not be excreted but can be reabsorbed. Thus, the amount of any substance excreted in the urine is equal to the amount filtered plus the amount secreted minus the amount reabsorbed.

\[
\text{Amount excreted} = \text{Amount filtered} + \text{Amount secreted} - \text{Amount reabsorbed}
\]
It should be stressed that not all these processes—filtration, secretion, reabsorption—apply to all substances.

To emphasize general principles, the renal handling of three hypothetical substances is illustrated in Figure 16–7. Approximately 20 percent of the plasma that enters the glomerular capillaries is filtered into Bowman’s space. This filtrate, which contains X, Y, and Z in the same concentrations as in the capillary plasma, enters the proximal tubule and begins its flow through the rest of the tubule. Simultaneously, the remaining 80 percent of the plasma, with its X, Y, and Z, leaves the glomerular capillaries via the efferent arteriole and enters the peritubular capillaries.

Assume that the tubule can secrete 100 percent of the peritubular-capillary X into the tubular lumen but cannot reabsorb X. Thus, by the combination of filtration and tubular secretion, all the plasma that originally entered the renal artery loses all of its substance X, which leaves the body via the urine.

Assume that the tubule can reabsorb, but not secrete, Y and Z. The amount of Y reabsorption is small, so that much of the filtered material is not reabsorbed and escapes from the body. But for Z the reabsorptive mechanism is so powerful that all the filtered Z is transported back into the plasma. Therefore, no Z is lost from the body. Hence, for Z the processes of filtration and reabsorption have canceled each other out, and the net result is as though Z had never entered the kidney.

For each substance in plasma, a particular combination of filtration, tubular reabsorption, and tubular secretion applies. The critical point is that, for many substances, the rates at which the processes proceed are subject to physiological control. By triggering changes in the rate of filtration, reabsorption, or secretion whenever the body content of a substance goes above or below normal, homeostatic mechanisms can regulate the substance’s bodily balance. For example, consider what happens when a normally hydrated person drinks a lot of water: Within 1–2 h all the excess water has been excreted in the urine, partly as a result of an increase in filtration but mainly as a result of decreased tubular reabsorption of water. In this example, the kidneys are effector organs of a reflex that maintains body water concentration within very narrow limits.
Although renal physiologists traditionally list glomerular filtration, tubular reabsorption, and tubular secretion as the three basic renal processes, a fourth process—metabolism by the tubular cells—is of considerable importance for some substances. In some cases, the renal tubular cells remove substances from blood or glomerular filtrate and metabolize them, resulting in their disappearance from the body. In other cases, the cells produce substances and add them to the blood or tubular fluid; the most important of these, as we shall see, are ammonium, hydrogen ion, and bicarbonate.

In summary, one can study the normal renal processing of any given substance by asking a series of questions:

1. To what degree is the substance filterable at the renal corpuscle?
2. Is it reabsorbed?
3. Is it secreted?
4. What factors homeostatically regulate the quantities filtered, reabsorbed, or secreted: that is, what are the pathways by which renal excretion of the substance is altered to maintain stable body balance?

**Glomerular Filtration**

As stated above, the glomerular filtrate—that is, the fluid in Bowman’s space—normally has no cells but contains all plasma substances except proteins in virtually the same concentrations as in plasma. This is because glomerular filtration is a bulk-flow process in which water and all low-molecular-weight substances move together. The overwhelming majority of plasma proteins—the albumins and globulins—are excluded almost entirely from the filtrate. One reason for their exclusion is that the renal corpuscles restrict the movement of such high-molecular-weight substances. A second reason is that the filtration pathways in the capillary membranes are negatively charged and so oppose the movement of these plasma proteins, most of which are themselves negatively charged. It should be noted, however, that low-molecular-weight plasma proteins do filter in varying degrees, but we shall ignore this fact.

The only exceptions to the generalization that all nonprotein plasma substances have the same concentrations in the glomerular filtrate as in the plasma are certain low-molecular-weight substances that would otherwise be filterable but are bound to plasma proteins and therefore are not filtered. For example, half the plasma calcium and virtually all of the plasma fatty acids are bound to plasma protein and so are not filtered.

**Forces Involved in Filtration**

As described in Chapter 14, filtration across capillaries is determined by opposing forces: The hydrostatic pressure difference across the capillary wall favors filtration, while the protein concentration difference across the wall creates an osmotic force that opposes filtration.

This also applies to the glomerular capillaries, as summarized in Figure 16–8. The pressure of the blood in the glomerular capillaries—the glomerular capillary hydrostatic pressure ($P_{GC}$)—is a force favoring filtration. The fluid in Bowman’s space exerts a hydrostatic pressure ($P_{BS}$) that opposes this filtration. Another opposing force is the osmotic force ($\pi_{GC}$) that results from the presence of protein in the glomerular capillary plasma. Recall that there is virtually no protein in the filtrate in Bowman’s space. The unequal distribution of protein causes the water concentration of the plasma to be slightly less than that of the fluid in Bowman’s space, and this difference in water concentration favors fluid movement by bulk-flow from Bowman’s space into the glomerular capillaries—that is, opposes glomerular filtration.

Note that in Figure 16–8 the value given for this osmotic force—29 mmHg—is larger than the value—24 mmHg—for the osmotic force given in Chapter 14 for plasma in all arteries and nonrenal capillaries. The reason is that, unlike the situation elsewhere in the body, so much water (about 20 percent of the plasma supplying the kidneys) filters out of the glomerular capillaries that the protein left behind in the plasma becomes significantly more concentrated than in arterial plasma. In other capillaries, in contrast, so little water filters that the capillary protein concentration remains essentially unchanged from its value in arterial plasma. In other words, unlike the situation in other capillaries, the plasma protein concentration and, hence, the osmotic force, increases from the beginning to the end of the glomerular capillaries. The value given in Figure 16–8 for the osmotic force is the average value along the length of the capillaries.

To summarize, the net glomerular filtration pressure is the sum of three relevant forces:

$$\text{Net glomerular filtration pressure} = P_{GC} - P_{BS} - \pi_{GC}$$

Normally the net filtration pressure is always positive because the glomerular capillary hydrostatic pressure is larger than the sum of the hydrostatic pressure in Bowman’s space and the osmotic force opposing filtration. The net glomerular filtration pressure initiates urine formation by forcing an essentially protein-free filtrate of plasma out of the glomeruli and into Bowman’s space and thence down the tubule into the renal pelvis.
It must be emphasized that the GFR is not a fixed value but is subject to physiological regulation. As we shall see, this is achieved mainly by neural and hormonal input to the afferent and efferent arterioles, which results in changes in net glomerular filtration pressure.

In this regard it must be emphasized that the glomerular capillaries are unique in that they are situated between two sets of arterioles—the afferent and efferent arterioles. Constriction of the afferent arterioles alone has the same effect on the hydrostatic pressure in the glomerular capillaries \( P_{GC} \) as does constriction of arterioles anywhere in the body on the pressure in the capillaries supplied by those arterioles: Capillary pressure decreases because the increased arteriolar resistance causes a greater loss of pressure between the arteries and the capillaries. In contrast, efferent arteriolar constriction alone has precisely the opposite effect on \( P_{GC} \)—it increases it. This occurs because the efferent arteriole lies beyond the glomerulus, so that efferent-arteriolar constriction tends to "dam back" the blood in the glomerular capillaries, raising \( P_{GC} \). Finally, simultaneous constriction of both sets of arterioles tends to leave \( P_{GC} \) unchanged because of the opposing effects. The effects of arteriolar dilation are the reverse of those described for constriction.

In addition to the neuroendocrine input to the arterioles, there is also input to the mesangial cells that surround the glomerular capillaries. Contraction of these cells reduces the surface area of the capillaries, which causes a decrease in GFR at any given net filtration pressure.

It is possible to measure the total amount of any nonprotein substance (assuming also that the substance is not bound to protein) filtered into Bowman’s space by multiplying the GFR by the plasma concentration of the substance. This amount is called the filtered load of the substance. For example, if the GFR is 180 L/day and plasma glucose concentration is 1 g/L, then the filtered load of glucose is 180 L/day \times 1 g/L = 180 g/day.

Once we know the filtered load of the substance, we can compare it to the amount of the substance excreted and tell whether the substance undergoes net tubular reabsorption or net secretion. Whenever the quantity of a substance excreted in the urine is less than the filtered load, tubular reabsorption must have occurred. Conversely, if the amount excreted in the urine is greater than the filtered load, tubular secretion must have occurred.

**Tubular Reabsorption**

Table 16–2, which summarizes data for a few plasma components that undergo filtration and reabsorption, gives an idea of the magnitude and importance of
TABLE 16–2 Average Values for Several Components That Undergo Filtration and Reabsorption

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount Filtered per Day</th>
<th>Amount Excreted per Day</th>
<th>Percent Reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water, L</td>
<td>180</td>
<td>1.8</td>
<td>99</td>
</tr>
<tr>
<td>Sodium, g</td>
<td>630</td>
<td>3.2</td>
<td>99.5</td>
</tr>
<tr>
<td>Glucose, g</td>
<td>180</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Urea, g</td>
<td>54</td>
<td>3.0</td>
<td>44</td>
</tr>
</tbody>
</table>

reabsorptive mechanisms. The values in this table are typical for a normal person on an average diet. There are at least three important conclusions to be drawn from this table: (1) The filtered loads are enormous, generally larger than the amounts of the substances in the body. For example, the body contains about 40 L of water, but the volume of water filtered each day is, as we have seen, 180 L. (2) Reabsorption of waste products is relatively incomplete (for example, only 44 percent in the case of urea) so that large fractions of their filtered loads are excreted in the urine. (3) Reabsorption of most useful plasma components (for example, water, inorganic ions, and organic nutrients) is relatively complete so that the amounts excreted in the urine represent very small fractions of their filtered loads.

In this last regard, an important distinction should be made between reabsorptive processes that can be controlled physiologically and those that cannot. The reabsorption rates of most organic nutrients (for example, glucose) are always very high and are not physiologically regulated, and so the filtered loads of these substances are normally completely reabsorbed, none appearing in the urine. For these substances, like substance Z in our earlier example, it is as though the kidneys do not exist since the kidneys do not eliminate these substances from the body at all. Therefore, the kidneys do not regulate the plasma concentrations of these organic nutrients—that is, they do not minimize changes from normal plasma levels. Rather, the kidneys merely maintain whatever plasma concentrations already exist. (As described in Chapter 18, these concentrations are generally the result of hormonal regulation of nutrient metabolism.)

In contrast, the reabsorptive rates for water and many ions, although also very high, are regulatable. Recall, for example, the situation given earlier in which a person drinks a lot of water, which decreases tubular water reabsorption and thereby leads to increased water excretion. The critical point is that the rates at which water and many inorganic ions are reabsorbed, and therefore the rates at which they are excreted, are subject to physiological control.

In contrast to glomerular filtration, the crucial steps in tubular reabsorption—those that achieve movement of a substance from tubular lumen to interstitial fluid—do not occur by bulk flow (there are inadequate pressure differences across the tubule and permeability of the tubular membranes). Instead, two other processes are involved. (1) The reabsorption of some substances is by diffusion, often across the tight junctions connecting the tubular epithelial cells (Figure 16–9). (2) The reabsorption of all other substances involves mediated transport, which requires the participation of transport proteins in the cell’s plasma membranes.

Regardless of how a substance being reabsorbed goes from the lumen to the interstitial fluid, the final step in reabsorption—movement from interstitial fluid into the peritubular capillaries—is by a combination of diffusion and bulk flow, the latter driven by the capillary Starling forces. We will not mention this final step again in our discussions of reabsorption, but simply assume it occurs automatically once the substance reaches the interstitial fluid.

![FIGURE 16–9](image)

Diagrammatic representation of tubular epithelium. In this and subsequent figures illustrating transport in this chapter, the basement membrane of the tubule—a homogeneous proteinaceous structure that plays no significant role in transport—will not be shown. (Do not confuse the basement membrane with the basolateral membrane of the tubular cells, as illustrated in this and subsequent figures.)
Reabsorption by Diffusion  
Urea reabsorption by the proximal tubule provides an example of passive reabsorption by diffusion. An analysis of urea concentrations in the proximal tubule will help elucidate the mechanism. Because the corpuscular membranes are freely filterable to urea, the urea concentration in the fluid within Bowman’s space is the same as that in the peritubular-capillary plasma and the interstitial fluid surrounding the tubule. Then, as the filtered fluid flows through the proximal tubule, water reabsorption occurs (by mechanisms to be described later). This removal of water increases the concentration of urea in the tubular fluid above that in the interstitial fluid and peritubular capillaries. Therefore, urea diffuses down this concentration gradient from tubular lumen to peritubular capillary. Urea reabsorption is thus dependent upon the reabsorption of water.

Reabsorption by diffusion in precisely this manner occurs for a variety of lipid-soluble organic substances, both naturally occurring and foreign (the pesticide DDT, for example).

Reabsorption by Mediated Transport  
Figure 16–9 highlights the fact that a substance reabsorbed by mediated transport must first cross the luminal membrane separating the tubular lumen from the cell interior, then diffuse through the cytosol of the cell, and finally cross the basolateral membrane, which begins at the tight junctions and constitutes the plasma membrane of the sides and base of the cell. This route is termed transcellular epithelial transport; its mechanisms were described in Chapter 6 and this material, particularly Figures 6–23 and 6–24, should be reviewed at this time.

Note in those two figures that a substance need not be actively transported across both the luminal and basolateral membranes in order to be actively transported across the overall epithelium—that is, to move from lumen to interstitial fluid against its electrochemical gradient. Thus, for example, sodium moves “downhill” (passively) into the cell across the luminal membrane either by diffusion (see Figure 6–23) or by facilitated diffusion (see Figure 6–24) and then moves “uphill” (actively) out of the cell across the basolateral membrane via the Na,K-ATPase pumps in this membrane. If the movement across either the luminal membrane or the basolateral membrane is active, then the entire process will achieve active reabsorption across the overall epithelium.

Figure 6–24 illustrates another important principle that applies to tubular reabsorption: The reabsorption of many substances is coupled to the reabsorption of sodium. Note in this figure that substance X moves uphill into the epithelial cell via a secondary active cotransporter as sodium moves downhill into the cell via this same cotransporter. The high intracellular concentration of substance X created by this active transport then drives “downhill” movement of the substance across the basolateral membrane to complete the reabsorptive process. This is precisely how glucose, many amino acids, and other organic substances undergo tubular reabsorption. The reabsorption of several inorganic ions is also coupled in a variety of ways to the reabsorption of sodium.

Many of the mediated-transport reabsorptive systems in the renal tubule have a limit, termed a transport maximum ($T_m$), to the amounts of material they can transport per unit time. This is because the binding sites on the membrane transport proteins become saturated. An important example is the secondary active-transport proteins for glucose, located in the proximal tubule and described in the previous paragraph. As noted earlier, normal persons do not excrete glucose in their urine because all filtered glucose is reabsorbed. Indeed, even by eating an extremely carbohydrate-rich meal, normal persons cannot raise their plasma glucose concentrations high enough so that the filtered load of glucose exceeds the renal glucose $T_m$. In contrast, in people with diabetes mellitus, a disease in which the hormonal control of the plasma glucose concentration is defective (Chapter 18), the plasma glucose concentration can become so high that the filtered load of glucose exceeds the ability of the tubules to reabsorb glucose—that is, exceeds the glucose $T_m$—therefore, glucose appears in the urine (glucosuria). In other words, the kidneys’ ability to reabsorb glucose is normal in diabetes, but the tubules cannot reabsorb the markedly increased filtered load.

The pattern described for glucose is also true for a large number of other organic nutrients. For example, most amino acids and water-soluble vitamins are filtered in large amounts each day, but almost all these filtered molecules are reabsorbed by the proximal tubule. If the plasma concentration becomes high enough, however, reabsorption of the filtered load will not be as complete, and the substance will appear in larger amounts in the urine. Thus, persons ingesting very large quantities of vitamin C manifest progressive increases in their plasma concentrations of vitamin C until the filtered load exceeds the tubular reabsptive $T_m$ for this substance, and any additional ingested vitamin C is excreted in the urine.

Tubular Secretion  
Tubular secretion moves substances from peritubular capillaries into the tubular lumen; like glomerular filtration, it constitutes a pathway into the tubule. Like reabsorption, secretion can occur by diffusion or by transcellular mediated transport. The most important substances secreted by the tubules are hydrogen ions.
and potassium, but a large number of normally occurring organic anions, such as choline and creatinine, are also secreted. So are many foreign chemicals, such as penicillin. Active secretion of a substance requires active transport either from the blood side (the interstitial fluid) into the cell (across the basolateral membrane) or out of the cell into the lumen (across the luminal membrane). Also as in reabsorption, tubular secretion of certain substances is coupled in one way or another to the reabsorption of sodium. We’ll describe this later in the context of the secretion of potassium and hydrogen ions.

**Metabolism by the Tubules**

We noted earlier that, during fasting, the cells of the renal tubules synthesize glucose and add it to the blood. They can also synthesize certain substances, notably ammonium, which are then secreted into the fluid in the tubular lumen and excreted. Why the cells would make something just to have it excreted will be made clear when we discuss the role of ammonium in the regulation of plasma hydrogen-ion concentration. Also, the cells can catabolize certain organic substances (peptides, for example) taken up from either the tubular lumen or peritubular capillaries. Catabolism eliminates these substances from the body as surely as if they had been excreted into the urine.

**Regulation of Membrane Channels and Transporters**

We emphasized earlier that tubular reabsorption and/or secretion of many substances is under physiological control. For most of these substances, the control is achieved by regulating the activity or concentrations of the membrane proteins involved in their transport—channels and transporters. This regulation is achieved largely by hormones, neurotransmitters, and paracrine/autocrine agents.

Interestingly, the recent explosion of information concerning the structures, functions, and regulation of renal tubular-cell ion channels and transporters has made it possible to explain the underlying defects in some genetic diseases. For example, a genetic mutation can lead to an abnormality in the Na/glucose transporter that mediates active reabsorption of glucose in the proximal tubule. This abnormality leads to inadequate glucose reabsorption and loss of glucose in the urine at normal or even subnormal plasma concentrations of glucose. Contrast this condition, termed *familial renal glucosuria*, to diabetes mellitus, in which the ability to reabsorb glucose is normal, but the filtered load of glucose is greater than the maximal ability of the tubules to reabsorb this sugar.

**“Division of Labor” in the Tubules**

Several generalizations concerning tubular function should be kept in mind as you proceed through subsequent sections of this chapter, which deal with the renal handling of individual substances. As we have seen, in order to excrete waste products adequately, the GFR must be very large. This, though, means that the filtered volume of water and the filtered loads of all the nonwaste low-molecular-weight plasma solutes are also very large. The primary role of the proximal tubule is to reabsorb much of this filtered water and solutes. This segment has been called a “mass reabsorber” since for every substance reabsorbed by the tubule, the proximal tubule does most of the reabsorbing. Similarly, with one major exception (potassium) the proximal tubule is quantitatively the major site of solute secretion. Henle’s loop also reabsorbs relatively large quantities of the major ions and, to a lesser extent, water.

Extensive reabsorption by the proximal tubule and Henle’s loop ensures that the masses of solutes and the volume of water entering the tubular segments beyond Henle’s loop are relatively small. These segments then do the fine-tuning for most substances, determining the final amounts excreted in the urine by adjusting their rates of reabsorption and, in a few cases, secretion. It should not be surprising, therefore, that most (but not all) homeostatic controls are exerted on these more distal segments.

**The Concept of Renal Clearance**

A useful way of quantitating renal functions is in terms of clearance. The renal clearance of any substance is the volume of plasma from which that substance is completely removed (“cleared”) by the kidneys per unit time. Every substance has its own distinct clearance value, but the units are always in volume of plasma per time. The basic clearance formula for any substance S is:

\[
\text{Clearance of } S = \frac{\text{Mass of } S \text{ excreted per unit time}}{\text{Plasma concentration of } S}
\]

Thus, the clearance of a substance really answers the question: How much plasma had to be completely cleared of the substance to account for the mass of the substance excreted in the urine.

Since the mass of S excreted per unit time is equal to the urine concentration of S multiplied by the urine volume during that time, the formula for the clearance of S becomes

\[
C_S = \frac{U_S V}{P_S}
\]
where
\[ C_S = \text{clearance of } S \]
\[ U_S = \text{urine concentration of } S \]
\[ V = \text{urine volume per unit time} \]
\[ P_S = \text{plasma concentration of } S \]

Let us take the particularly important example of a polysaccharide named inulin (not insulin). This substance is an important research tool in renal physiology because, as will be described, its clearance is equal to the glomerular filtration rate. It is not found normally in the body, but we will administer it intravenously to a person at a rate sufficient to maintain plasma concentration constant at 4 mg/L; thus, inulin excretion equals 0.1 L/h × 300 mg/L, or 30 mg/h. How much plasma had to be completely cleared of its inulin to supply this 30 mg/h? We simply divide 30 mg/h by the plasma concentration, 4 mg/L, to obtain the volume cleared—7.5 L/h. In other words, we are calculating the inulin clearance \( (C_{in}) \) from the measured plasma concentration \( (P_S) \), and plasma inulin concentration \( (P_{In}) \):

\[
C_{in} = \frac{U_{in}V}{P_{In}} \\
C_{in} = 300 \text{ mg/L} \times 0.1 \text{ L/h} \\
C_{in} = 7.5 \text{ L/h}
\]

Now for the crucial points. From a variety of experiments, it is known that inulin is filterable at the renal corpuscle but is not reabsorbed, secreted, or metabolized by the tubule. Therefore, the mass of inulin excreted in our experiment—30 mg/h—must be equal to the mass filtered during the same time period (Figure 16–10). Accordingly, the clearance of inulin must equal the volume of plasma originally filtered; that is, \( C_{in} \) is equal to GFR.

It is important to realize that the clearance of any substance handled by the kidneys in the same way as inulin—filtered, but not reabsorbed, secreted, or metabolized—would equal the GFR. Unfortunately, there are no substances normally present in the plasma that meet these criteria. For clinical purposes, the creatinine clearance \( (C_{Cr}) \) is commonly used to approximate the GFR as follows. The waste product creatinine produced by muscle is filtered at the renal corpuscle and does not undergo reabsorption. It does undergo a small amount of secretion, however, so that some plasma is cleared of its creatinine by secretion. Accordingly, the \( C_{Cr} \) overestimates the GFR but is close enough to be highly useful.

This leads to an important generalization: When the clearance of any substance is greater than the GFR, as measured by the inulin clearance, that substance must undergo tubular secretion. Look back now at our hypothetical substance X (see Figure 16–7): X is filtered, and all the X that escapes filtration is secreted; no X is reabsorbed. Accordingly, all the plasma that enters the kidney per unit time is cleared of its X, and the clearance of X is therefore a measure of renal plasma flow. A substance that is handled like X is the organic anion para-amino-hippurate (PAH), which is used for this purpose (unfortunately, like inulin, it must be administered intravenously).

A similar logic leads to another important generalization: When the clearance of a filterable substance is less than the GFR, as measured by the inulin clearance, that substance must undergo reabsorption.

The remainder of this chapter describes how the kidneys function in the homeostasis of individual substances and how renal function is coordinated with that of other organs. Before turning to these individual substances, however, we complete the general story by describing the mechanisms of eliminating urine from the body—micturition.

**Micturition**

Urine flow through the ureters to the bladder is propelled by contractions of the ureter-wall smooth muscle. The urine is stored in the bladder and intermittently ejected during urination, or micturition.
The bladder is a balloon-like chamber with walls of smooth muscle collectively termed the **detrusor muscle**. The contraction of the detrusor muscle squeezes on the urine in the bladder lumen to produce urination. That part of the detrusor muscle at the base (or “neck”) of the bladder where the urethra begins functions as a sphincter called the **internal urethral sphincter**. Just below the internal urethral sphincter, a ring of skeletal muscle surrounds the urethra. This is the **external urethral sphincter**, the contraction of which can prevent urination even when the detrusor muscle contracts strongly.

What factors influence these bladder structures (Figure 16–11)? (1) The detrusor muscle is innervated by parasympathetic neurons, which cause muscular contraction. Because of the arrangement of the smooth-muscle fibers, when the detrusor muscle is relaxed, the internal urethral sphincter is closed; when the detrusor muscle contracts, changes in its shape tend to pull open the internal urethral sphincter. (2) In addition, the internal sphincter receives sympathetic innervation, which causes contraction of the sphincter. (3) The external urethral sphincter, being skeletal muscle, is innervated by somatic motor neurons, which cause contraction.

As might be predicted from these inputs, while the bladder is filling, there is little parasympathetic input to the detrusor muscle but strong sympathetic input to the internal urethral sphincter and strong input by the somatic motor neurons to the external urethral sphincter. Therefore, the detrusor muscle is relaxed, and the sphincters are closed.

What happens during micturition? As the bladder fills with urine, the pressure within it increases, and this stimulates stretch receptors in the bladder wall. The afferent fibers from these receptors enter the spinal cord and **stimulate** the parasympathetic neurons, which then cause the detrusor muscle to contract. As noted above, this contraction facilitates the opening of the internal urethral sphincter. Simultaneously, the afferent input from the stretch receptors reflexly **inhibits** the sympathetic neurons to the internal urethral sphincter, which further contributes to its opening. In addition, the afferent input also reflexly **inhibits** the somatic motor neurons to the external urethral sphincter, causing it to relax. Both sphincters are now open, and the contraction of the detrusor muscle is able to produce urination.

We have thus far described micturition as a local spinal reflex, but descending pathways from the brain can also profoundly influence this reflex, determining the ability to prevent or initiate micturition voluntarily. Loss of these descending pathways as a result of spinal-cord damage eliminates one’s ability to voluntarily control micturition. Prevention of micturition, learned during childhood, operates in the following way. As the bladder distends, the input from the bladder stretch receptors causes, via ascending pathways to the brain, a sense of bladder fullness and the urge to urinate. But in response to this, urination can be voluntarily prevented by activating descending pathways that stimulate both the sympathetic nerves to the internal urethral sphincter and the somatic motor nerves to the external urethral sphincter.

In contrast, urination can be voluntarily initiated via the descending pathways to the appropriate neurons.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Innervation</th>
<th>During filling</th>
<th>During micturition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor (smooth muscle)</td>
<td>Parasympathetic (causes contraction)</td>
<td>Inhibited</td>
<td>Stimulated</td>
</tr>
<tr>
<td>Internal urethral sphincter</td>
<td>Sympathetic (causes contraction)</td>
<td>Stimulated</td>
<td>Inhibited</td>
</tr>
<tr>
<td>(smooth muscle)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External urethral sphincter</td>
<td>Somatic motor (causes contraction)</td>
<td>Stimulated</td>
<td>Inhibited</td>
</tr>
<tr>
<td>(skeletal muscle)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 16–11**
Control of the bladder.
SECTION A SUMMARY

Functions and Structure of the Kidneys and Urinary System

I. The kidneys regulate the water and ionic composition of the body, excrete waste products, excrete foreign chemicals, produce glucose during prolonged fasting, and secrete three hormones—renin, 1,25-dihydroxyvitamin D₃, and erythropoietin. The first three functions are accomplished by continuous processing of the plasma.

II. Each nephron in the kidneys consists of a renal corpuscle and a tubule.
   a. Each renal corpuscle comprises a capillary tuft, termed a glomerulus, and a Bowman’s capsule, into which the tuft protrudes.
   b. The tubule extends out from Bowman’s capsule and is subdivided into many segments, which can be combined for reference purposes into the proximal tubule, loop of Henle, distal convoluted tubule, and collecting-duct system. At the level of the collecting ducts, multiple tubules join and empty into the renal pelvis, from which urine flows through the ureters to the bladder.
   c. Each glomerulus is supplied by an afferent arteriole, and an efferent arteriole leaves the glomerulus to branch into peritubular capillaries, which supply the tubule.

Basic Renal Processes

I. The three basic renal processes are glomerular filtration, tubular reabsorption, and tubular secretion. In addition, the kidneys synthesize and/or catabolize certain substances. The excretion of a substance is equal to the amount filtered plus the amount secreted minus the amount reabsorbed.

II. Urine formation begins with glomerular filtration—approximately 180 L/day—of essentially protein-free plasma into Bowman’s space.
   a. Glomerular filtrate contains all plasma substances other than proteins (and substances bound to proteins) in virtually the same concentrations as in plasma.
   b. Glomerular filtration is driven by the hydrostatic pressure in the glomerular capillaries and is opposed by both the hydrostatic pressure in Bowman’s space and the osmotic force due to the proteins in the glomerular capillary plasma.

III. As the filtrate moves through the tubules, certain substances are reabsorbed either by diffusion or mediated transport.
   a. Substances to which the tubular epithelium is permeable are reabsorbed by diffusion because water reabsorption creates tubule-interstitium concentration gradients for them.
   b. Active reabsorption of a substance requires the participation of transporters in the luminal or basolateral membrane.
   c. Tubular reabsorption rates are generally very high for nutrients, ions, and water, but are lower for waste products.

d. Many of the mediated-transport systems manifest transport maximums, so that when the filtered load of a substance exceeds the transport maximum, large amounts may appear in the urine.

IV. Tubular secretion, like glomerular filtration, is a pathway for entrance of a substance into the tubule.

The Concept of Renal Clearance

I. The clearance of any substance can be calculated by dividing the mass of the substance excreted per unit time by the plasma concentration of the substance.

II. GFR can be measured by means of the inulin clearance and estimated by means of the creatinine clearance.

Micturition

I. In the basic micturition reflex, bladder distention stimulates stretch receptors that trigger spinal reflexes; these reflexes lead to contraction of the detrusor muscle, mediated by parasympathetic neurons, and relaxation of both the internal and the external urethral sphincters, mediated by inhibition of the neurons to these muscles.

II. Voluntary control is exerted via descending pathways to the parasympathetic nerves supplying the detrusor muscle, the sympathetic nerves supplying the internal urethral sphincter, and the motor nerves supplying the external urethral sphincter.
1. What are the functions of the kidneys?
2. What three hormones do the kidneys secrete?
3. Fluid flows in sequence through what structures from the glomerulus to the bladder? Blood flows through what structures from the renal artery to the renal vein?
4. What are the three basic renal processes that lead to the formation of urine?

5. How does the composition of the glomerular filtrate compare with that of plasma?
6. Describe the forces that determine the magnitude of the GFR. What is a normal value of GFR?
7. Contrast the mechanisms of reabsorption for glucose and urea. Which one shows a Tm?
8. Diagram the sequence of events leading to micturition in infants and in adults.

**Total-Body Balance of Sodium and Water**

Table 16–3 summarizes total-body water balance. These are average values, which are subject to considerable normal variation. There are two sources of body water gain: (1) water produced from the oxidation of organic nutrients, and (2) water ingested in liquids and so-called solid food (a rare steak is approximately 70 percent water). There are four sites from which water is lost to the external environment: skin, respiratory passageways, gastrointestinally tract, and urinary tract. Menstrual flow constitutes a fifth potential source of water loss in women.

The loss of water by evaporation from the skin and the lining of respiratory passageways is a continuous process. It is called insensible water loss because the person is unaware of its occurrence. Additional water can be made available for evaporation from the skin by the production of sweat. Normal gastrointestinal loss of water in feces is generally quite small, but can be severe in diarrhea. Gastrointestinal loss can also be large in vomiting.

Table 16–4 is a summary of total-body balance for sodium chloride. The excretion of sodium and chloride via the skin and gastrointestinal tract is normally quite small but may increase markedly during severe sweating, vomiting, or diarrhea. Hemorrhage can also result in loss of large quantities of both salt and water.

Under normal conditions, as can be seen from Tables 16–3 and 16–4, salt and water losses exactly equal salt and water gains, and no net change in body salt and water occurs. This matching of losses and gains is primarily the result of regulation of urinary loss, which can be varied over an extremely wide range. For example, urinary water excretion can vary from approximately 0.4 L/day to 25 L/day,
depending upon whether one is lost in the desert or participating in a beer-drinking contest. Similarly, some individuals ingest 20 to 25 g of sodium chloride per day, whereas a person on a low-salt diet may ingest only 0.05 g; normal kidneys can readily alter their excretion of salt over this range to match loss with gain.

We will first present the basic renal processes for sodium and water and then describe the homeostatic reflexes that influence these processes. The renal processing of chloride is usually coupled directly or indirectly to that of sodium, and so we shall have little more to say about chloride even though it is the most abundant anion in the extracellular fluid.

Basic Renal Processes for Sodium and Water

Having low molecular weights and not being bound to protein, both sodium and water freely filter from the glomerular capillaries into Bowman’s space. They both undergo considerable reabsorption—normally more than 99 percent (see Table 16–2)—but no secretion. Most renal energy utilization goes to accomplish this enormous reabsorptive task. The bulk of sodium and water reabsorption (about two-thirds) occurs in the proximal tubule, but the major hormonal controls of reabsorption are exerted on the collecting ducts.

The mechanisms of sodium and water reabsorption can be summarized by two generalizations: (1) Sodium reabsorption is an active process occurring in all tubular segments except the descending limb of the loop of Henle; and (2) water reabsorption is by diffusion and is dependent upon sodium reabsorption.

Primary Active Sodium Reabsorption

The essential feature underlying sodium reabsorption throughout the tubule is the primary active transport of sodium out of the cells and into the interstitial fluid, as illustrated for the cortical collecting duct in Figure 16–12. This transport is achieved by Na,K-ATPase pumps in the basolateral membrane of the cells. The active transport of sodium out of the cell keeps the intracellular concentration of sodium low compared to the luminal concentration, and so sodium moves “downhill” out of the lumen into the tubular epithelial cells. (The fact that the cell interior is negatively charged relative to the lumen also contributes to the electrochemical gradient favoring this movement from lumen to cell.)

The precise mechanism of the downhill sodium movement across the luminal membrane into the cell varies from segment to segment of the tubule depending upon which channels and/or transport proteins are present in their luminal membranes. For example, as illustrated in Figure 16–12, the luminal entry step for sodium in the cortical collecting duct is by diffusion through sodium channels. To take another example, in the proximal tubule the luminal entry step is either by cotransport with a variety of organic molecules (glucose, for example) or by countertransport with hydrogen ions (that is, the hydrogen ions move from cell to lumen as the sodium moves into the cell). In this manner, in the proximal tubule sodium reabsorption drives the reabsorption of the cotransported substances and the secretion of hydrogen ions.

While the movement of sodium downhill from lumen into cell across the luminal membrane varies from one segment of the tubule to another, the basolateral membrane step is the same in all sodium-reabsorbing tubular segments—the primary active transport of sodium out of the cell is via Na,K-ATPase pumps in this membrane. It is this transport process that lowers intracellular sodium concentration and so makes possible the downhill luminal entry step, whatever its mechanism.

Coupling of Water Reabsorption to Sodium Reabsorption

How does active sodium reabsorption lead to passive water reabsorption? This type of coupling was described in Chapter 6 (see Figure 6–25) and is summarized again in Figure 16–13. (1) Sodium (and other
Coordinated Body Functions

The water permeability of the last portions of the tubular segments—the loop of Henle and distal convoluted tubule—depends largely on the presence of water channels, termed aquaporins, in the plasma membranes of the tubular cells (Chapter 6). The water permeability of the proximal tubule is always very high, and so water molecules are reabsorbed by this segment almost as rapidly as sodium ions. As a result, the proximal tubule always reabsorbs sodium and water in the same proportions.

We will describe the water permeability of the next tubular segments—the loop of Henle and distal convoluted tubule—later. Now for the really crucial point: The water permeability of the last portions of the tubules, the cortical and medullary collecting ducts, can be high or low because it is subject to physiological control, the only tubular segments in which water permeability is under such control.

The major determinant of this controlled permeability is vasopressin, also known as antidiuretic hormone, ADH. Vasopressin stimulates the insertion into the luminal membrane, by exocytosis, of a particular group of aquaporin water channels made by the collecting-duct cells. Accordingly, in the presence of a high plasma concentration of vasopressin, the water permeability of the collecting ducts becomes very great. Therefore, water reabsorption is maximal, and the final urine volume is small—less than 1 percent of the filtered water.

Without vasopressin, the water permeability of the collecting ducts is extremely low, and very little water is reabsorbed from these sites. Therefore, a large volume of water remains behind in the tubule to be excreted in the urine. This increased urine excretion resulting from low vasopressin is termed water diuresis (diuresis simply means a large urine flow from any cause). In a subsequent section, we will describe the reflexes that control vasopressin secretion.

The disease diabetes insipidus, which is distinct from the other kind of diabetes mentioned earlier in this chapter (diabetes mellitus or “sugar diabetes”), illustrates what happens when the vasopressin system malfunctions. Most people with this disease have lost the ability to produce vasopressin, usually as a result of damage to the hypothalamus. Thus, the permeability to water of the collecting ducts is low and unchanging regardless of the state of the body fluids. Therefore a constant water diuresis is present—as much as 25 L/day.

Note that in water diuresis, there is an increased urine flow, but not an increased solute excretion. In all other cases of diuresis, termed osmotic diuresis, the increased urine flow is the result of a primary increase in solute excretion. For example, failure of normal sodium reabsorption causes both increased sodium excretion and increased water excretion, since, as we have seen, water reabsorption is absolutely dependent on solute reabsorption. Another example of osmotic diuresis occurs in people with uncontrolled, marked diabetes mellitus: In this case, the glucose that escapes reabsorption causes the huge filtered load to retain water in the lumen, causing it to be excreted along with the glucose. We’ll talk more about the consequences of this in Chapter 18.

To summarize, any loss of solute in the urine must be accompanied by water loss (osmotic diuresis), but the reverse is not true; that is, water diuresis is not accompanied by equivalent solute loss.
Urine Concentration: The Countercurrent Multiplier System

Before reading this section you should review, by looking up in the glossary, several terms presented in Chapter 6—hypoosmotic, isoosmotic, and hyperosmotic.

In the section just concluded, we described how the kidneys produce a small volume of urine when the plasma concentration of vasopressin is high. Under these conditions, the urine is concentrated (hyperosmotic) relative to plasma. This section describes the mechanisms by which this hyperosmolarity is achieved.

The ability of the kidneys to produce hyperosmotic urine is a major determinant of one’s ability to survive with limited amounts of water. The human kidney can produce a maximal urinary concentration of 1400 mOsmol/L, almost five times the osmolarity of plasma, which is 290 mOsmol/L (for ease of calculation, we shall round this off to 300 mOsmol/L in future discussions). The typical daily excretion of urea, sulfate, phosphate, other waste products, and ions amounts to approximately 600 mOsmol. Therefore, the minimal volume of urine water in which this mass of solute can be dissolved equals

\[
\frac{600 \text{ mOsmol/day}}{1400 \text{ mOsmol/L}} = 0.444 \text{ L/day}
\]

This volume of urine is known as the obligatory water loss. The loss of this minimal volume of urine (it would be somewhat lower if no food were available) contributes to dehydration when a person is deprived of water intake.

Urinary concentration takes place as tubular fluid flows through the medullary collecting ducts. The interstitial fluid surrounding these ducts is very hyperosmotic, and in the presence of vasopressin, water diffuses out of the ducts into the interstitial fluid of the medulla and then enters the blood vessels of the medulla to be carried away. The key question is: How does the medullary interstitial fluid become hyperosmotic? The answer is: through the function of Henle’s loop. Recall that Henle’s loop forms a hairpin-like loop between the proximal tubule and the distal convoluted tubule (see Figure 16–2). The fluid entering the loop from the proximal tubule flows down the descending limb, turns the corner, and then flows up the ascending limb. The opposing flows in the two limbs is termed a countercurrent flow, and as described next, the entire loop functions as a countercurrent multiplier system to create a hyperosmotic medullary interstitial fluid.

Because the proximal tubule always reabsorbs sodium and water in the same proportions, the fluid entering the descending limb of the loop from the proximal tubule has the same osmolarity as plasma—300 mOsmol/L. For the moment, let’s skip the descending limb since the events in it can only be understood in the context of what the ascending limb is doing. Along the entire length of the ascending limb, sodium and chloride are reabsorbed into the medullary interstitial fluid. In the upper (thick) portion of the ascending limb, this reabsorption is achieved by transporters that actively cotransport sodium and chloride (as well as potassium, which we shall ignore). Such transporters are not present in the lower (thin) portion of the ascending limb, and the reabsorption there is a passive process. For simplicity, however, we shall treat the entire ascending limb as a homogeneous structure that actively reabsorbs sodium and chloride.

Very importantly, the ascending limb is relatively impermeable to water, so that little water follows the salt. The net result is that the interstitial fluid of the medulla becomes hyperosmotic compared to the fluid in the ascending limb.

Now back to the descending limb. This segment, in contrast to the ascending limb, does not reabsorb sodium chloride and is highly permeable to water. Therefore, there is a net diffusion of water out of the descending limb into the more concentrated interstitial fluid until the osmolarities inside this limb and in the interstitial fluid are again equal. The interstitial hyperosmolarity is maintained during this equilibration because the ascending limb continues to pump sodium chloride to maintain the concentration difference between it and the interstitial fluid.
Thus, because of diffusion of water the osmolarities of the descending limb and interstitial fluid become equal, and both are higher—by 200 mOsmol/L in our example—than that of the ascending limb. This is the essence of the system: The loop countercurrent multiplier causes the interstitial fluid of the medulla to become concentrated. It is this hyperosmolarity that will draw water out of the collecting ducts and concentrate the urine. However, one more crucial feature—the “multiplication”—must be considered.

So far we have been analyzing this system as though the flow through the loop of Henle stopped while the ion pumping and water diffusion were occurring. This is not true, so let us see what happens when we allow flow in the system: As shown in the loop portion of Figure 16–14, the osmolarity difference—200 mOsmol/L—that exists at each horizontal level is “multiplied” to a much higher value—1400 mOsmol/L—at the bend in the loop. It should be emphasized that the active sodium chloride transport mechanism in the ascending limb (coupled with low water permeability in this segment) is the essential component of the system. Without it, the countercurrent flow would have no effect whatever on loop and medullary interstitial osmolarity, which would simply remain 300 mOsmol/L throughout.

Now we have our concentrated medullary interstitial fluid, but we must still follow the fluid within the tubules from the loop of Henle through the distal convoluted tubule and into the collecting-duct system, using Figure 16–14 as our guide. As we have seen, the countercurrent multiplier system concentrates the descending-loop fluid, but then lowers the osmolarity in the ascending loop so that the fluid entering the distal convoluted tubule is actually more dilute (hyposmotic)—100 mOsmol/L in Figure 16–14—than the plasma. The fluid becomes even more dilute during its passage through the distal convoluted tubule, since this tubular segment, like the ascending loop, actively transports sodium and chloride out of the tubule but is relatively impermeable to water. This hypoosmotic fluid then enters the cortical collecting duct.

As noted earlier, vasopressin increases tubular permeability to water in both the cortical and medullary collecting ducts. In contrast vasopressin does not influence water reabsorption in the parts of the tubule prior to the collecting ducts, and so, regardless of the plasma concentration of this hormone, the fluid entering the cortical collecting duct is always hypoosmotic. From there on, however, vasopressin is crucial. In the presence of high levels of vasopressin, water reabsorption occurs by diffusion from the hypoosmotic fluid in the cortical collecting duct until the fluid in this segment becomes isoosmotic to plasma in the peritubular capillaries of the cortex—that is, until it is once again at 300 mOsmol/L.

The isoosmotic tubular fluid then enters and flows through the medullary collecting ducts. In the presence of high plasma concentrations of vasopressin, water diffuses out of the ducts into the medullary interstitial fluid as a result of the high osmolarity set up there by the loop countercurrent multiplier system. This water then enters the medullary capillaries and is carried out of the kidneys by the venous blood. Water reabsorption occurs all along the lengths of the medullary collecting ducts so that, in the presence of vasopressin, the fluid at the end of these ducts has essentially the same osmolarity as the interstitial fluid surrounding the bend in the loops—that is, at the bottom of the medulla. By this means, the final urine is hyperosmotic. By retaining as much water as possible, the kidneys minimize the rate at which dehydration occurs during water deprivation.
In contrast, as we saw earlier, when plasma vasopressin concentration is low, both the cortical and medullary collecting ducts are relatively impermeable to water. As a result, a large volume of hypoosmotic urine is excreted, thereby eliminating an excess of water in the body.

In describing how the countercurrent gradient is created, we have presented only the absolutely essential components, namely the interactions between sodium, chloride, and water. The story is actually more complex and not fully understood, but includes at least one important role for urea in determining the maximal urine concentration attainable. It also includes a unique function of the medullary circulation, to which we now turn.

**The Medullary Circulation** A major problem with the countercurrent system as described above is this: Why doesn’t the blood flowing through medullary capillaries eliminate the countercurrent gradient set up by the loops of Henle? One would think that as plasma having the usual osmolarity of 300 mOsm/L enters the highly concentrated environment of the medulla, there would be massive net diffusion of sodium and chloride into the capillaries and water out of them, and thus the interstitial gradient would be “washed away.” However, the solution to this problem is as follows. The blood vessels in the medulla—termed **vasa recta**—form hairpin loops that run parallel to the loops of Henle and medullary collecting ducts. As shown in Figure 16–15, blood enters the top of the vessel loop at an osmolarity of 300 mOsm/L, and as the blood flows down the loop deeper and deeper into the medulla, sodium and chloride do indeed diffuse into, and water out of, the vessel. However, after the bend in the loop is reached, the blood then flows up the ascending vessel loop, where the process is almost completely reversed. Thus, the hairpin-loop structure of the vasa recta minimizes excessive loss of solute from the interstitium by **diffusion**. At the same time, both the salt and water being reabsorbed from the loops of Henle and collecting ducts are carried away in equivalent amounts by **bulk-flow**, as determined by the usual capillary Starling forces, and the steady-state countercurrent gradient set up by the loops of Henle is maintained.

**Renal Sodium Regulation**

Now we turn to the reflexes that act upon the basic renal processes for sodium and, in the next section, water to regulate their excretion. In normal individuals, urinary sodium excretion is reflexly increased when there is a sodium excess in the body and reflexly decreased when there is a sodium deficit. These reflexes are so precise that total-body sodium normally varies by only a few percent despite a wide range of sodium intakes and the sporadic occurrence of large losses via the skin and gastrointestinal tract.

As we have seen, sodium is freely filterable from the glomerular capillaries into Bowman’s space and is actively reabsorbed, but not secreted. Therefore:

\[
\text{Sodium excreted} = \text{Sodium filtered} - \text{Sodium reabsorbed}
\]

The body can reflexly adjust sodium excretion by changing both processes on the right of the equation. Thus, for example, when total-body sodium decreases for any reason, sodium excretion is reflexly decreased below normal levels by lowering the GFR and simultaneously raising sodium reabsorption. Under most physiological conditions, however, the reflexly induced changes in GFR are relatively small, and sodium reabsorption is the major controlled process.

Our first problem in understanding the reflexes controlling sodium reabsorption is to determine what inputs initiate them; that is, what variables are actually being sensed by receptors? It may come as a surprise, but there are no important receptors capable of detecting either sodium concentration or the total amount of sodium in the body. Rather, the reflexes that
regulate urinary sodium excretion are initiated mainly by various cardiovascular baroreceptors, such as the carotid sinus.

As described in Chapter 14, baroreceptors respond to pressure changes within the cardiovascular system and initiate reflexes that rapidly regulate these pressures by acting on the heart, arterioles, and veins. The new information in this chapter is that regulation of cardiovascular pressures by baroreceptors also simultaneously achieves regulation of total-body sodium.

Because sodium is the major extracellular solute (constituting, along with associated anions, approximately 90 percent of these solutes), changes in total-body sodium result in similar changes in extracellular volume. Since extracellular volume comprises plasma volume and interstitial volume, plasma volume is also positively related to total-body sodium. We saw in Chapter 14 that plasma volume is an important determinant of, in sequence, the blood pressures in the veins, cardiac chambers, and arteries. Thus, the chain linking total-body sodium to cardiovascular pressures is completed: Low total-body sodium leads to low plasma volume, which leads to low cardiovascular pressures, which, via baroreceptors, initiate reflexes that influence the renal arterioles and tubules so as to lower GFR and increase sodium reabsorption. These latter events decrease sodium excretion, thereby retaining sodium in the body and preventing further decreases in plasma volume and cardiovascular pressures. Increases in total-body sodium have the reverse reflex effects.

To summarize, the amount of sodium in the body determines the extracellular fluid volume, the plasma volume component of which helps determine cardiovascular pressures, which initiate the reflexes that control sodium excretion.

**Control of GFR**

Figure 16–16 summarizes the major mechanisms by which a lower total-body sodium, as caused by diarrhea, for example, elicits a decrease in GFR. The main direct cause of the reduced GFR—a reduced net glomerular filtration pressure—occurs both as a consequence of a lowered arterial pressure in the kidneys and, more importantly, as a result of reflexes acting on the renal arterioles. Note that these reflexes are simply the basic baroreceptor reflexes described in Chapter 14, where it was pointed out that a decrease in cardiovascular pressures causes neurally mediated reflex vasoconstriction in many areas of the body. As we shall see later, the hormones angiotensin II and vasopressin also participate in this renal vasoconstrictor response.

Conversely, an increased GFR is reflexly elicited by neuroendocrine inputs when an increased total-body sodium level causes increased plasma volume. This increased GFR contributes to the increased renal sodium loss that returns extracellular volume to normal.

**Control of Sodium Reabsorption**

For long-term regulation of sodium excretion, the control of sodium reabsorption is more important than the control of GFR. The major factor determining the rate of tubular sodium reabsorption is the hormone aldosterone.

**Aldosterone and the Renin-Angiotensin System**

The adrenal cortex produces a steroid hormone, aldosterone, which stimulates sodium reabsorption by the cortical collecting ducts. An action on this late portion of the tubule is just what one would expect for a fine-tuning input since most of the filtered sodium has been reabsorbed by the time the filtrate reaches the collecting-duct system. When aldosterone is completely absent, approximately 2 percent of the filtered sodium (equivalent to 35 g of sodium chloride per day) is not reabsorbed but is excreted. In contrast, when the plasma concentration of aldosterone is high, essentially all the sodium reaching the cortical collecting ducts is reabsorbed. In a normal person, the plasma concentration of aldosterone and the amount of sodium excreted lie somewhere between these extremes.

Aldosterone, like other steroids, acts by inducing the synthesis of proteins in its target cells; in the case of the cortical collecting ducts, the proteins participate in sodium transport. Look again at Figure 16–12; aldosterone induces the synthesis of all the channels and pumps shown in this figure. (By this same mechanism, aldosterone also stimulates sodium absorption from the lumen of both the large intestine and the ducts carrying fluid from the sweat glands and salivary glands. In this manner, less sodium is lost in the feces and from the surface of the skin in sweat.)

When a person is eating a lot of sodium, aldosterone secretion is low, whereas it is high when the person ingests a low-sodium diet or becomes sodium-depleted for some other reason. What controls the secretion of aldosterone under these circumstances? The answer is the hormone angiotensin II, which acts directly on the adrenal cortex to stimulate the secretion of aldosterone.

Angiotensin II is a component of the hormonal complex termed the renin-angiotensin system, summarized in Figure 16–17. As stated earlier, renin is an enzyme secreted by the juxtaglomerular cells of the juxtaglomerular apparatuses in the kidneys. Once in the bloodstream, renin splits a small polypeptide, angiotensin I, from a large plasma protein, angiotensinogen, which is produced by the liver. Angiotensin I then undergoes further cleavage to form the active agent of the renin-angiotensin
FIGURE 16–16
Direct and neurally mediated reflex pathways by which the GFR and hence sodium and water excretion are decreased when plasma volume decreases. The renal nerves also cause contraction of glomerular mesangial cells, resulting in a decreased surface area for filtration.
system, angiotensin II. This conversion is mediated by an enzyme known as angiotensin converting enzyme, which is found in very high concentration on the luminal surface of capillary endothelial cells, particularly those in the lung. Angiotensin II exerts many effects, but the most important are its stimulation of the secretion of aldosterone and its constriction of arterioles (described in Chapter 14). Plasma angiotensin II is high during salt depletion and low when the individual is sodium replete, and it is this change in angiotensin II that brings about the changes in aldosterone secretion. Now we must ask the question: What causes the changes in plasma angiotensin II concentration with changes in salt balance?

Angiotensinogen and angiotensin converting enzyme are normally present in high and relatively unchanging concentrations, so the rate-limiting factor in angiotensin II formation is the plasma renin concentration. Normally, this concentration depends upon the rate of renin secretion by the kidneys. Thus the chain of events in salt depletion is: increased renin secretion → increased plasma renin concentration → increased angiotensin concentration → increased aldosterone secretion → increased plasma aldosterone concentration.

First, the renal sympathetic nerves directly innervate the juxtaglomerular cells, and an increase in the activity of these nerves stimulates renin secretion. This makes excellent sense since, as have seen, these nerves are reflexly activated via baroreceptors whenever a reduction in body sodium (and, hence, plasma volume) lowers cardiovascular pressures (see Figure 16–16).

The other two inputs for controlling renin release—intrarenal baroreceptors and the macula densa—are totally contained within the kidneys and require no external neuroendocrine input (although they can be influenced by such input). As noted earlier, the juxtaglomerular cells are located in the walls of the afferent arterioles; they are themselves sensitive to the pressure within these arterioles, and so function as intrarenal baroreceptors. When blood pressure in the kidneys decreases, as occurs when plasma volume is down, these cells are stretched less and, therefore, secrete more renin (Figure 16–18). Thus, the juxtaglomerular cells respond simultaneously to the combined effects of sympathetic input, triggered by baroreceptors external to the kidneys, and to their own pressure sensitivity.

The other completely internal input to the juxtaglomerular cells is via the macula densa, which, as noted earlier, is located near the ends of the ascending loops of Henle (see Figure 16–5). The macula densa senses the sodium and/or chloride concentration in the tubular fluid flowing past it, a decreased salt concentration causing increased renin secretion. For several reasons, including a decrease in GFR and hence tubular flow rate, macula densa sodium and
chloride concentrations tend to decrease when a person's arterial pressure is decreased. This input therefore also signals for increased renin release at the same time that the sympathetic nerves and intrarenal baroreceptors are doing so (Figure 16–18).

Obviously, there is considerable redundancy in the control of renin secretion. As illustrated in Figure 16–18, the various mechanisms can all be participating at the same time.

By helping to regulate sodium balance and thereby plasma volume, the renin-angiotensin system contributes to the control of arterial blood pressure. However, this is not the only way in which it influences arterial pressure. Recall from Chapter 14 that angiotensin
II is a potent constrictor of arterioles all over the body and that this effect on peripheral resistance increases arterial pressure.

Other Factors  Although aldosterone is the most important controller of sodium reabsorption, many other factors also play roles. For example, in addition to their indirect roles via control of aldosterone secretion, the renal nerves and angiotensin II also act directly on the tubules to stimulate sodium reabsorption.

Another input is the peptide hormone known as atrial natriuretic factor (ANF), which is synthesized and secreted by cells in the cardiac atria. ANF acts on the tubules (several tubular segments and mechanisms are involved) to inhibit sodium reabsorption. It can also act on the renal blood vessels to increase GFR, which further contributes to increased sodium excretion. As would be predicted, the secretion of ANF is increased when there is an excess of sodium in the body, but the stimulus for this increased secretion is not alterations in sodium concentration. Rather, using the same logic (only in reverse) that applies to the control of renin and aldosterone secretion, ANF secretion increases because of the expansion of plasma volume that accompanies an increase in body sodium. The specific stimulus is increased atrial distension (Figure 16–19).

Finally, another important input controlling sodium reabsorption is the arterial blood pressure. We have previously described how the arterial blood pressure constitutes a signal for important reflexes (involving the renin-angiotensin system and aldosterone) that influence sodium reabsorption, but now we are emphasizing that arterial pressure also acts locally on the tubules themselves. Specifically, an increase in arterial pressure inhibits sodium reabsorption and thereby increases sodium excretion; this is termed pressure natriuresis ("natriuresis" means increased urinary sodium loss). Thus, an increased blood pressure reduces sodium reabsorption by two mechanisms: It reduces the activity of the renin-angiotensin-aldosterone system, and it also acts locally on the tubules. Conversely, a decreased blood pressure decreases sodium excretion both by stimulating the renin-angiotensin-aldosterone system and acting on the tubules to enhance sodium reabsorption. Now is a good time to look back at Figure 14–60, which describes the strong causal, reciprocal relationship between arterial blood pressure and blood volume, the result of which is that blood volume is perhaps the major long-term determinant of blood pressure. The direct effect of blood pressure on sodium excretion is, as shown in Figure 14–60, one of the major links in these relationships. Thus, for example, an important hypothesis is that most people who develop hypertension do so because their kidneys, for some reason, do not excrete enough sodium in response to a normal arterial pressure. Accordingly, at this normal pressure some dietary sodium is retained, which causes the pressure to rise enough to produce adequate sodium excretion to balance sodium intake, albeit at an increased body sodium content.

This completes our survey of the control of sodium excretion, which depends upon the control of two renal variables—the GFR and sodium reabsorption. The latter is controlled by the renin-angiotensin-aldosterone hormone system and by other factors, including atrial natriuretic factor and arterial blood pressure. The reflexes that control both GFR and sodium reabsorption are essentially reflexes that regulate blood pressure, since they are most frequently initiated by changes in arterial or venous pressures.

Renal Water Regulation

Water excretion is the difference between the volume of water filtered (the GFR) and the volume reabsorbed. Accordingly, the baroreceptor-initiated GFR-controlling reflexes described in the previous section tend to have the same effects on water excretion as on sodium excretion. As is true for sodium, however, the major regulated determinant of water excretion is not GFR but rather the rate of water reabsorption. As we have seen,
this is determined by vasopressin, and so total-body water is regulated mainly by reflexes that alter the secretion of this hormone.

As described in Chapter 10, vasopressin is produced by a discrete group of hypothalamic neurons whose axons terminate in the posterior pituitary, from which vasopressin is released into the blood. The most important of the inputs to these neurons are from baroreceptors and osmoreceptors.

**Baroreceptor Control of Vasopressin Secretion**

We have seen that a decreased extracellular volume, due say to diarrhea or hemorrhage, reflexly calls forth, via the renin-angiotensin system, an increased aldosterone secretion. But the decreased extracellular volume also triggers increased vasopressin secretion. This increased vasopressin increases the water permeability of the collecting ducts, more water is reabsorbed and less is excreted, and so water is retained in the body to help stabilize the extracellular volume.

This reflex is initiated by several baroreceptors in the cardiovascular system (Figure 16–20). The baroreceptors decrease their rate of firing when cardiovascular pressures decrease, as occurs when blood volume decreases. Therefore, few impulses are transmitted from the baroreceptors via afferent neurons and ascending pathways to the hypothalamus, and the result is increased vasopressin secretion. Conversely, increased cardiovascular pressures cause more firing by the baroreceptors, resulting in a decrease in vasopressin secretion.

In addition to its effect on water excretion, if the plasma vasopressin concentration becomes very high, it, like angiotensin II, causes widespread arteriolar constriction. This helps restore arterial blood pressure toward normal (Chapter 14).

The baroreceptor reflex for vasopressin, as just described, has a relatively high threshold—that is, there must be a sizable reduction in cardiovascular pressures to trigger it. Therefore, this reflex, compared to the osmoreceptor reflex described next, generally plays a lesser role under most physiological circumstances, but it can become very important in pathological states such as hemorrhage.

**Osmoreceptor Control of Vasopressin Secretion**

We have seen how changes in extracellular volume simultaneously elicit reflex changes in the excretion of both sodium and water. This is adaptive since the situations causing extracellular volume alterations are very often associated with loss or gain of both sodium and water in approximately proportional amounts. In contrast, we shall see now that changes in total-body water in which no change in total-body sodium occurs are compensated for reflexly by altering water excretion without altering sodium excretion.

FIGURE 16–20

Baroreceptor pathway by which vasopressin secretion is increased when plasma volume is decreased. The opposite events (culminating in a decrease in vasopressin secretion) occur when plasma volume increases.

A crucial point in understanding how such reflexes are initiated is that changes in water alone, in contrast to sodium, have relatively little effect on extracellular volume. The reason is that water, unlike sodium, distributes throughout all the body-fluid compartments, about two-thirds entering the intracellular compartment rather than simply staying in the extracellular compartment as sodium does. Therefore, cardiovascular pressures and, hence, baroreceptors are little affected by pure water gains or losses. In contrast, the major change caused by water loss or gain out of proportion to sodium loss or gain is a change in the osmolarity of the body fluids. This is a key point because, under conditions due predominantly to water gain or loss, the receptors that initiate the reflexes controlling vasopressin
secretion are osmoreceptors in the hypothalamus, receptors responsive to changes in osmolarity.

As an example, take a person drinking 2 L of sugar-free soft drink, which contains little sodium or other solute. The excess water lowers the body-fluid osmolarity (raises the water concentration), which reflexly inhibits vasopressin secretion via the hypothalamic osmoreceptors (Figure 16–21). As a result, the water permeability of the collecting ducts becomes very low, water is not reabsorbed from these segments, and a large volume of hypoosmotic urine is excreted. In this manner, the excess water is eliminated.

At the other end of the spectrum, when the osmolarity of the body fluids increases (water concentration decreases), say, because of water deprivation, vasopressin secretion is reflexly increased via the osmoreceptors, water reabsorption by the collecting ducts is increased, and a very small volume of highly concentrated urine is excreted. By retaining relatively more water than solute, the kidneys help reduce the body-fluid osmolarity back toward normal.

To summarize, regulation of body-fluid osmolarity requires separation of water excretion from sodium excretion—that is, requires the kidneys to excrete a urine that, relative to plasma, either contains more water than sodium and other solutes (water diuresis) or less water than solute (concentrated urine). This is made possible by two physiological factors: (1) osmoreceptors and (2) vasopressin-dependent dissociation of water reabsorption from sodium reabsorption in the collecting ducts.

We have now described two afferent pathways controlling the vasopressin-secreting hypothalamic cells, one from baroreceptors and one from osmoreceptors. To add to the complexity, the hypothalamic cells receive synaptic input from many other brain areas, so that vasopressin secretion, and therefore urine volume and concentration, can be altered by pain, fear, and a variety of drugs. For example, alcohol is a powerful inhibitor of vasopressin release, and this probably accounts for much of the increased urine volume produced following ingestion of alcohol, a urine volume well in excess of the volume of beverage consumed.

A Summary Example: The Response to Sweating

Figure 16–22 shows the factors that control renal sodium and water excretion in response to severe sweating. Sweat is a hypoosmotic solution containing mainly water, sodium, and chloride. Therefore, sweating causes both a decrease in extracellular volume and an increase in body-fluid osmolarity (a decrease in water concentration). The renal retention of water and sodium minimizes the deviations from normal caused by the loss of water and salt in the sweat.

**Thirst and Salt Appetite**

Now we turn to the other component of any balance—control of intake. Deficits of salt and water must eventually be compensated for by ingestion of these substances, because the kidneys cannot create new sodium ions or water, they can only minimize their excretion until ingestion replaces the losses.
The subjective feeling of thirst, which leads us to obtain and ingest water, is stimulated both by a lower extracellular volume and a higher plasma osmolarity (Figure 16–23), the latter being the single most important stimulus under normal physiological conditions. Note that these are precisely the same two changes that stimulate vasopressin production, and the osmoreceptors and baroreceptors that control vasopressin secretion are identical to those for thirst. The brain centers that receive input from these receptors and mediate thirst are located in the hypothalamus, very close to those areas that produce vasopressin.

**FIGURE 16–22**
Pathways by which sodium and water excretion are decreased in response to severe sweating. This figure is an amalgamation of Figures 16–16, 16–18, 16–20, and the reverse of 16–21.

The subject feeling of thirst, which leads us to obtain and ingest water, is stimulated both by a lower extracellular volume and a higher plasma osmolarity (Figure 16–23), the latter being the single most important stimulus under normal physiological conditions. Note that these are precisely the same two changes that stimulate vasopressin production, and the osmoreceptors and baroreceptors that control vasopressin secretion are identical to those for thirst. The brain centers that receive input from these receptors and mediate thirst are located in the hypothalamus, very close to those areas that produce vasopressin.

**FIGURE 16–23**
Inputs reflexly controlling thirst. The osmoreceptor input is the single most important stimulus under most physiological conditions. Psychosocial factors and conditioned responses are not shown.
Another influencing factor is angiotensin II, which stimulates thirst by a direct effect on the brain. Thus, the renin-angiotensin system helps regulate not only sodium balance but water balance as well and constitutes one of the pathways by which thirst is stimulated when extracellular volume is decreased.

There are still other pathways controlling thirst. For example, dryness of the mouth and throat causes profound thirst, which is relieved by merely moistening them. Some kind of “metering” of water intake by other parts of the gastrointestinal tract also occurs; that is, a thirsty individual given access to water stops drinking after replacing the lost water but before most of the water has been absorbed from the gastrointestinal tract and has a chance to eliminate the stimulatory inputs to the systemic baroreceptors and osmoreceptors. How this metering occurs remains a mystery, but one function of this feedforward process is to prevent overhydration.

The analog of thirst for sodium, salt appetite, is an important part of sodium homeostasis in most mammals. Salt appetite consists of two components: “hedonistic” appetite and “regulatory” appetite; that is, animals “like” salt and eat it whenever they can, regardless of whether they are salt-deficient, and, in addition, their drive to obtain salt is markedly increased in the presence of bodily salt deficiency. Human beings certainly have a strong hedonistic appetite for salt, as manifested by almost universally large intakes of salt whenever it is cheap and readily available (for example, the average American consumes 10–15 g/day despite the fact that human beings can survive quite normally on less than 0.5 g/day). However, unlike most other mammals, humans have relatively little regulatory salt appetite, at least until a bodily salt deficit becomes extremely large.

**Potassium Regulation**

Potassium is, as we have seen, the most abundant intracellular ion. However, although only 2 percent of total-body potassium is in the extracellular fluid, the potassium concentration in this fluid is extremely important for the function of excitable tissues, notably nerve and muscle. Recall (Chapter 8) that the resting-membrane potentials of these tissues are directly related to the relative intracellular and extracellular potassium concentrations. Accordingly, either increases or decreases in extracellular potassium concentration can cause abnormal rhythms of the heart (arrhythmias) and abnormalities of skeletal-muscle contraction.

A normal person remains in potassium balance by daily excreting an amount of potassium in the urine equal to the amount ingested minus the amounts eliminated in the feces and sweat. Also, like sodium, potassium losses via sweat and the gastrointestinal tract are normally quite small, although vomiting or diarrhea can cause large quantities to be lost. The control of urinary potassium excretion is the major mechanism by which body potassium is regulated.
Renal Regulation of Potassium

Potassium is freely filterable in the renal corpuscle. Normally, the tubules reabsorb most of this filtered potassium so that very little of the filtered potassium appears in the urine. However, the cortical collecting ducts can secrete potassium, and changes in potassium excretion are due mainly to changes in potassium secretion by this tubular segment (Figure 16–24).

During potassium depletion, when the homeostatic response is to minimize potassium loss, there is no potassium secretion by the cortical collecting ducts, and only the small amount of filtered potassium that escapes tubular reabsorption is excreted. In all other situations, to the small amount of potassium not reabsorbed is added a variable amount of potassium secreted by the cortical collecting ducts, an amount necessary to maintain total-body potassium balance.

The mechanism of potassium secretion by the cortical collecting ducts was illustrated in Figure 16–12. In this tubular segment, the K⁺ pumped into the cell across the basolateral membrane by Na,K-ATPases diffuses into the tubular lumen through K⁺ channels in the luminal membrane. Thus, the secretion of potassium by the cortical collecting duct is associated with the reabsorption of sodium by this tubular segment. (Potassium secretion does not occur in other sodium-reabsorbing tubular segments because there are few potassium channels in the luminal membranes of their cells; rather, in these segments the potassium pumped into the cell by Na,K-ATPases simply diffuses back across the basolateral membrane through potassium channels located there.)

What factors influence potassium secretion by the cortical collecting ducts to achieve homeostasis of bodily potassium? The single most important factor is as follows: When a high-potassium diet is ingested (Figure 16–25), plasma potassium concentration increases, though very slightly, and this drives enhanced basolateral uptake via the Na,K-ATPase pumps and hence an enhanced potassium secretion. Conversely, a low-potassium diet or a negative potassium balance, for example, from diarrhea, lowers basolateral potassium uptake; this reduces potassium secretion and excretion, thereby helping to reestablish potassium balance.

A second important factor linking potassium secretion to potassium balance is the hormone aldosterone (Figure 16–25). Besides stimulating tubular sodium reabsorption by the cortical collecting ducts, aldosterone simultaneously enhances tubular potassium secretion by this tubular segment.

The reflex by which an excess or deficit of potassium controls aldosterone production (Figure 16–25) is completely different from the reflex described earlier involving the renin-angiotensin system. The aldosterone-secreting cells of the adrenal cortex are sensitive to the potassium concentration of the extracellular fluid bathing them. Thus, an increased intake of potassium leads to an increased extracellular potassium concentration, which in turn directly stimulates aldosterone production by the adrenal cortex. The resulting increased plasma aldosterone concentration increases potassium secretion and thereby eliminates the excess potassium from the body.

Conversely, a lowered extracellular potassium concentration decreases aldosterone production and thereby reduces potassium secretion. Less potassium than usual is excreted in the urine, thus helping to restore the normal extracellular concentration.

The control and major renal tubular effects of aldosterone are summarized in Figure 16–26. The fact that a single hormone regulates both sodium and potassium excretion raises the question of potential conflicts between homeostasis of the two ions. For

**FIGURE 16–26** Summary of the control of aldosterone and its effects on sodium reabsorption and potassium secretion.
c. The luminal fluid then enters and flows through the medullary collecting ducts, and the concentrated medullary interstitium causes water to move out of these ducts, made highly permeable to water by vasopressin. The result is concentration of the collecting duct fluid and the urine.

d. The hairpin-loop structure of the vasa recta prevents the countercurrent gradient from being washed away.

Renal Sodium Regulation

I. Sodium excretion is the difference between the amount of sodium filtered and the amount reabsorbed.

II. GFR, and hence the filtered load of sodium, is controlled by baroreceptor reflexes. Decreased vascular pressures cause decreased baroreceptor firing and hence increased sympathetic outflow to the renal arterioles, resulting in vasoconstriction and decreased GFR. These changes are generally relatively small under most physiological conditions.

III. The major control of tubular sodium reabsorption is the adrenal cortical hormone aldosterone, which stimulates sodium reabsorption in the cortical collecting ducts.

IV. The renin-angiotensin system is one of the two major controllers of aldosterone secretion. When extracellular volume decreases, renin secretion is stimulated by three inputs: (1) stimulation of the renal sympathetic nerves to the juxtaglomerular cells; (2) pressure decreases sensed by the juxtaglomerular cells, themselves acting as intrarenal baroreceptors; and (3) a signal generated by low sodium or chloride concentration in the lumen of the macula densa.

V. Many other factors influence sodium reabsorption. One of these, atrial natriuretic factor, is secreted by cells in the atria in response to atrial distension; it inhibits sodium reabsorption and it also increases GFR.

VI. Arterial pressure acts locally on the renal tubules to influence sodium reabsorption, an increased pressure causing decreased reabsorption and hence increased excretion.

Renal Water Regulation

I. Water excretion is the difference between the amount of water filtered and the amount reabsorbed.

II. GFR regulation via the baroreceptor reflexes plays some role in regulating water excretion, but the major control is via vasopressin-mediated control of water reabsorption.

III. Vasopressin secretion by the posterior pituitary is controlled by cardiovascular baroreceptors and by osmoreceptors in the hypothalamus.
a. Via the baroreceptor reflexes, a low extracellular volume stimulates vasopressin secretion, and a high extracellular volume inhibits it.

b. Via the osmoreceptors, a high body-fluid osmolarity stimulates vasopressin secretion, and a low osmolarity inhibits it.

**Thirst and Salt Appetite**

I. Thirst is stimulated by a variety of inputs, including baroreceptors, osmoreceptors, and angiotensin II.

II. Salt appetite is not of major regulatory importance in human beings.

**Potassium Regulation**

I. A person remains in potassium balance by excreting an amount of potassium in the urine equal to the amount ingested minus the amounts lost in the feces and sweat.

II. Potassium is freely filterable at the renal corpuscle and undergoes both reabsorption and secretion, the latter occurring in the cortical collecting ducts and being the major controlled variable determining potassium excretion.

III. When body potassium is increased, extracellular potassium concentration increases. This increase acts directly on the cortical collecting ducts to increase potassium secretion and also stimulates aldosterone secretion, the increased plasma aldosterone then also stimulating potassium secretion.

### SECTION B KEY TERMS

- insensible water loss
- aquaporins
- vasopressin (antidiuretic hormone, ADH)
- water diuresis
- diuresis
- osmotic diuresis
- hypoosmotic
- isoosmotic
- hyperosmotic
- obligatory water loss
- countercurrent multiplier system
- vasa recta
- aldosterone
- renin-angiotensin system
- renin
- angiotensin I
- angiotensinogen
- angiotensin II
- angiotensin converting enzyme
- intrarenal baroreceptors
- atrial natriuretic factor (ANF)
- pressure natriuresis
- osmoreceptors
- salt appetite

### SECTION B REVIEW QUESTIONS

1. What are the sources of water gain and loss in the body? What are the sources of sodium gain and loss?
2. Describe the distribution of water and sodium between intracellular and extracellular fluids.
3. What is the relationship between body sodium and extracellular-fluid volume?
4. What is the mechanism of sodium reabsorption, and how is the reabsorption of other solutes coupled to it?
5. What is the mechanism of water reabsorption, and how is it coupled to sodium reabsorption?
6. What is the effect of vasopressin on the renal tubules, and what are the sites affected?
7. Describe the characteristics of the two limbs of the loop of Henle with regard to their transport of sodium, chloride, and water.
8. Diagram the osmolarities in the two limbs of the loop of Henle, distal convoluted tubule, cortical collecting duct, cortical interstitium, medullary collecting duct, and medullary interstitium in the presence of vasopressin. What happens to the cortical and medullary collecting-duct values in the absence of vasopressin?
9. What two processes determine how much sodium is excreted per unit time?
10. Diagram the sequence of events by which a decrease in blood pressure leads to a decreased GFR.
11. List the sequence of events leading from increased renin secretion to increased aldosterone secretion.
12. What are the three inputs controlling renin secretion?
13. Diagram the sequence of events leading from decreased cardiovascular pressures or from an increased plasma osmolarity to an increased secretion of vasopressin.
14. What are the stimuli for thirst?
15. Which of the basic renal processes apply to potassium? Which of them is the controlled process, and which tubular segment performs it?
16. Diagram the steps leading from increased plasma potassium to increased potassium excretion.
17. What are the two major controls of aldosterone secretion, and what are this hormone’s major actions?
Extracellular calcium concentration normally remains relatively constant. Large deviations in either direction would cause problems. A low plasma calcium concentration increases the excitability of nerve and muscle plasma membranes, so that individuals with low plasma calcium suffer from hypocalcemic tetany, characterized by skeletal-muscle spasms. A high plasma calcium concentration causes cardiac arrhythmias as well as depressed neuromuscular excitability. These effects reflect, in part, the ability of extracellular calcium to bind to plasma-membrane proteins that function as ion channels, thereby altering membrane potentials. The binding alters the open or closed state of the channels. This effect of calcium on plasma membranes is totally distinct from its role as an intracellular excitation-contraction coupler, as described in Chapter 11.

**Effector Sites for Calcium Homeostasis**

The sections in this chapter on sodium, water, and potassium homeostasis were concerned almost entirely with the renal handling of these substances. In contrast, the regulation of calcium depends not only on the kidneys but also on bone and the gastrointestinal tract. The activities of the gastrointestinal tract and kidneys determine the net intake and output of calcium for the entire body and, thereby, the overall state of calcium balance. In contrast, interchanges of calcium between extracellular fluid and bone do not alter total-body balance but, rather, the distribution of calcium within the body. We will first describe how the effector sites handle calcium and then discuss how they are influenced by hormones in the homeostatic control of plasma calcium concentration.

**Bone**

Approximately 90 percent of total-body calcium is contained in bone. Therefore, deposition of calcium in bone or its removal very importantly influences plasma calcium concentration.

Bone has functions, summarized in Table 16–5, other than regulating plasma calcium concentration. It is important to recognize that its role in maintaining normal plasma calcium concentration takes precedence over the mechanical supportive role, sometimes to the detriment of the latter.

<table>
<thead>
<tr>
<th>TABLE 16–5 Functions of Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Supports the body and imposed loads against gravity.</td>
</tr>
<tr>
<td>2. Provides the rigidity that permits locomotion.</td>
</tr>
<tr>
<td>3. Affords protection to the internal organs. The rib cage, vertebrae, and skull perform this function.</td>
</tr>
<tr>
<td>4. Serves as a reservoir for calcium, inorganic phosphate, and other mineral elements.</td>
</tr>
<tr>
<td>5. Produces blood cells in the bone marrow.</td>
</tr>
</tbody>
</table>

Bone is a special connective tissue made up of several cell types surrounded by a collagen matrix, called osteoid, upon which are deposited minerals, particularly the crystals of calcium and phosphate known as hydroxyapatite. In some instances, bones have central marrow cavities where blood cells are formed (Chapter 14). Typically, approximately one-third of a bone, by weight, is osteoid, and two-thirds is mineral (the bone cells contribute negligible weight).

The three types of bone cells (the blood-forming cells of the marrow are not included in this term) are osteoblasts, osteocytes, and osteoclasts (Figure 16–27). Osteoblasts are the bone-forming cells. They secrete collagen to form a surrounding matrix, which then becomes calcified; just how this mineralization is brought about remains controversial. Once surrounded by calcified matrix, the osteoblasts are called osteocytes. The osteocytes have long cytoplasmic processes that extend throughout the bone and form tight junctions with other osteocytes. Osteoclasts are large multinucleated cells that break down (resorb) previously formed bone by secreting hydrogen ions, which dissolve the crystals, and hydrolytic enzymes, which digest the osteoid.

The growth of bones during childhood will be discussed in Chapter 18. What is important here is that throughout life, bone is being constantly “remodeled” by the osteoblasts and osteoclasts working together. Osteoclasts resorb old bone, and then osteoblasts move into the area and lay down new matrix, which becomes calcified. This process is dependent, in part, on the stresses imposed on the bones by gravity and muscle tension, both of which stimulate osteoblastic activity. It is also influenced by many hormones, as summarized in Table 16–6, and a bewildering variety...
of autocrine/paracrine growth factors produced locally in the bone. Of the hormones listed, only parathyroid hormone and 1,25-dihydroxyvitamin D₃ are controlled primarily by reflexes that regulate plasma calcium concentration. Nonetheless, changes in the other listed hormones have important influences on bone mass and plasma calcium concentration.

**Kidneys**

About 60 percent of plasma calcium is filterable at the renal corpuscle (the rest is bound to plasma protein), and most of this filtered calcium is reabsorbed. There is no tubular secretion of calcium. Accordingly, the urinary excretion of calcium is the difference between the amount filtered and the amount reabsorbed. Like that of sodium, the control of calcium excretion is exerted mainly on reabsorption; that is, reabsorption is reflexly decreased when plasma calcium concentration goes up for whatever reason, and reflexly increased when plasma calcium goes down.

In addition, as we shall see, the renal handling of phosphate plays a role in the regulation of extracellular calcium. Phosphate, too, is handled by a combination of filtration and reabsorption, the latter being hormonally controlled.

**Gastrointestinal Tract**

The absorption of sodium, water, and potassium from the gastrointestinal tract normally approximates 100 percent. There is some homeostatic control of these processes, but it is relatively unimportant and so we ignored it. In contrast, a considerable amount of ingested calcium is not absorbed from the intestine and simply leaves the body along with the feces. Moreover, the active transport system that achieves calcium absorption is under important hormonal control. Accordingly, there can be large regulated increases or decreases in the amount of calcium absorbed. Indeed, hormonal control of this absorptive process is the major means for homeostatically regulating total-body calcium balance, more important than the control of renal calcium excretion.

**Hormonal Controls**

The two major hormones that homeostatically regulate plasma calcium concentration are parathyroid hormone and 1,25-dihydroxyvitamin D₃. A third hormone, calcitonin, plays a more limited role.
Parathyroid Hormone

All three of the effector sites described previously—bone, kidneys, and gastrointestinal tract—are subject, directly or indirectly, to control by a protein hormone called parathyroid hormone, produced by the parathyroid glands. These glands are in the neck, embedded in the surface of the thyroid gland, but are distinct from it. Parathyroid hormone production is controlled by the extracellular calcium concentration acting directly on the secretory cells (via a plasma-membrane calcium receptor). Decreased plasma calcium concentration stimulates parathyroid hormone secretion, and an increased plasma calcium concentration does just the opposite.

Parathyroid hormone exerts multiple actions that increase extracellular calcium concentration, thus compensating for the decreased concentration that originally stimulated secretion of this hormone (Figure 16–28).

1. It directly increases the resorption of bone by osteoclasts, which results in the movement of calcium (and phosphate) from bone into extracellular fluid.

**FIGURE 16–28**
Reflexes by which a reduction in plasma calcium concentration is restored toward normal via the actions of parathyroid hormone. See Figure 16–29 for a more complete description of 1,25-(OH)_{2}D_{3}. 
2. It directly stimulates the formation of 1,25-dihydroxyvitamin D₃, (discussed below), and this latter hormone then increases intestinal absorption of calcium. Thus, the effect of parathyroid hormone on the intestinal tract is an indirect one.

3. It directly increases renal tubular calcium reabsorption, thus decreasing urinary calcium excretion.

In addition, parathyroid hormone directly reduces the tubular reabsorption of phosphate, thus raising its urinary excretion. This keeps plasma phosphate from increasing at a time when parathyroid hormone is simultaneously causing increased release of both calcium and phosphate from bone.

1,25-Dihydroxyvitamin D₃

The term vitamin D denotes a group of closely related compounds. One of these, called vitamin D₃, is formed by the action of ultraviolet radiation (from sunlight, usually) on a cholesterol derivative (7-dehydrocholesterol) in skin. Another form of vitamin D very similar to vitamin D₃ is ingested in food, specifically from plants. (Both forms can be found in vitamin pills and foods enriched with vitamin D.)

Because of clothing and decreased outdoor living, people are often dependent upon dietary vitamin D, and for this reason it was originally classified as a vitamin. However, regardless of source, vitamin D₃ and its similar ingested form are metabolized by addition of hydroxyl groups, first in the liver and then in certain kidney tubular cells (Figure 16–29). The end result of these changes is 1,25-dihydroxyvitamin D₃ (abbreviated 1,25-(OH)₂D₃, also called calcitriol), the active form of vitamin D. It should be clear from this description that since 1,25-(OH)₂D₃ is made in the body, it is not, itself, a vitamin: instead, it fulfills the criteria for a hormone.

The major action of 1,25-(OH)₂D₃ is to stimulate absorption of calcium by the intestine. Thus, the major event in vitamin D deficiency is decreased intestinal calcium absorption, resulting in decreased plasma calcium.

The blood concentration of 1,25-(OH)₂D₃ is subject to physiological control. The major control point is the second hydroxylation step, the one that occurs in the kidneys. The enzyme catalyzing this step is stimulated by parathyroid hormone. Thus, as we have seen, a low plasma calcium concentration stimulates the secretion of parathyroid hormone, which in turn enhances the production of 1,25-(OH)₂D₃, and both hormones contribute to restoration of the plasma calcium toward normal.

Calcitonin

Calcitonin is a peptide hormone secreted by cells (termed parafollicular cells) that are within the thyroid gland but are distinct from the thyroid folicles.
Calcitonin decreases plasma calcium concentration, mainly by inhibiting osteoclasts, thereby reducing bone resorption. Its secretion is stimulated by an increased plasma calcium concentration, just the opposite of the stimulus for parathyroid hormone secretion. Unlike parathyroid hormone and 1,25-(OH)₂D₃, however, calcitonin plays little role in the normal day-to-day regulation of plasma calcium regulation, but is involved primarily in protecting the skeleton from excessive resorption during periods of “calcium stress” such as growth, pregnancy, and lactation.

**Metabolic Bone Diseases**

Various diseases reflect abnormalities in the metabolism of bone. Rickets (in children) and osteomalacia (in adults) are conditions in which mineralization of bone matrix is deficient, causing the bones to be soft and easily fractured. In addition, a child suffering from rickets typically is severely bowlegged due to the effect of weight-bearing on the developing leg bones. A major cause of rickets and osteomalacia is deficiency of 1,25-(OH)₂D₃.

In contrast to these diseases, in osteoporosis both matrix and minerals are lost as a result of an imbalance between bone resorption and bone formation. The resulting decrease in bone mass and strength leads to an increased incidence of fractures. Osteoporosis can occur in people who are immobilized (disuse osteoporosis), in people who have an excessive plasma concentration of a hormone that favors bone resorption, and in people who have a deficient plasma concentration of a hormone that favors bone formation (Table 16–6). It is most commonly seen, however, with aging. Everyone loses bone as he or she ages, but osteoporosis is much more common in elderly women than men for several reasons: Women have a smaller bone mass to begin with, and the loss that occurs with aging occurs more rapidly, particularly after menopause removes the bone-promoting influence of estrogen.

Prevention is the focus of attention for osteoporosis. Estrogen treatment in postmenopausal women is very effective in reducing the rate of bone loss. A regular weight-bearing exercise program (brisk walking and stair-climbing, for example) is also helpful. Adequate dietary calcium (1000 mg/day before menopause and 1200–1500 mg/day after menopause) throughout life is important to build up and maintain bone mass. Several agents also provide effective therapy once osteoporosis is established. Most prominent is a group of drugs, called bisphosphonates, that interfere with the resorption of bone by osteoclasts. Other therapeutic agents include the hormones calcitonin, 1,25-(OH)₂D₃, and estrogen, as well as sodium fluoride, which stimulates osteoblasts to form bone.

**SECTION C SUMMARY**

**Effector Sites for Calcium Homeostasis**

I. The effector sites for the regulation of plasma calcium concentration are bone, the gastrointestinal tract, and the kidneys.

II. Approximately 99 percent of total-body calcium is contained in bone as minerals on a collagen matrix. Bone is constantly remodeled as a result of the interaction of osteoblasts and osteoclasts, a process that determines bone mass and provides a means for raising or lowering plasma calcium concentration.

III. Calcium is actively absorbed by the gastrointestinal tract, and this process is under hormonal control.

IV. The amount of calcium excreted in the urine is the difference between the amount filtered and the amount reabsorbed, the latter process being under hormonal control.

**Hormonal Controls**

I. Parathyroid hormone increases plasma calcium concentration by influencing all the effector sites.

a. It stimulates tubular reabsorption of calcium, bone resorption with release of calcium, and formation of the hormone 1,25-dihydroxyvitamin D₃, which stimulates calcium absorption by the intestine.

b. It also inhibits the tubular reabsorption of phosphate.

II. Vitamin D₃ is formed in the skin or ingested and then undergoes hydroxylations in the liver and kidneys, in the latter stimulated by parathyroid hormone, to the active form, 1,25-dihydroxyvitamin D₃.

**SECTION C KEY TERMS**

- osteoid
- vitamin D
- osteoblast
- vitamin D₃
- osteocyte
- 1,25-dihydroxyvitamin D₃
- osteoclast
- [1,25-(OH)₂D₃]
- parathyroid hormone
- calcitonin

**SECTION C REVIEW QUESTIONS**

1. List the functions of bone.
2. Describe bone remodeling.
3. Describe the handling of calcium by the kidneys and gastrointestinal tract.
4. What controls the secretion of parathyroid hormone, and what are this hormone’s four major effects?
5. Describe the formation and action of 1,25-(OH)₂D₃. How does parathyroid hormone influence the production of this hormone?
Metabolic reactions are highly sensitive to the hydrogen-ion concentration of the fluid in which they occur. This sensitivity is due to the influence on enzyme function exerted by hydrogen ions, which change the shapes of proteins. Accordingly, the hydrogen-ion concentration of the extracellular fluid is closely regulated. (At this point the reader might want to review the section on hydrogen ions, acidity, and pH in Chapter 2.)

This regulation can be viewed in the same way as the balance of any other ion—that is, as the matching of gains and losses. When loss exceeds gain, the arterial plasma hydrogen-ion concentration goes down (pH goes above 7.4), and this is termed an alkalosis. When gain exceeds loss, the arterial plasma hydrogen-ion concentration goes up (pH goes below 7.4), and this is termed an acidosis.

**Sources of Hydrogen-Ion Gain or Loss**

Table 16–7 summarizes the major routes for gains and losses of hydrogen ion. First, as described in Chapter 15, a huge quantity of CO₂—about 20,000 mmol—is generated daily as the result of oxidative metabolism, and these CO₂ molecules participate in the generation of hydrogen ions during passage of blood through peripheral tissues via the reactions:

\[
\text{carbonic anhydrase} \quad \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+ \tag{16-1}
\]

This source does not normally constitute a net gain of hydrogen ions, however, since all the hydrogen ions generated via these reactions are reincorporated into water when the reactions are reversed during passage of blood through the lungs (Chapter 15). Net retention of CO₂ does occur, however, in hypoventilation or respiratory disease and causes a net gain of hydrogen ions. Conversely, net loss of CO₂ occurs in hyperventilation, and this causes net elimination of hydrogen ions.

The body also produces acids, both organic and inorganic, from sources other than CO₂. These are collectively termed nonvolatile acids. They include phosphoric acid and sulfuric acid, generated mainly by the catabolism of proteins, as well as lactic acid and several other organic acids. Dissociation of all these acids yields anions and hydrogen ions. But simultaneously the metabolism of a variety of organic anions utilizes hydrogen ions and produces bicarbonate. Thus, metabolism of “nonvolatile” solutes both generates and utilizes hydrogen ions. In the United States, where the diet is high in protein, the generation of nonvolatile acids predominates in most people and there is an average net production of 40 to 80 mmol of hydrogen ions per day.

A third potential source of net body gain or loss of hydrogen ion is gastrointestinal secretions leaving the body. Vomitus contains a high concentration of hydrogen ions and so constitutes a source of net loss. In contrast, the other gastrointestinal secretions are alkaline; they contain very little hydrogen ion, but their concentration of bicarbonate is higher than exists in plasma. Loss of these fluids, as in diarrhea, constitutes in essence a body gain of hydrogen ions. This is an extremely important point: Given the mass action relationship shown in Equation 16-1, when a bicarbonate ion is lost from the body it is the same as if the body had gained a hydrogen ion. The reason is that loss of the bicarbonate causes the reactions shown in Equation 16-1 to be driven to the right, thereby generating a hydrogen ion within the body. Similarly, when the body gains a bicarbonate ion, it is the same as if the body had lost a hydrogen ion, as the reactions of Equation 16-1 are driven to the left.
Finally, the kidneys constitute the fourth source of net hydrogen-ion gain or loss; that is, the kidneys can either remove hydrogen ions from the plasma or add them.

Buffering of Hydrogen Ions in the Body

Any substance that can reversibly bind hydrogen ions is called a buffer. Between their generation in the body and their elimination, most hydrogen ions are buffered by extracellular and intracellular buffers. The normal extracellular-fluid pH of 7.4 corresponds to a hydrogen-ion concentration of only 0.00004 mmol/L (40 nanomols/L). Without buffering, the daily turnover of the 40 to 80 mmol of H⁺ produced from nonvolatile acids generated in the body from metabolism would cause huge changes in the body-fluid hydrogen-ion concentration.

The general form of buffering reactions is:

\[ \text{Buffer}^- + \text{H}^+ \rightarrow \text{HBuffer} \]  (16-2)

HBuffer is a weak acid in that it can dissociate to Buffer⁻ plus H⁺ or it can exist as the undissociated molecule (HBuffer). When H⁺ concentration increases for whatever reason, the reaction is forced to the right, and more H⁺ is bound by Buffer⁻ to form HBuffer. For example, when H⁺ concentration is increased because of increased production of lactic acid, some of the hydrogen ions combine with the body’s buffers, so the hydrogen-ion concentration does not increase as much as it otherwise would have. Conversely, when H⁺ concentration decreases because of the loss of hydrogen ions or the addition of alkali, Equation 16-2 proceeds to the left and H⁺ is released from HBuffer. In this manner, the body buffers stabilize H⁺ concentration against changes in either direction.

The major extracellular buffer is the CO₂/HCO₃⁻ system summarized in Equation 16-1. This system also plays some role in buffering within cells, but the major intracellular buffers are phosphates and proteins. One intracellular protein buffer is hemoglobin, as described in Chapter 15.

You must recognize that buffering does not eliminate hydrogen ions from the body or add them to the body; it only keeps them “locked-up” until balance can be restored. How balance is achieved is the subject of the rest of our description of hydrogen-ion regulation.

Integration of Homeostatic Controls

The kidneys are ultimately responsible for balancing hydrogen-ion gains and losses so as to maintain a relatively constant plasma hydrogen-ion concentration. Thus, the kidneys normally excrete the excess hydrogen ions from nonvolatile acids generated in the body from metabolism—that is, all acids other than carbonic acid. Moreover, if there is an additional net gain of hydrogen ions due to abnormally increased production of these nonvolatile acids, or to hypoventilation or respiratory malfunction, or to loss of alkaline gastrointestinal secretions, the kidneys increase their elimination of hydrogen ions from the body so as to restore balance. Alternatively, if there is a net loss of hydrogen ions from the body due to increased metabolic utilization of hydrogen ions (as in a vegetarian diet), hyperventilation, or vomiting, the kidneys replenish these hydrogen ions.

Although the kidneys are the ultimate hydrogen-ion balancers, the respiratory system also plays a very important homeostatic role. We have pointed out that hypoventilation, respiratory malfunction, and hyperventilation can cause a hydrogen-ion imbalance; now we emphasize that when a hydrogen-ion imbalance is due to a nonrespiratory cause, then ventilation is reflexly altered so as to help compensate for the imbalance. We described this phenomenon in Chapter 15 (see Figure 15-34): An elevated arterial hydrogen-ion concentration stimulates ventilation, and this reflex hyperventilation causes reduced arterial \( P_{CO_2} \), and hence, by mass action, reduced hydrogen-ion concentration. Alternatively, a decreased plasma hydrogen-ion concentration inhibits ventilation, thereby raising arterial \( P_{CO_2} \) and increasing the hydrogen-ion concentration.

Thus, the respiratory system and kidneys work together. The respiratory response to altered plasma hydrogen-ion concentration is very rapid (minutes) and keeps this concentration from changing too much until the more slowly responding kidneys (hours to days) can actually eliminate the imbalance. Of course, if the respiratory system is the actual cause of the hydrogen-ion imbalance, then the kidneys are the sole homeostatic responder. By the same token, malfunctioning kidneys can create a hydrogen-ion imbalance by eliminating too little or too much hydrogen ion from the body, and then the respiratory response is the only one operating.

Renal Mechanisms

In the previous section we wrote of the kidneys eliminating hydrogen ions from the body or replenishing them. The kidneys perform this task by altering plasma bicarbonate concentration. The key to understanding how altering plasma bicarbonate concentration eliminates or replenishes hydrogen ions was stated earlier: The excretion of a bicarbonate in the urine increases the plasma hydrogen-ion concentration just as if a hydrogen ion had been added to the plasma. Similarly,
the addition of a bicarbonate to the plasma lowers the plasma hydrogen-ion concentration just as if a hydrogen ion had been removed from the plasma.

Thus, when there is a lowering of plasma hydrogen-ion concentration (alkalosis) for whatever reason, the kidneys’ homeostatic response is to excrete large quantities of bicarbonate. This raises plasma hydrogen-ion concentration back toward normal. In contrast, in response to a rise in plasma hydrogen-ion concentration (acidosis), the kidneys do not excrete bicarbonate in the urine, but instead kidney tubular cells produce new bicarbonate and add it to the plasma. This lowers the plasma hydrogen-ion concentration back toward normal.

Let us now look at the basic mechanisms by which bicarbonate excretion or addition of new bicarbonate to the plasma is achieved.

**Bicarbonate Handling**

Bicarbonate is completely filterable at the renal corpuscles and undergoes marked tubular reabsorption in various tubular segments (the proximal tubule, ascending loop of Henle, and cortical collecting ducts). Bicarbonate can also be secreted (in the collecting ducts). Therefore:

\[ \text{HCO}_3^- \text{ excretion} = \text{HCO}_3^- \text{ filtered} + \text{HCO}_3^- \text{ secreted} - \text{HCO}_3^- \text{ reabsorbed} \]

For simplicity, we will ignore the secretion of bicarbonate (because it is always quantitatively much less than tubular reabsorption) and treat bicarbonate excretion as the difference between filtration and reabsorption.

Bicarbonate reabsorption is an active process, but it is not accomplished in the conventional manner of simply having an active pump for bicarbonate ions at the luminal or basolateral membrane of the tubular cells. Instead, bicarbonate reabsorption is absolutely dependent upon the tubular secretion of hydrogen ions, which combine in the lumen with filtered bicarbonates.

Figure 16–30 illustrates the sequence of events. Start this figure inside the cell with the combination of CO₂ and H₂O to form H₂CO₃, a reaction catalyzed by the enzyme carbonic anhydrase. The H₂CO₃ immediately dissociates to yield H⁺ and bicarbonate (HCO₃⁻). The HCO₃⁻ moves down its concentration gradient across the basolateral membrane into interstitial fluid and then into the blood. Simultaneously the H⁺ is secreted into the lumen; depending on the tubular segment, this secretion is achieved by some combination of primary H⁺-ATPase pumps, primary H⁺,K⁺-ATPase pumps, and Na⁺/H⁺ countertransporters.

*But the secreted H⁺ is not excreted.* Instead, it combines in the lumen with a filtered HCO₃⁻ and generates CO₂ and H₂O (both of which can diffuse into the cell and be used for another cycle of hydrogen-ion generation). The overall result is that the bicarbonate filtered from the plasma at the renal corpuscle has disappeared, but its place in the plasma has been taken by the bicarbonate that was produced inside the cell, and so no net change in plasma bicarbonate concentration has occurred. It may seem inaccurate to refer to this process as bicarbonate “reabsorption,” since the bicarbonate that appears in the peritubular plasma is not the same bicarbonate ion that was filtered. Yet the overall result is, in effect, the same as if the filtered bicarbonate had been more conventionally reabsorbed like a sodium or potassium ion.

Except in response to alkalosis (discussed below), the kidneys normally reabsorb all filtered bicarbonate, thereby preventing the loss of bicarbonate in the urine.

**Addition of New Bicarbonate to the Plasma**

It is essential to realize in Figure 16–30 that as long as there are still significant amounts of filtered bicarbonate ions in the lumen, almost all secreted hydrogen ions will combine with them. But what happens to any secreted hydrogen ions once almost all the bicarbonate has been reabsorbed and is no longer available in the lumen to combine with the hydrogen ions?
The answer, illustrated in Figure 16–31, is that the extra secreted hydrogen ions combine in the lumen with a filtered nonbicarbonate buffer, usually HPO$_4^{2-}$. (Other filtered buffers can also participate, but HPO$_4^{2-}$ is the most important.) The hydrogen ion is then excreted in the urine as part of an H$_2$PO$_4^-$ ion. Now for the critical point: Note in Figure 16–31 that, under these conditions, the bicarbonate generated within the tubular cell by the carbonic anhydrase reaction and entering the plasma constitutes a net gain of bicarbonate by the plasma, not merely a replacement for a filtered bicarbonate. Thus, when a secreted hydrogen ion combines in the lumen with a buffer other than bicarbonate, the overall effect is not merely one of bicarbonate conservation, as in Figure 16–30, but rather of addition to the plasma of a new bicarbonate. This raises the bicarbonate concentration of the plasma and alkalizes it.

To repeat, significant numbers of hydrogen ions combine with filtered nonbicarbonate buffers like HPO$_4^{2-}$ only after the filtered bicarbonate has virtually all been reabsorbed. The main reason is that there is such a large load of filtered bicarbonate buffers—25 times more than the load of filtered nonbicarbonate buffers—competing for the secreted hydrogen ions.

There is a second mechanism by which the tubules contribute new bicarbonate to the plasma, one that involves not hydrogen-ion secretion but rather the renal production and secretion of ammonium (NH$_4^+$) (Figure 16–32). Tubular cells, mainly those of the proximal tubule, take up glutamine from both the glomerular filtrate and peritubular plasma and, by a series of steps, metabolize it. In the process, both NH$_4^+$ and bicarbonate are formed inside the cells. The NH$_4^+$ is actively secreted (via Na$^+$/NH$_4^+$ countertransport) into the lumen and excreted, while the bicarbonate moves into the peritubular capillaries and constitutes new plasma bicarbonate.

A comparison of Figures 16–31 and 16–32 demonstrates that the overall result—renal contribution of new bicarbonate to the plasma—is the same regardless of whether it is achieved by: (1) H$^+$ secretion and excretion on nonbicarbonate buffers such as phosphate (Figure 16–31); or (2) by glutamine metabolism with NH$_4^+$ excretion (Figure 16–32). It is convenient, therefore, to view the latter case as representing H$^+$ excretion “bound” to NH$_3$, just as the former case constitutes H$^+$ excretion bound to nonbicarbonate buffers.
two forms is a measure of the amount of new bicarbonate added to the plasma by the kidneys. Indeed, “urinary H+ excretion” and “renal contribution of new bicarbonate to the plasma” are really two sides of the same coin and are synonymous phrases.

The kidneys normally contribute enough new bicarbonate to the blood (excrete enough hydrogen ions) to compensate for the hydrogen ions from nonvolatile acids generated in the body.

One last point needs to be emphasized: The last paragraphs summarize the two forms in which H+ is excreted in the urine, but to be completely accurate there is also a third form—as free H+. However, the amount of free H+ is always so small that it can be ignored. For example, even the most acid of urines (4.4 is the lowest pH achievable by the tubules) contains less than 0.1 mmol of free H+, compared to several hundred mmols of H+ bound up in nonbicarbonate buffers and NH4+. This emphasizes how important these two sources are in achieving the excretion of H+.

Renal Responses to Acidosis and Alkalosis

We can now apply this material to the renal responses to the presence of an acidosis or alkalosis. These are summarized in Table 16–8.

Conversely, a person with metabolic alkalosis will Respiratory acidosis results from altered respiration. Respiratory acidosis occurs when the respiratory system fails to eliminate carbon dioxide as fast as it is produced. Respiratory alkalosis occurs when the respiratory system eliminates carbon dioxide faster than it is produced. As described earlier, the imbalance of arterial hydrogen-ion concentrations in such cases is completely explainable in terms of mass action. Thus, the hallmark of a respiratory acidosis is an elevation in both arterial Pco2 and hydrogen-ion concentration; that of respiratory alkalosis is a reduction in both.

Classification of Acidosis and Alkalosis

To repeat, acidosis refers to any situation in which the hydrogen-ion concentration of arterial plasma is elevated; alkalosis denotes a reduction. All such situations fit into two distinct categories (Table 16–9): (1) respiratory acidosis or alkalosis; (2) metabolic acidosis or alkalosis.

As its name implies, respiratory acidosis results from altered respiration. Respiratory acidosis occurs when the respiratory system fails to eliminate carbon dioxide as fast as it is produced. Respiratory alkalosis occurs when the respiratory system eliminates carbon dioxide faster than it is produced. As described earlier, the imbalance of arterial hydrogen-ion concentrations in such cases is completely explainable in terms of mass action. Thus, the hallmark of a respiratory acidosis is an elevation in both arterial Pco2 and hydrogen-ion concentration; that of respiratory alkalosis is a reduction in both.

Metabolic acidosis or alkalosis includes all situations other than those in which the primary problem is respiratory. Some common causes of metabolic acidosis are excessive production of lactic acid (during severe exercise or hypoxia) or of ketone bodies (in uncontrolled diabetes mellitus or fasting, as described in Chapter 18). Metabolic acidosis can also result from excessive loss of bicarbonate, as in diarrhea. A frequent cause of metabolic alkalosis is persistent vomiting, with its associated loss of hydrogen ions as HCl from the stomach.

What is the arterial Pco2 in metabolic acidosis or alkalosis? Since, by definition, metabolic acidosis and alkalosis must be due to something other than excess retention or loss of carbon dioxide, you might have predicted that arterial Pco2 would be unchanged, but such is not the case. As emphasized earlier in this chapter, the elevated hydrogen-ion concentration associated with metabolic acidosis reflexly stimulates ventilation and lowers arterial Pco2. By mass action, this helps restore the hydrogen-ion concentration toward normal. Conversely, a person with metabolic alkalosis will reflexly have ventilation inhibited. The result is a rise in arterial Pco2 and, by mass action, an associated restoration of hydrogen-ion concentration toward normal.

TABLE 16–8 Renal Responses to Acidosis and Alkalosis

<table>
<thead>
<tr>
<th>Responses to Acidosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sufficient hydrogen ions are secreted to reabsorb all the filtered bicarbonate.</td>
<td></td>
</tr>
<tr>
<td>2. Still more hydrogen ions are secreted, and this contributes new bicarbonate to the plasma as these hydrogen ions are excreted bound to nonbicarbonate urinary buffers such as HPO42-.</td>
<td></td>
</tr>
<tr>
<td>3. Tubular glutamine metabolism and ammonium excretion are enhanced, which also contributes new bicarbonate to the plasma.</td>
<td></td>
</tr>
<tr>
<td><strong>Net result:</strong> More new bicarbonate ions than usual are added to the blood, and plasma bicarbonate is increased, thereby compensating for the acidosis. The urine is highly acidic (lowest attainable pH = 4.4).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Responses to Alkalosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate of hydrogen-ion secretion is inadequate to reabsorb all the filtered bicarbonate, so that significant amounts of bicarbonate are excreted in the urine, and there is little or no excretion of hydrogen ions on nonbicarbonate urinary buffers.</td>
<td></td>
</tr>
<tr>
<td>2. Tubular glutamine metabolism and ammonium excretion are decreased so that little or no new bicarbonate is contributed to the plasma from this source.</td>
<td></td>
</tr>
<tr>
<td><strong>Net result:</strong> Plasma bicarbonate concentration is decreased, thereby compensating for the alkalosis. The urine is alkaline (pH &gt; 7.4).</td>
<td></td>
</tr>
</tbody>
</table>
To reiterate, the plasma $P_{CO_2}$ changes in metabolic acidosis and alkalosis are not the cause of the acidosis or alkalosis but are the result of compensatory reflex responses to nonrespiratory abnormalities. Thus, in metabolic, as opposed to respiratory conditions, the arterial plasma $P_{CO_2}$ and hydrogen-ion concentration go in opposite directions, as summarized in Table 16–9.

**S E C T I O N  D  S U M M A R Y**

**Sources of Hydrogen-Ion Gain or Loss**

I. Total-body balance of hydrogen ions is the result of both metabolic production of these ions and of net gains or losses via the respiratory system, gastrointestinal tract, and urine (Table 16–7).

II. A stable balance is achieved by regulation of urinary losses.

**Buffering of Hydrogen Ions in the Body**

I. Buffering is a means of minimizing changes in hydrogen-ion concentration by combining these ions reversibly with anions such as bicarbonate and intracellular proteins.

II. The major extracellular buffering system is the $CO_2/HCO_3^-$ system, and the major intracellular buffers are proteins and phosphates.

**Integration of Homeostatic Controls**

I. The kidneys and the respiratory system are the homeostatic regulators of plasma hydrogen-ion concentration.

II. The kidneys are the organs that achieve body hydrogen-ion balance.

III. A decrease in arterial plasma hydrogen-ion concentration causes reflex hyperventilation, which raises arterial $P_{CO_2}$ and, hence, raises plasma hydrogen-ion concentration toward normal. An increase in plasma hydrogen-ion concentration causes reflex hyperventilation, which lowers arterial $P_{CO_2}$ and, hence, lowers hydrogen-ion concentration toward normal.

**Renal Mechanisms**

I. The kidneys maintain a stable plasma hydrogen-ion concentration by regulating plasma bicarbonate concentration. They can either excrete bicarbonate or contribute new bicarbonate to the blood.

II. Bicarbonate is reabsorbed when hydrogen ions, generated in the tubular cells by a process catalyzed by carbonic anhydrase, are secreted into the lumen and combine with filtered bicarbonate. The secreted hydrogen ions are not excreted in this situation.

III. In contrast, when the secreted hydrogen ions combine in the lumen with filtered phosphate or other nonbicarbonate buffer, they are excreted, and the kidneys have contributed new bicarbonate to the blood.

IV. The kidneys also contribute new bicarbonate to the blood when they produce and excrete ammonium.

**Classification of Acidosis and Alkalosis**

I. Acid-base disorders are categorized as respiratory or metabolic.

a. Respiratory acidosis is due to retention of carbon dioxide, and respiratory alkalosis to excessive elimination of carbon dioxide.

b. All other causes of acidosis or alkalosis are termed metabolic and reflect gain or loss, respectively, of hydrogen ions from a source other than carbon dioxide.

**S E C T I O N  D  K E Y  T E R M S**

nonvolatile acids  buffer

**S E C T I O N  D  R E V I E W  Q U E S T I O N S**

1. What are the sources of gain and loss of hydrogen ions in the body?

2. List the body’s major buffer systems.

3. Describe the role of the respiratory system in the regulation of hydrogen-ion concentration.

4. How does the tubular secretion of hydrogen ions occur, and how does it achieve bicarbonate reabsorption?

5. How does hydrogen-ion secretion contribute to the renal addition of new bicarbonate to the blood? What determines whether a secreted hydrogen ion will achieve these events or will instead cause bicarbonate reabsorption?
6. How does the metabolism of glutamine by the tubular cells contribute new bicarbonate to the blood and ammonium to the urine?

7. What two quantities make up “hydrogen-ion excretion?” Why can this term be equated with “contribution of new bicarbonate to the plasma?”

8. How do the kidneys respond to the presence of an acidosis or alkalosis?

9. Classify the four types of acid-base disorders according to plasma hydrogen-ion concentration, bicarbonate concentration, and $P_{CO_2}$.

**Diuretics and Kidney Disease**

**Diuretics**

Drugs used clinically to increase the volume of urine excreted are known as diuretics. Such agents act on the tubules to inhibit the reabsorption of sodium, along with chloride and/or bicarbonate, resulting in increased excretion of these ions. Since water reabsorption is dependent upon sodium reabsorption, water reabsorption is also reduced, resulting in increased water excretion.

A large variety of clinically useful diuretics are available and are classified according to the specific mechanisms by which they inhibit sodium reabsorption. For example, one type, called loop diuretics, acts on the ascending limb of the loop of Henle to inhibit the transport protein that mediates the first step in sodium reabsorption in this segment—cotransport of sodium and chloride (and potassium) into the cell across the luminal membrane.

Except for one category of diuretics, called potassium-sparing diuretics, all diuretics not only increase sodium excretion but also cause increased potassium excretion, an unwanted side effect. By several mechanisms, the potassium-sparing diuretics inhibit sodium reabsorption in the cortical collecting duct, and they simultaneously inhibit potassium secretion there. This explains why they do not cause increased potassium excretion.

Diuretics are among the most commonly used medications. For one thing, they are used to treat diseases characterized by renal retention of salt and water. As emphasized earlier in this chapter, in normal persons the regulation of blood pressure simultaneously produces stability of total-body sodium mass and extracellular volume because there is a close correlation between these variables. In contrast, in several types of disease, this correlation is broken and the reflexes that maintain blood pressure can cause renal retention of sodium. Sodium excretion may fall virtually to zero despite continued sodium ingestion, leading to abnormal expansion of the extracellular fluid and formation of edema. Diuretics are used to prevent or reverse this renal retention of sodium and water.

**Kidney Disease**

The term “kidney disease” is no more specific than “car trouble,” since many diseases affect the kidneys. Bacteria, allergies, congenital defects, kidney stones, tumors, and toxic chemicals are some possible sources of kidney damage. Obstruction of the urethra or a ureter may cause injury as the result of a buildup of pressure and may predispose the kidneys to bacterial infection.

One frequent sign of kidney disease is the appearance of protein in the urine. In normal kidneys, there is a very tiny amount of protein in the glomerular filtrate because the corpuscular membranes are not completely impermeable to proteins, particularly those with lower molecular weights. However, the cells of the proximal tubule completely remove this filtered protein from the tubular lumen, and no protein appears in the final urine. In contrast, diseased renal corpuscles may become much more permeable to protein, and diseased proximal tubules may lose their ability to remove filtered protein from the tubular lumen. The result is that protein will appear in the urine.
Although many diseases of the kidney are self-limited and produce no permanent damage, others progress if untreated. The symptoms of profound renal malfunction are relatively independent of the damaging agent and are collectively known as uremia, literally, “urine in the blood.”

The severity of uremia depends upon how well the impaired kidneys are able to preserve the constancy of the internal environment. Assuming that the person continues to ingest a normal diet containing the usual quantities of nutrients and electrolytes, what problems arise? The key fact to keep in mind is that the kidney destruction markedly reduces the number of functioning nephrons. Accordingly, the many substances, particularly potentially toxic waste products, that gain entry to the tubule by filtration build up in the blood. In addition, the excretion of potassium is impaired because there are too few nephrons capable of normal tubular secretion of this ion. The person may also develop acidosis because the reduced number of nephrons fail to add enough new bicarbonate to the blood to compensate for the daily metabolic production of non-volatile acids.

The remarkable fact is how large the safety factor is in renal function. In general, the kidneys are still able to perform their regulatory function quite well as long as 10 percent of the nephrons are functioning. This is because these remaining nephrons undergo alterations in function—filtration, reabsorption, and secretion—so as to compensate for the missing nephrons. For example, each remaining nephron increases its rate of potassium secretion so that the total amount of potassium excreted by the kidneys can be maintained at normal levels. The limits of regulation are restricted, however. To use potassium as our example again, if someone with severe renal disease were to go on a diet high in potassium, the remaining nephrons might not be able to secrete enough potassium to prevent potassium retention.

Other problems arise in uremia because of abnormal secretion of the hormones produced by the kidneys. Thus, decreased secretion of erythropoietin results in anemia (Chapter 14). Decreased ability to form 1,25-(OH)2D3 results in deficient absorption of calcium from the gastrointestinal tract, with a resulting decrease in plasma calcium and inadequate bone calcification. Both of these hormones are now available for administration to patients with uremia.

The problem with renin, the third of the renal hormones, is rarely too little secretion but rather too much secretion by the juxtaglomerular cells of the damaged kidneys. The result is increased plasma angiotensin II concentration and the development of renal hypertension.

### Hemodialysis, Peritoneal Dialysis, and Transplantation

As described above, failing kidneys reach a point when they can no longer excrete water and ions at rates that maintain body balances of these substances, nor can they excrete waste products as fast as they are produced. Dietary alterations can minimize these problems, for example, by lowering potassium intake and thereby reducing the amount of potassium to be excreted, but such alterations cannot eliminate the problems. The techniques used to perform the kidneys’ excretory functions are hemodialysis and peritoneal dialysis. The general term “dialysis” means to separate substances using a membrane.

The artificial kidney is an apparatus that utilizes a process termed hemodialysis to remove excess substances from the blood. During hemodialysis, blood is pumped from one of the patient’s arteries through tubing that is surrounded by special dialysis fluid. The tubing then conducts the blood back into the patient by way of a vein. The tubing is generally made of cellophane that is highly permeable to most solutes but relatively impermeable to protein and completely impermeable to blood cells—characteristics quite similar to those of capillaries. The dialysis fluid is a salt solution with ionic concentrations similar to or lower than those in normal plasma, and it contains no creatinine, urea, or other substances to be completely removed from the plasma. As blood flows through the tubing, the concentrations of nonprotein plasma solutes tend to reach diffusion equilibrium with those of the solutes in the bath fluid. For example, if the plasma potassium concentration of the patient is above normal, potassium diffuses out of the blood across the cellophane tubing and into the dialysis fluid. Similarly, waste products and excesses of other substances also diffuse into the dialysis fluid and thus are eliminated from the body.

Patients with acute reversible renal failure may require hemodialysis for only days or weeks. Patients with chronic irreversible renal failure require treatment for the rest of their lives, however, unless they receive a renal transplant. Such patients undergo hemodialysis several times a week, often at home.

Another way of removing excess substances from the blood is peritoneal dialysis, which uses the lining of the patient’s own abdominal cavity (peritoneum) as a dialysis membrane. Fluid is injected, via a needle inserted through the abdominal wall, into this cavity and allowed to remain there for hours, during which solutes diffuse into the fluid from the person’s blood. The dialysis fluid is then removed by reinserting the needle and is replaced with new fluid. This procedure can be performed several times daily by a patient who is simultaneously doing normal activities.
The treatment of choice for most patients with permanent renal failure is kidney transplantation. Rejection of the transplanted kidney by the recipient’s body is a potential problem with transplants, but great strides have been made in reducing the frequency of rejection (Chapter 20). Many people who might benefit from a transplant, however, do not receive one. Presently, the major source of kidneys for transplanting is recently deceased persons, and improved public understanding should lead to many more individuals giving permission in advance to have their kidneys and other organs used following their death.

**Diuretics and Kidney Disease**

I. Diuretics inhibit reabsorption of sodium and water, thereby enhancing the excretion of these substances. Different diuretics act on different nephron segments.

II. Many of the symptoms of uremia—general renal malfunction—are due to retention of substances because of reduced GFR and, in the case of potassium and hydrogen ion, reduced secretion. Other symptoms are due to inadequate secretion of erythropoietin and 1,25-dihydroxyvitamin D₃, and too much secretion of renin.

III. Either hemodialysis or peritoneal dialysis can be used chronically to eliminate water, ions, and waste products retained during uremia.

**CHAPTER 16 CLINICAL TERMS**

- glucosuria
- familial renal glycosuria
- diabetes insipidus
- arrhythmias
- hypocalcemic tetany
- rickets
- osteomalacia
- osteoporosis
- bisphosphonates
- alkalosis
- acidosis
- respiratory acidosis
- respiratory alkalosis
- metabolic acidosis
- metabolic alkalosis
- diuretics
- potassium-sparing diuretics
- edema
- congestive heart failure
- uremia
- renal hypertension
- hemodialysis
- peritoneal dialysis

**CHAPTER 16 THOUGHT QUESTIONS**

(Asswers are in Appendix A.)

1. Substance T is present in the urine. Does this prove that it is filterable at the glomerulus?
2. Substance V is not normally present in the urine. Does this prove that it is neither filtered nor secreted?
3. The concentration of glucose in plasma is 100 mg/100 ml, and the GFR is 125 ml/min. How much glucose is filtered per minute?
4. A person is found to be excreting abnormally large amounts of a particular amino acid. Just from the theoretical description of $T_{\text{m}}$-limited reabsorptive mechanisms in the text, list several possible causes.
5. The concentration of urea in urine is always much higher than the concentration in plasma. Does this mean that urea is secreted?
6. If a drug that blocks the reabsorption of sodium is taken, what will happen to the reabsorption of water, urea, chloride, glucose, and amino acids and to the secretion of hydrogen ions?
7. Compare the changes in GFR and renin secretion occurring in response to a moderate hemorrhage in two individuals—one taking a drug that blocks the sympathetic nerves to the kidneys and the other not taking such a drug.
8. If a person is taking a drug that completely inhibits angiotensin converting enzyme, what will happen to aldosterone secretion when the person goes on a low-sodium diet?
9. In the steady state, is the amount of sodium chloride excreted daily in the urine by a normal person ingesting 12 g of sodium chloride per day: (a) 12 g/day or (b) less than 12 g/day? Explain.
10. A young woman who has suffered a head injury seems to have recovered but is thirsty all the time. What do you think might be the cause?
11. A patient has a tumor in the adrenal cortex that continuously secretes large amounts of aldosterone. What effects does this have on the total amount of sodium and potassium in her body?
12. A person is taking a drug that inhibits the tubular secretion of hydrogen ions. What effect does this drug have on the body’s balance of sodium, water, and hydrogen ion?