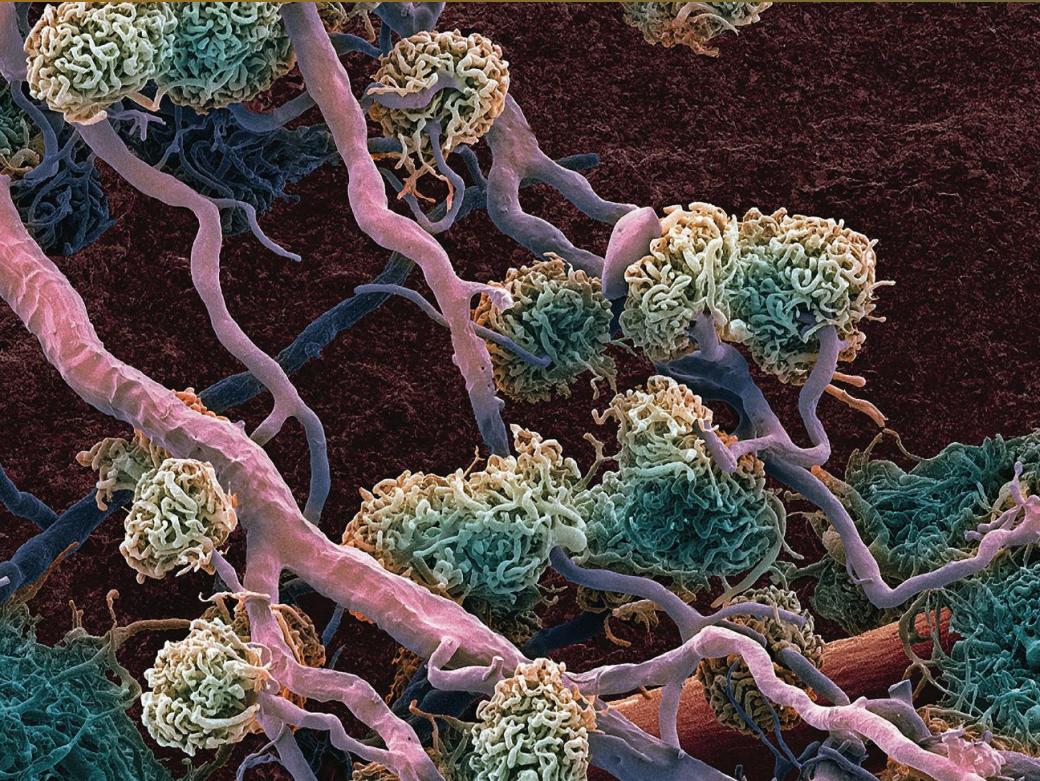


14

The Kidneys and Regulation of Water and Inorganic Ions



Glomeruli and associated blood vessels in the kidney (colorized scanning electron micrograph)

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Chapter 14 Clinical Case Study

Hemodialysis, Peritoneal Dialysis, and Transplantation

The importance of electrolyte concentrations in the function of excitable tissue was explained in reference to neurons (Chapter 6) and muscle (Chapter 9) and in the homeostasis of bone (Chapter 11). You have also learned about how the maintenance of hydration is important in cardiovascular function in Chapter 12. Finally, Chapter 13 highlighted the importance of the respiratory system in the short-term control of acid–base balance. We now deal with the regulation of body water volume and balance, and the inorganic ion composition of the internal environment. Furthermore, this chapter explains how the urinary system eliminates organic waste products of metabolism and, working with the respiratory system, is critical to the long-term control of acid–base balance. The urinary system in humans consists of all of the structures involved in removing soluble waste products from the blood and forming the urine; this includes the two kidneys, two ureters, the urinary bladder, and the urethra. The kidneys have the most important functions in these processes.

Regulation of the total-body balance of any substance can be studied in terms of the balance concept described in Chapter 1. Theoretically, a substance can appear in the body either as a result of ingestion or synthesized as a product of metabolism. On the loss side of the balance, a substance can be excreted from the body or can be broken down by metabolism. If the quantity of any substance in the body is to be maintained over a period of time, the total amounts ingested and produced must equal the total amounts excreted and broken down. Reflexes that alter 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. Typical values for the extracellular concentrations of these ions appeared in Table 4.1. We will first describe the general principles of kidney function, then apply this information to how the kidneys process specific substances like Na^+ , H_2O , H^+ , and K^+ and participate in reflexes that regulate these substances.

As you read about the structure, function, and control of the function of kidney, you will encounter numerous examples of the general principles of physiology that were outlined in Chapter 1. The regulation of the excretion of metabolic wastes, as well as the ability of the kidneys to reclaim needed ions and organic molecules that would otherwise be lost in the process, is a hallmark of the general principle of physiology that homeostasis is essential for health and survival; failure of kidney function not only causes a buildup of toxic waste products in the body but can also lead to a loss of important ions and nutrients (such as glucose and amino acids) in the urine. Another general principle of physiology—that most physiological functions are controlled by multiple regulatory systems, often working in opposition—is apparent in the renal system. An example is the control of the filtration rate of the kidney. The general principle of physiology that controlled exchange of materials occurs between compartments and across cellular membranes is also integral to this chapter—as already mentioned, total-body balance of important nutrients and ions is precisely controlled by the healthy kidneys. Finally, the functional unit of the kidney—the nephron—and the blood vessels associated with it are elegant examples of the general principle of physiology that structure is a determinant of—and has coevolved with—function; form and function are inextricably intertwined. ■

SECTION A

Basic Principles of Renal Physiology

14.1 Renal Functions

The adjective **renal** means “pertaining to the kidneys.” 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 14.1**.

First, the kidneys have a central function in regulating the water concentration, inorganic ion composition, acid–base balance, and the fluid 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 within a narrow range. For example, if you increase your consumption of NaCl (common known as table salt), your kidneys will increase the amount of the Na^+ and Cl^- excreted to match the intake. Alternatively, if there is not enough Na^+ and Cl^- in the body, the kidneys will reduce the excretion of these ions.

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 urinary excretion 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 (see Figure 3.49).

Finally, the kidneys act as endocrine glands, releasing at least two hormones: erythropoietin (described in Chapter 12), and 1,25-dihydroxyvitamin D (described in Chapter 11). The kidneys also secrete an enzyme, renin (pronounced “REE-nin”), that is important in the control of blood pressure and sodium balance (described later in this chapter).

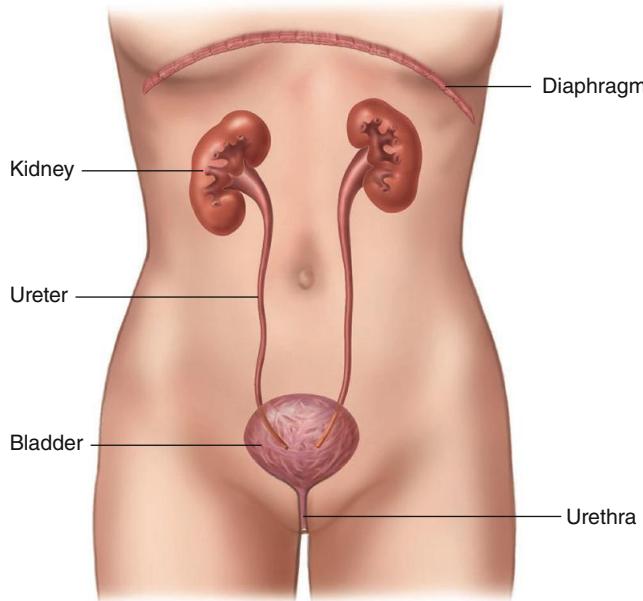
14.2 Structure of the Kidneys and Urinary System

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** and then is eliminated via the **urethra** (Figure 14.1). The major structural components of the kidney are shown in cross section in Figure 14.2. The indented surface of the kidney is called the

TABLE 14.1**Functions of the Kidneys**

I.	Regulation of water, inorganic ion balance, and acid–base balance (in cooperation with the lungs; Chapter 13)
II.	Removal of metabolic waste products from the blood and their excretion in the urine
III.	Removal of foreign chemicals from the blood and their excretion in the urine
IV.	Gluconeogenesis
V.	Production of hormones/enzymes: <ul style="list-style-type: none"> A. Erythropoietin, which controls erythrocyte production (Chapter 12) B. Renin, an enzyme that controls the formation of angiotensin, which influences blood pressure and sodium balance (this chapter) C. Conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which influences calcium balance (Chapter 11)

hilum, through which courses the blood vessels perfusing (**renal artery**) and draining (**renal vein**) the kidneys. The nerves that innervate the kidney and the tube that drains urine from the kidney (the ureter) also pass through the hilum. The ureter is formed from the **calyces** (singular, **calyx**), which are funnel-shaped structures that drain urine into the **renal pelvis**, from where the urine enters the ureter. Also notice that the kidney is surrounded by a protective capsule made of connective tissue. The kidney is divided into an outer **renal cortex** and inner **renal medulla**, described in more detail later. The connection between the tip of the medulla and the calyx is called the **papilla**.

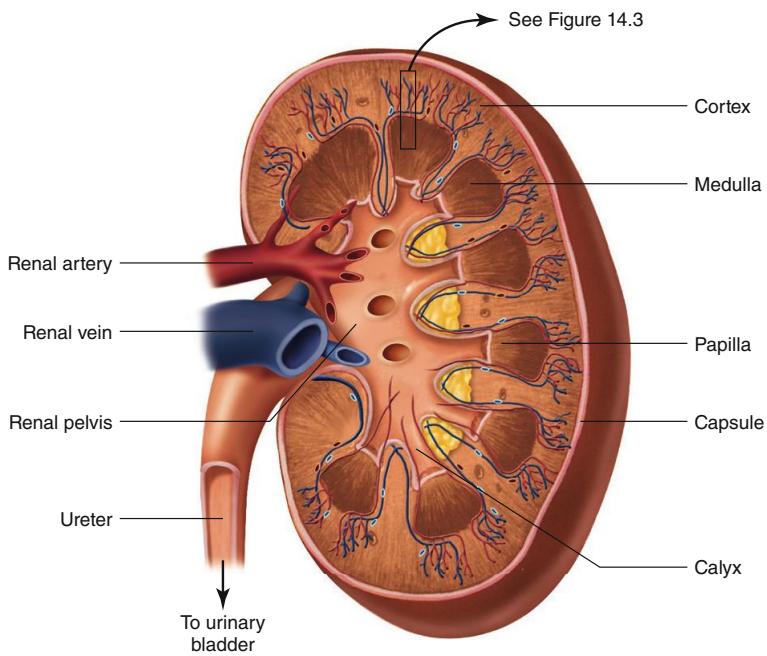


AP|R **Figure 14.1** Urinary system in a woman. In the male, the urethra passes through the penis (Chapter 17). The diaphragm is shown for orientation.

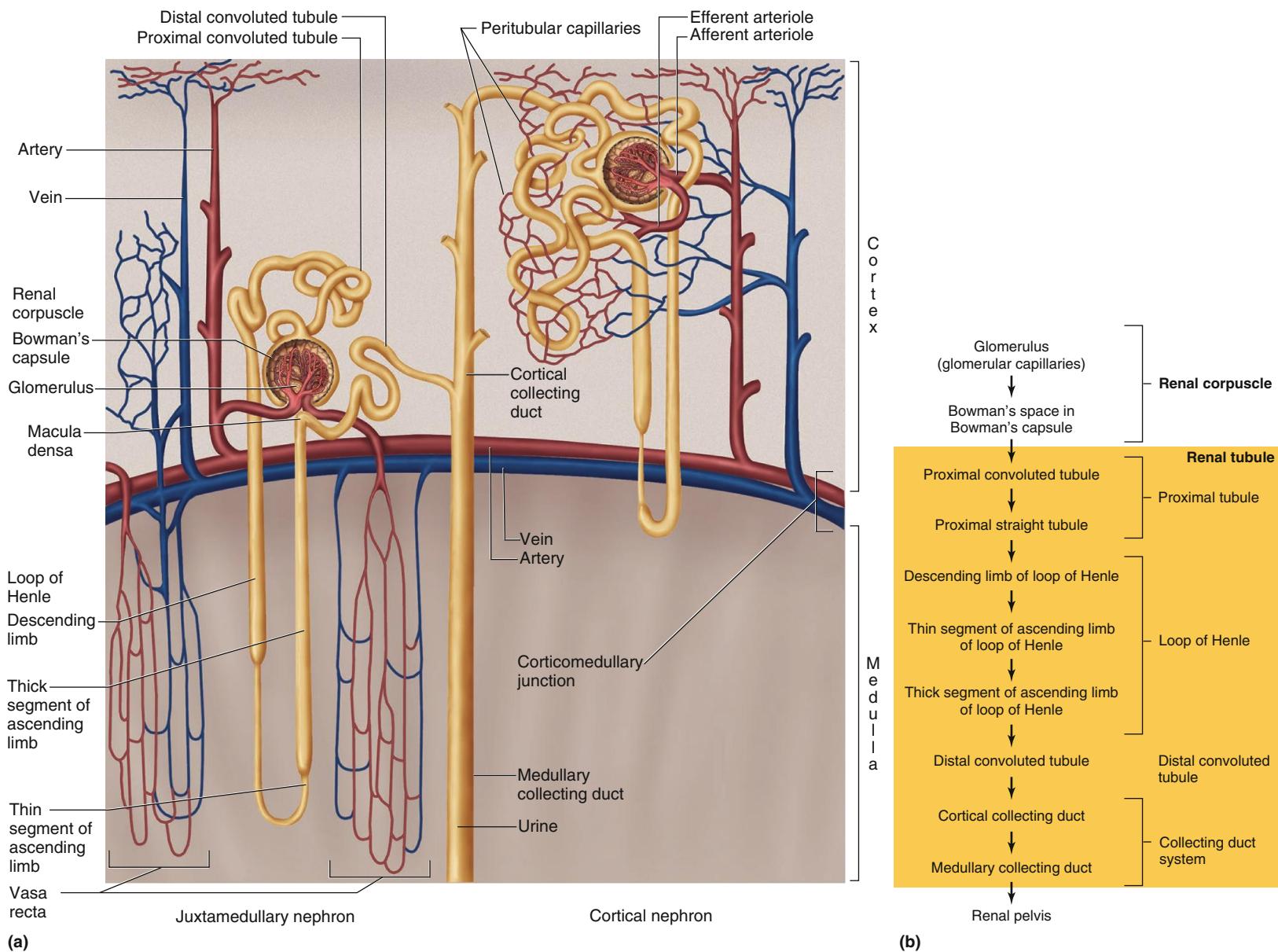
Each kidney contains approximately 1 million similar functional units called **nephrons**. Each nephron consists of (1) an initial filtering component called the **renal corpuscle** and (2) a **tubule** that extends from the renal corpuscle (Figure 14.3a). The renal tubule is a very narrow, fluid-filled 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 length of the tubule, and at least eight distinct segments are now recognized (Figure 14.3b). It is customary, however, to group two or more contiguous tubular segments when discussing function, and we will follow this practice.

The renal corpuscle forms a filtrate from blood that is free of cells, larger polypeptides, and proteins. This filtrate then leaves the renal corpuscle and enters the tubule. As it flows through the tubule, substances are added to or removed from it. Ultimately, the fluid remaining at the end of each nephron combines in the collecting ducts and exits the kidneys as urine.

Let us look first at the anatomy of the renal corpuscles—the filters. The renal corpuscle is a classic example of the general principle of physiology that structure is a determinant of function. Not only do the many capillaries in each corpuscle greatly increase the surface area for filtration of waste products from the plasma but their structure creates an efficient sieve for the ultrafiltration of plasma. Each renal corpuscle contains a compact tuft of interconnected capillary loops called the **glomerulus** (plural, *glomeruli*), or **glomerular capillaries** (Figure 14.3 and Figure 14.4a). 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, about 20% of the plasma filters into Bowman's capsule. The remaining blood then leaves the glomerulus by the **efferent arteriole**.



AP|R **Figure 14.2** Major structural components of the kidney. The outer kidney is the cortex; the inner kidney is the medulla. The renal artery enters, and the renal vein and ureter exit through the hilum (not labeled).

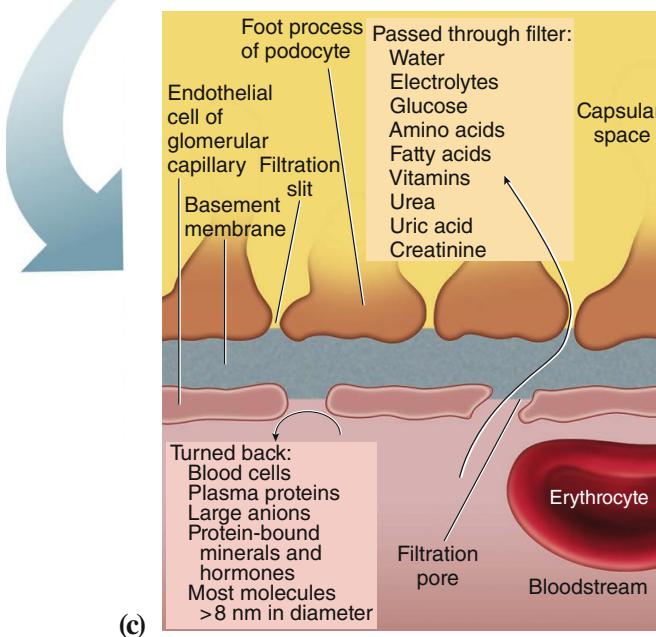
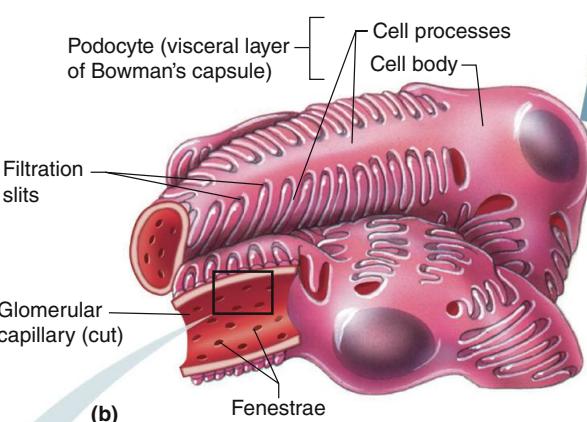
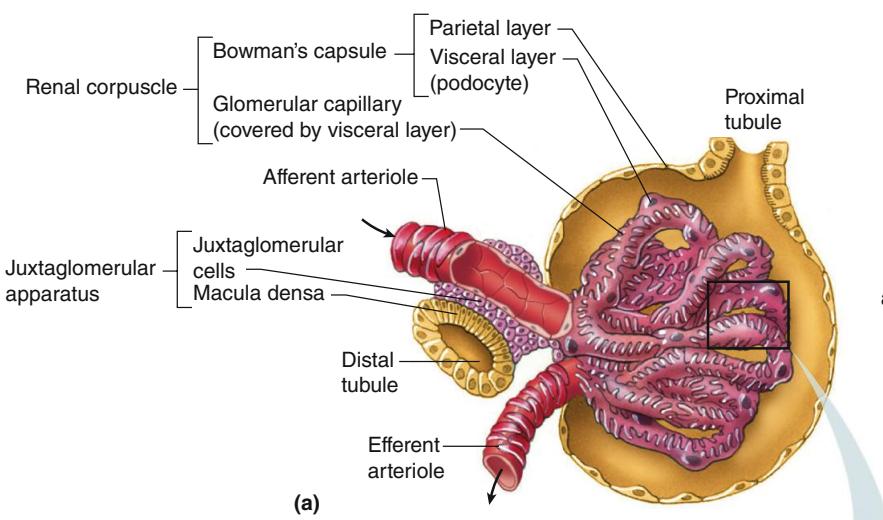


AP|R **Figure 14.3** Basic structure of a nephron and the collecting duct system. (a) Anatomical organization. The macula densa is not a distinct segment but a plaque of cells in the ascending loop of Henle where the loop passes between the arterioles supplying its renal corpuscle of origin. The cortex is where all of the renal corpuscles are located. In the medulla, the loops of Henle and collecting ducts run parallel to each other. The medullary collecting ducts drain into the renal pelvis. Two types of nephrons are shown—the juxtamedullary nephrons have long loops of Henle that penetrate deeply into the medulla, whereas the cortical nephrons have short (or no) loops of Henle. Note that the efferent arterioles of juxtamedullary nephrons give rise to long, looping capillaries called vasa recta, whereas efferent arterioles of cortical nephrons give rise to peritubular capillaries. Not shown (for clarity) are the peritubular capillaries surrounding the portions of the juxtamedullary nephron's tubules located in the cortex. These peritubular capillaries arise primarily from other cortical nephrons. (b) Consecutive segments of the nephron. All segments in the yellow area are parts of the renal tubule; the terms to the right of the brackets are commonly used for several consecutive segments.

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 called the **Bowman's space** exists within the capsule. Protein-free fluid filters from the glomerulus into this space.

Blood in the glomerulus is separated from the fluid in Bowman's space by a filtration barrier consisting of three layers (**Figure 14.4b,c**). These include (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, and (3) the single-celled epithelial lining of Bowman's capsule. The epithelial cells in this region, called **podocytes**, are quite different from the simple flattened cells that line the rest of Bowman's capsule (the part of the “fist” not in contact with the “balloon”). 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.



a. Blood flows into the glomerulus through the afferent arterioles and leaves the glomerulus through the efferent arterioles. The proximal tubule exits Bowman's capsule.

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

c. Substances in the blood are filtered through capillary pores between endothelial cells (single layer). The filtrate then passes across the basement membrane and through filtration slit between the foot processes (also called pedicels) and enters the capsular space. From here, the filtrate is transported to the lumen of the proximal convoluted tubule.

AP|R **Figure 14.4** The renal corpuscle. (a) Anatomy of the renal corpuscle. (b) Inset view of podocytes and capillaries. (c) Glomerular filtration membrane.

PHYSIOLOGICAL INQUIRY

- What would happen if a significant number of glomerular capillaries were clogged, as can happen in someone with very high blood glucose concentrations for a long period of time (as can occur in untreated diabetes mellitus)?

Answer can be found at end of chapter.

In addition to the capillary endothelial cells and the podocytes, **mesangial cells**—a third cell type—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 segment of the tubule that drains Bowman's capsule is the **proximal tubule**, comprising the proximal convoluted tubule and the proximal straight tubule shown in Figure 14.3b. The next portion of the tubule is the **loop of Henle**, which is a sharp, hairpinlike 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**, which is comprised of the **cortical collecting duct** and then the **medullary collecting duct**. The reasons for the terms *cortical* and *medullary* will be apparent shortly.

From Bowman's capsule to the start of 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 urine drains into the kidney's central cavity, the renal pelvis, via several hundred large medullary collecting ducts. The renal pelvis is continuous with the ureter draining into the bladder from that kidney (see Figure 14.2).

There are important regional differences in the kidney (see Figures 14.2 and 14.3). The outer portion is the renal cortex, and the inner portion is 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, the part of each tubule in the cortex is surrounded by capillaries called the **peritubular capillaries**. Note that we have now mentioned two sets of capillaries in the 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 Figure 14.3 and Figure 14.4a). 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 to form the veins by which blood leaves the kidney.

There are two types of nephrons (see Figure 14.3a). About 15% of the nephrons are **juxtamedullary**, which means that the renal corpuscle lies in the part of the cortex closest to the cortical-medullary junction. The Henle's loops of these nephrons plunge deep into the medulla and, as we will see, are responsible for generating an osmotic gradient in the medulla responsible for the reabsorption of water. In close proximity to the juxtamedullary nephrons are long capillaries known as the **vasa recta**, which also loop deeply into the medulla and then return to the cortical-medullary junction. The majority of nephrons are **cortical**, meaning their renal corpuscles are located in the outer cortex and their Henle's loops do not penetrate deep into the medulla. In fact, some cortical nephrons do not have a Henle's loop at all; they are involved in reabsorption and secretion but do not contribute to the hypertonic medullary interstitium described later in the chapter.

One additional anatomical detail involving both the tubule and the arterioles is important. 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 14.3). At this point, there is a patch of cells in the wall of the ascending limb as it becomes the distal convoluted tubule 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)** (see Figure 14.4a and [Figure 14.5](#)). As described later, the JGA has important functions in the regulation of ion and water balance, and the production of factors that control blood pressure.

14.3 Basic Renal Processes

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 larger proteins, contains all the substances in virtually the same concentrations as in plasma. This type of filtrate, in which only low-molecular weight solutes appear, is also called 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 14.6](#)). When the direction of movement is from tubular lumen to peritubular capillary plasma, the process is called **tubular reabsorption** or, simply, reabsorption. 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 or both. Once in the tubule, however, the substance does not have to be excreted but can be partially or completely 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.

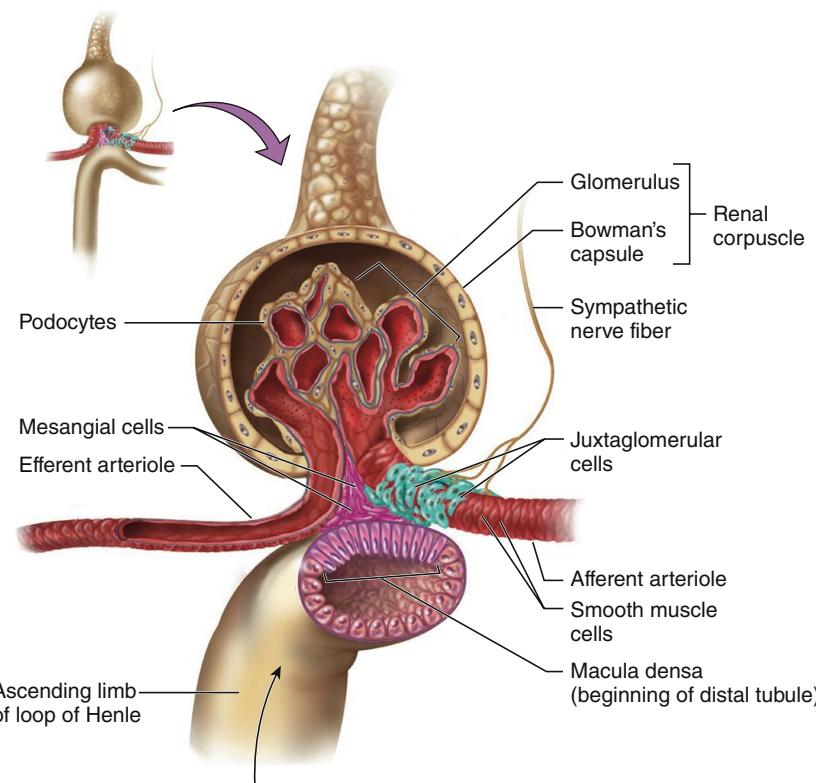
$$\text{Amount excreted} = \frac{\text{Amount filtered}}{\text{Amount secreted}} - \frac{\text{Amount reabsorbed}}{\text{Amount secreted}}$$

It is important to stress that not all these processes—filtration, secretion, and reabsorption—apply to all substances. For example, important solutes like glucose are completely reabsorbed, whereas most toxins are secreted and not reabsorbed.

To emphasize the general principles of renal function, [Figure 14.7](#) illustrates the renal handling of three hypothetical substances that might be found in blood. Approximately 20% 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 to flow through the rest of the tubule. Simultaneously, the remaining 80% of the plasma, containing X, Y, and Z, leaves the glomerular capillaries via the efferent arteriole and enters the peritubular capillaries.

Assume that the tubule can secrete 100% of the peritubular capillary substance X into the tubular lumen but cannot reabsorb X. Therefore, by the combination of filtration and tubular secretion, the plasma that originally entered the renal artery is cleared of all of its substance X, which leaves the body via the urine. Logically, this tends to be the pattern for renal handling of foreign substances that are potentially harmful to the body.

By contrast, assume that the tubule can reabsorb but not secrete Y and Z. The amount of Y reabsorption is moderate so that some of the filtered material is not reabsorbed and escapes from the body. For Z, however, the reabsorptive mechanism is so powerful



AP|R **Figure 14.5** The juxtaglomerular apparatus.

that all the filtered Z is reabsorbed 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. Again, it is logical to assume that substance Y is important to retain but requires maintenance within a homeostatic range; substance Z is presumably very important for health and is therefore completely reabsorbed.

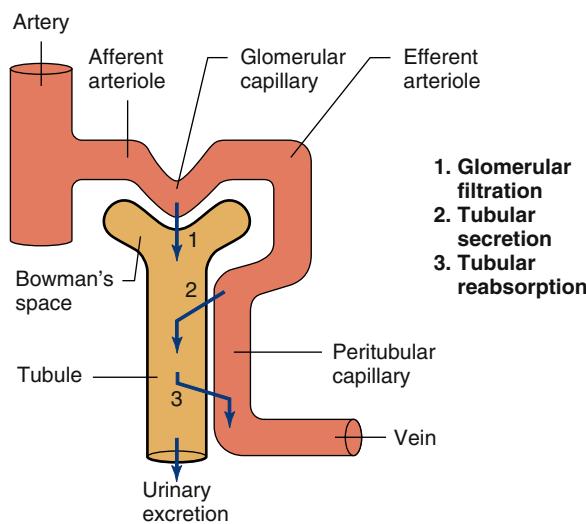
A specific combination of filtration, tubular reabsorption, and tubular secretion applies to each substance in the plasma. The

critical point is that, for many substances, the rates at which the processes proceed are subject to physiological control. By triggering changes in the rates of filtration, reabsorption, or secretion whenever the amount of a substance in the body is higher or lower than the normal limits, homeostatic mechanisms can regulate the substance's bodily balance. For example, consider what happens when a normally hydrated person drinks more water than usual. Within 1 to 2 hours, 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 the effector organs of a homeostatic process that maintains total-body water within very narrow limits.

Although glomerular filtration, tubular reabsorption, and tubular secretion are the three basic renal processes, a fourth process—metabolism by the tubular cells—is also important 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 either to the blood or tubular fluid; the most important of these, as we will see, are NH_4^+ (ammonium ion), H^+ , and HCO_3^- .

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

1. To what degree is the substance filtered at the renal corpuscle?
2. Is the substance reabsorbed?
3. Is the substance secreted?
4. What factors regulate the quantities filtered, reabsorbed, or secreted?
5. What are the pathways for altering renal excretion of the substance to maintain stable body balance?

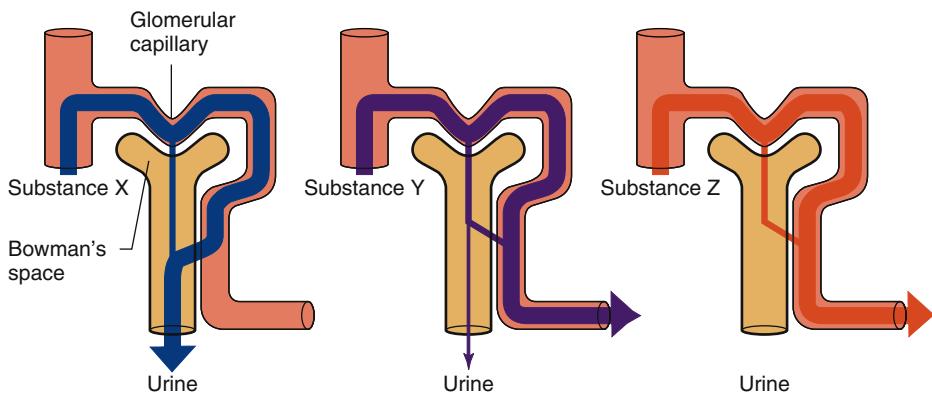


AP|R **Figure 14.6** The three basic components of renal function. This figure is to illustrate only the *directions* of reabsorption and secretion, not specific sites or order of occurrence. Depending on the particular substance, reabsorption and secretion can occur at various sites along the tubule.

Glomerular Filtration

As stated previously, the glomerular filtrate—that is, the fluid in Bowman's space—normally contains 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 (including smaller polypeptides) move together. Most plasma proteins—the albumins and globulins—are excluded from the filtrate in a healthy kidney. 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 corpuscular membranes are negatively charged, so they oppose the movement of these plasma proteins, most of which are also negatively charged.

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 not filtered. For example, the half of the plasma calcium bound to plasma proteins and virtually all of the plasma fatty acids that are bound to plasma protein are not filtered.



AP|R **Figure 14.7** Renal handling of three hypothetical filtered substances X, Y, and Z. X is filtered and secreted but not reabsorbed. Y is filtered, and a fraction is then reabsorbed. Z is filtered and completely reabsorbed. The thickness of each line in this hypothetical example suggests the magnitude of the process.

Forces Involved in Filtration Once again we return to the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics; the importance of physical forces is critical to understanding the fundamental processes of homeostasis. As was discussed in Chapter 12, filtration across capillaries is determined by opposing Starling forces. To review, Starling forces are (1) the hydrostatic pressure difference across the capillary wall that favors filtration and (2) the protein concentration difference across the wall that creates an osmotic force that opposes filtration (see Figure 12.45).

This also applies to the glomerular capillaries, as summarized in **Figure 14.8**. The blood pressure 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 (π_{GC}) that results from the presence of protein in the glomerular capillary plasma. Recall that there is usually no protein in the filtrate in Bowman's space because of the unique structure of the areas of filtration in the glomerulus, so the osmotic force in Bowman's space (π_{BS}) is zero. 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 osmosis from Bowman's space into the glomerular capillaries—that is, it opposes glomerular filtration.

Note that, in Figure 14.8, the value given for this osmotic force—29 mmHg—is slightly higher than the value—28 mmHg—for the osmotic force given in Chapter 12 for plasma in all arteries and nonrenal capillaries. The reason is that, unlike the situation elsewhere in the body, enough water filters out of the glomerular capillaries that the protein left behind in the plasma becomes slightly more concentrated than in arterial plasma. In other capillaries, in contrast, little water filters out and 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, therefore, the osmotic force increase from the beginning to the end of the glomerular capillaries. The value given in Figure 14.8 for the osmotic force is the average value along the length of the capillaries.

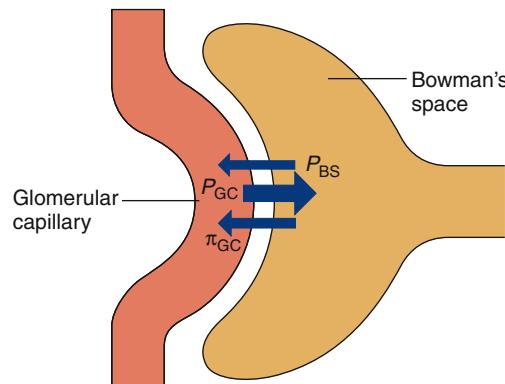
To summarize, the **net glomerular filtration pressure** is the sum of three relevant forces:

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

Normally, the net filtration pressure is positive because the glomerular capillary hydrostatic pressure (P_{GC}) is larger than the

sum of the hydrostatic pressure in Bowman's space (P_{BS}) and the osmotic force opposing filtration (π_{GC}). The net glomerular filtration pressure initiates urine formation by forcing an essentially protein-free filtrate of plasma out of the glomerulus and into Bowman's space and then down the tubule into the renal pelvis.

Rate of Glomerular Filtration The volume of fluid filtered from the glomeruli into Bowman's space per unit time is known as the **glomerular filtration rate (GFR)**. GFR is



Forces	mmHg
Favoring filtration:	
Glomerular capillary blood pressure (P_{GC})	60
Opposing filtration:	
Fluid pressure in Bowman's space (P_{BS})	15
Osmotic force due to protein in plasma (π_{GC})	29
Net glomerular filtration pressure = $P_{GC} - P_{BS} - \pi_{GC}$	16

AP|R **Figure 14.8** Forces involved in glomerular filtration. The symbol π denotes the osmotic force due to the presence of protein in glomerular capillary plasma. (Note: The concentration of protein in Bowman's space is so low that π_{BS} , a force that would favor filtration, is considered zero.)

PHYSIOLOGICAL INQUIRY

- What would be the effect of an increase in plasma albumin (the most abundant plasma protein) on glomerular filtration rate (GFR)?

Answer can be found at end of chapter.

determined not only by the net filtration pressure but also by the permeability of the corpuscular membranes and the surface area available for filtration. In other words, at any given net filtration pressure, the GFR will be directly proportional to the membrane permeability and the surface area. The glomerular capillaries are much more permeable to fluid than most other capillaries. Therefore, the net glomerular filtration pressure causes massive filtration of fluid into Bowman's space. In a 70 kg person, the GFR averages 180 L/day (125 mL/min)! This is much higher than the combined net filtration of 4 L/day of fluid across all the other capillaries in the body, as described in Chapter 12.

When we recall that the total volume of plasma in the circulatory system is approximately 3 L, it follows that the kidneys filter the entire plasma volume about 60 times a day. This opportunity to process such huge volumes of plasma enables the kidneys to rapidly regulate the constituents of the internal environment and to excrete large quantities of waste products.

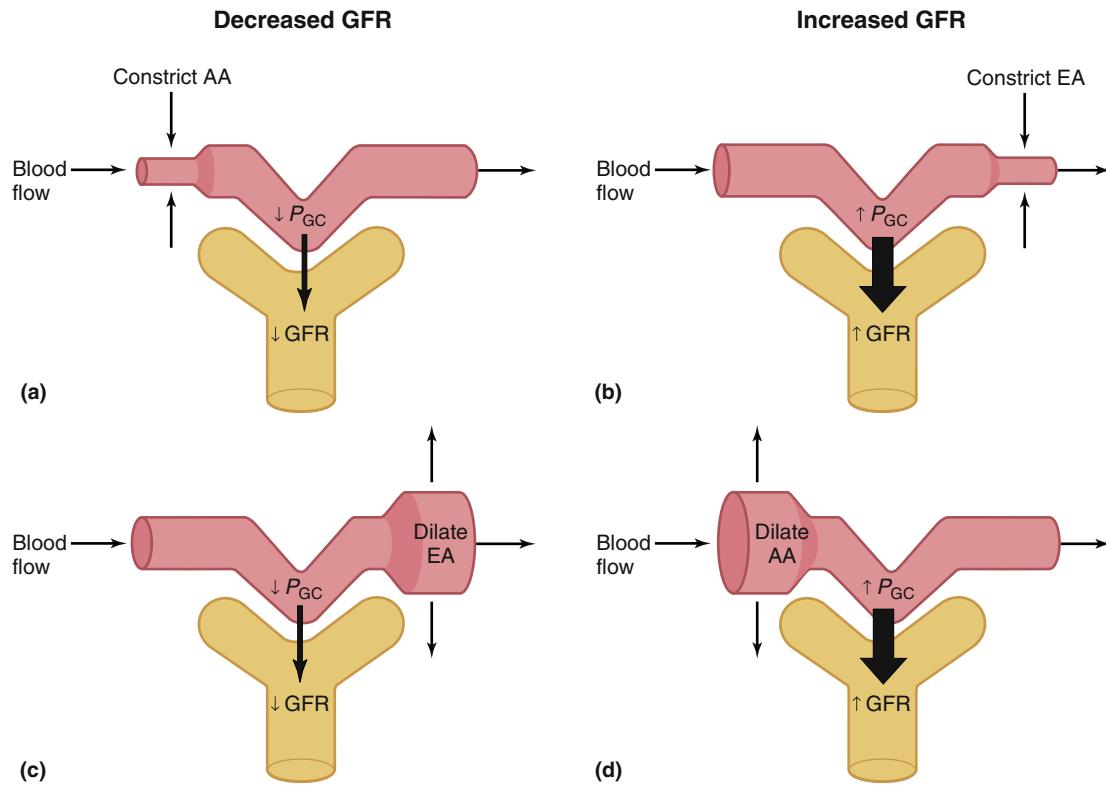
GFR is not a fixed value but is subject to physiological regulation. This is achieved mainly by neural and hormonal input to the afferent and efferent arterioles, which causes changes in net glomerular filtration pressure (**Figure 14.9**). The glomerular capillaries are unique in that they are situated between two sets of arterioles—the afferent and efferent arterioles. Constriction of the afferent arterioles decreases hydrostatic pressure in the glomerular

capillaries (P_{GC}). This is similar to arteriolar constriction in other organs and is due to a greater loss of pressure between arteries and capillaries (**Figure 14.9a**).

In contrast, efferent arteriolar constriction alone has the opposite effect on P_{GC} in that it *increases* it (**Figure 14.9b**). 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, increasing P_{GC} . Dilation of the efferent arteriole (**Figure 14.9c**) decreases P_{GC} and thus GFR, whereas dilation of the afferent arteriole increases P_{GC} and thus GFR (**Figure 14.9d**). Finally, simultaneous constriction or dilation of both sets of arterioles tends to leave P_{GC} unchanged because of the opposing effects. The control of GFR is an example of the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition.

In addition to the neural and endocrine input to the arterioles, there is also neural and humoral input to the mesangial cells that surround the glomerular capillaries. Contraction of these cells decreases 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 or non-protein-bound substance filtered into Bowman's space by multiplying the GFR by the plasma concentration of



AP|R **Figure 14.9** Control of GFR by constriction or dilation of afferent arterioles (AA) or efferent arterioles (EA). (a) Constriction of the afferent arteriole or (c) dilation of the efferent arteriole reduces P_{GC} , thus decreasing GFR. (b) Constriction of the efferent arteriole or (d) dilation of the afferent arteriole increases P_{GC} , thus increasing GFR.

PHYSIOLOGICAL INQUIRY

- Describe the immediate consequences of a blood clot occluding the afferent arteriole or the efferent arteriole.

Answer can be found at end of chapter.

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 $180 \text{ L/day} \times 1 \text{ g/L} = 180 \text{ g/day}$.

Once the filtered load of the substance is known, it can be compared to the amount of the substance excreted. This indicates 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 14.2 summarizes data for a few plasma components that undergo filtration and reabsorption. It gives an idea of the magnitude and importance of reabsorptive mechanisms. The values in this table are typical for a healthy person on an average diet. There are at least three important conclusions we can draw from this table: (1) The filtered loads are enormous, generally larger than the total 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 180 L. (2) Reabsorption of waste products is relatively incomplete (as 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, such as water, inorganic ions, and organic nutrients, is relatively complete so that the amounts excreted in the urine are very small fractions of their filtered loads.

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, such as glucose, are always very high and are not physiologically regulated. Therefore, the filtered loads of these substances are completely reabsorbed in a healthy kidney, with none appearing in the urine. For these substances, like substance Z in Figure 14.7, it is as though the kidneys do not exist because 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. Rather, the kidneys merely maintain whatever plasma concentrations already exist.

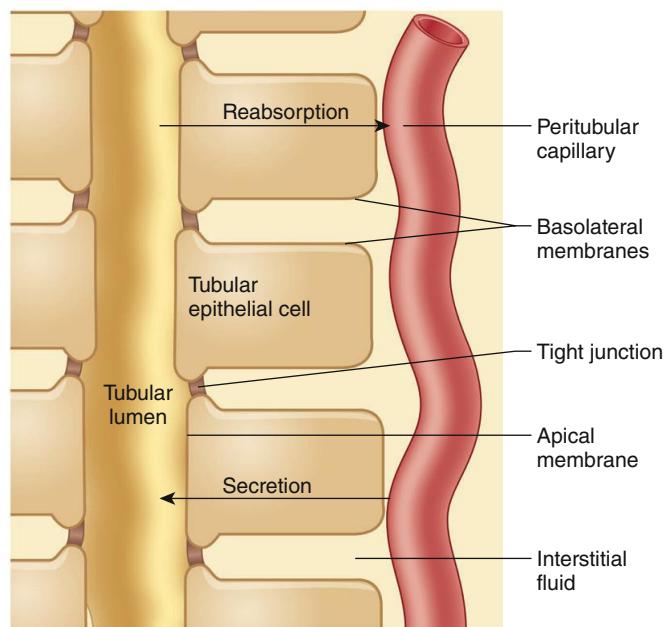
Recall that a major function of the kidneys is to eliminate soluble waste products. To do this, the blood is filtered in the glomeruli. One consequence of this is that substances necessary for normal body functions are filtered from the plasma into the tubular fluid. To prevent the loss of these important nonwaste products, the kidneys have powerful mechanisms to reclaim useful substances from tubular fluid while simultaneously allowing

waste products to be excreted. The reabsorptive rates for water and many ions, although also very high, are under physiological control. For example, if water intake is decreased, the kidneys can increase water reabsorption to minimize water loss.

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 because there are inadequate pressure differences across the tubule and limited permeability of the tubular membranes. Instead, two other processes are involved. (1) The reabsorption of some substances from the tubular lumen is by diffusion, often across the tight junctions connecting the tubular epithelial cells (**Figure 14.10**). (2) The reabsorption of all other substances involves mediated transport, which requires the participation of transport proteins in the plasma membranes of tubular cells.

The final step in reabsorption is the movement of substances from the interstitial fluid into peritubular capillaries that occurs by a combination of diffusion and bulk flow. We will assume that this final process occurs automatically once the substance reaches the interstitial fluid.

Reabsorption by Diffusion The reabsorption of urea by the proximal tubule provides an example of passive reabsorption by diffusion. An analysis of urea concentrations in the proximal tubule will help clarify the mechanism. As stated earlier, urea is a waste product; however, as you will learn shortly, some urea is reabsorbed from the proximal tubule in a process that facilitates water reabsorption farther down the nephron. Because the corporeal 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



AP|R **Figure 14.10** Diagrammatic representation of tubular epithelium. The apical membrane is also called the luminal membrane. **Reabsorption** is defined as the movement of a substance from the fluid in the tubular lumen or material produced within the epithelial cell into the peritubular capillary. This can occur through the cell or across tight junctions. **Secretion** is defined as the movement of a substance from the blood or produced within the epithelial cell into the fluid within the tubular lumen.

Average Values for Several Components That Undergo Filtration and Reabsorption			
Substance	Amount Filtered per Day	Amount Excreted per Day	Percentage Reabsorbed
Water, L	180	1.8	99
Sodium, g	630	3.2	99.5
Glucose, g	180	0	100
Urea, g	54	30	44

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 so it is higher than 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 Mediated Transport Many solutes are reabsorbed by primary or secondary active transport. These substances must first cross the **apical membrane** (also called the *luminal membrane*) that separates the tubular lumen from the cell interior. Then, the substance diffuses through the cytosol of the cell and, finally, crosses the **basolateral membrane**, which begins at the tight junctions and constitutes the plasma membrane of the sides and base of the cell. The movement by this route is termed *transcellular epithelial transport*.

A substance does not need to be actively transported across *both* the apical and basolateral membranes in order to be actively transported across the overall epithelium, moving from lumen to interstitial fluid against its electrochemical gradient. For example, Na^+ moves “downhill” (passively) into the cell across the apical membrane through specific channels or transporters and then is actively transported “uphill” out of the cell across the basolateral membrane via Na^+/K^+ -ATPases in this membrane.

The reabsorption of many substances is coupled to the reabsorption of Na^+ . The cotransported substance moves uphill into the cell via a secondary active cotransporter as Na^+ moves downhill into the cell via this same cotransporter. 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 Na^+ .

Many of the mediated-transport-reabsorptive systems in the renal tubule have a limit to the amounts of material they can transport per unit time known as the **transport maximum (T_m)**. This is because the binding sites on the membrane transport proteins become saturated when the concentration of the transported substance increases to a certain level. An important example is the secondary active-transport proteins for glucose, located in the proximal tubule. As noted earlier, glucose does not usually appear in the urine because all of the filtered glucose is reabsorbed. This is illustrated in **Figure 14.11**, which shows the relationship between plasma glucose concentrations and the filtered load, reabsorption, and excretion of glucose. Plasma glucose concentration in a healthy person normally does not exceed 150 mg/100 mL even after the person eats a sugary meal. Notice that this concentration of plasma glucose is below the threshold at which glucose starts to appear in urine (**glucosuria**). Also notice that the T_m is reached at a glucose concentration that is higher than the threshold for glucosuria. This is because the nephrons have a range of T_m values that, when averaged, give a T_m for the entire kidney, as shown in Figure 14.11. When plasma glucose concentration exceeds the transport maximum for a significant number of nephrons, glucose starts to appear in urine. In people with significant hyperglycemia (for example, in poorly controlled **diabetes mellitus**), the plasma glucose concentration often exceeds the threshold value of 200 mg/100 mL, so that the filtered load exceeds the ability of the nephrons to reabsorb glucose. In

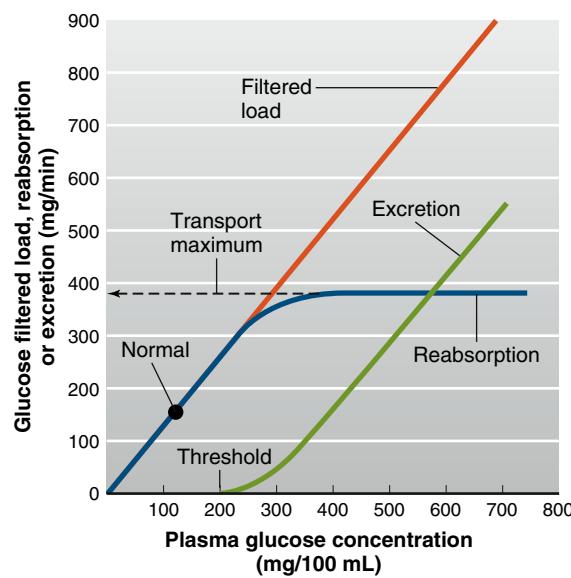


Figure 14.11 The relationship between plasma glucose concentration and the rate of glucose filtered (filtered load), reabsorbed, or excreted. The dotted line shows the transport maximum, which is the maximum rate at which glucose can be reabsorbed. Notice that as plasma glucose exceeds its threshold, glucose begins to appear in the urine.

PHYSIOLOGICAL INQUIRY

- How would you calculate the filtered load and excretion rate of glucose?

Answer can be found at end of chapter.

other words, although the capacity of the kidneys to reabsorb glucose can be normal in diabetes mellitus, the tubules cannot reabsorb the large increase in the filtered load of glucose. As you will learn later in this chapter and in Chapter 16, the high filtered load of glucose can also lead to significant disruption of normal renal function (**diabetic nephropathy**).

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 of 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, people who ingest very large quantities of vitamin C have increased plasma concentrations of vitamin C. Eventually, the filtered load may exceed the tubular reabsorptive 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 from the blood into the tubule. Like reabsorption, secretion can occur by diffusion or by transcellular mediated transport. The most important substances secreted by the tubules are H^+

and K^+ . However, 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 tubule cell (across the basolateral membrane) or out of the cell into the lumen (across the apical membrane). As in reabsorption, tubular secretion is usually coupled to the reabsorption of Na^+ . Secretion from the interstitial space into the tubular fluid, which draws substances from the peritubular capillaries, is a mechanism to increase the ability of the kidneys to dispose of substances at a higher rate rather than depending only on the filtered load.

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 catabolize certain organic substances, such as peptides, taken up from either the tubular lumen or peritubular capillaries. Catabolism eliminates these substances from the body just as if they had been excreted into the urine.

Regulation of Membrane Channels and Transporters

Tubular reabsorption or secretion of many substances is under physiological control. For most of these substances, control is achieved by regulating the activity or concentrations of the membrane channel and transporter proteins involved in their transport. This regulation is achieved by hormones and paracrine or autocrine factors.

Understanding the structure, function, and regulation of renal, tubular-cell ion channels and transporters makes 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 cotransporter that mediates reabsorption of glucose in the proximal tubule. This can lead to the appearance of glucose in the urine (*familial renal glucosuria*). Contrast this condition to diabetes mellitus, in which the ability to reabsorb glucose is usually normal but the filtered load of glucose exceeds the threshold for the tubules to reabsorb glucose (see Figure 14.11).

“Division of Labor” in the Tubules

To excrete waste products adequately, the GFR must be very large. This means that the filtered volume of water and the filtered loads of all the nonwaste plasma solutes are also very large. *The primary role of the proximal tubule is to reabsorb most of this filtered water and these solutes.* Furthermore, with K^+ as the one major exception, the proximal tubule is 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 distal segments then do the fine-tuning for most low-molecular weight 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 homeostatic controls act upon the more distal segments of the tubule.

14.4 The Concept of Renal Clearance

A useful way of quantifying renal function 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 unit of time. The basic clearance formula for any substance S is

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

Therefore, the clearance of a substance is a measure of the volume of plasma completely cleared of the substance per unit time. This accounts for the mass of the substance excreted in the urine.

Because 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 examine some particularly interesting examples of clearance. What would be the clearance of glucose, for example, under normal conditions? Recall from Figure 14.11 that all of the glucose filtered from the plasma into Bowman’s space is normally reabsorbed by the epithelial cells of the proximal tubules. Therefore, the clearance of glucose (C_{gl}) can be written as the following equation:

$$C_{gl} = \frac{(U_{gl})(V)}{(P_{gl})}$$

where the subscript “gl” indicates glucose. Because glucose is usually completely reabsorbed, its urinary concentration (U_{gl}) under normal conditions is zero (see Table 14.2). Therefore, this equation reduces to

$$C_{gl} = \frac{(0)(V)}{(P_{gl})} \text{ or } C_{gl} = 0$$

The clearance of glucose is normally zero because all of the glucose that is filtered from the plasma into the glomeruli is reabsorbed back into the blood. As shown in Figure 14.11, only when the T_m for glucose is exceeded (and $U_{gl} > 0$) would the clearance become a positive value, which, as described earlier, would suggest the possibility of renal disease or very high blood glucose such as in untreated diabetes mellitus.

Now imagine a substance that is freely filtered but neither reabsorbed nor secreted. In other words, such a substance is not physiologically important like glucose—nor toxic like certain compounds that are secreted—and is, therefore, “ignored” by the renal tubular cells. The human body does not produce such compounds that perfectly fit these characteristics, but there are examples found in nature. One such compound is the polysaccharide called **inulin** (not insulin), which is present in some of the vegetables and fruits that we eat. If inulin were infused intravenously in a person, what would happen? The amount of inulin entering the nephrons from the

plasma—that is, the filtered load—would be equal to the amount of inulin excreted in the urine, and none of it would be reabsorbed or secreted. Recall that the filtered load of a substance is the glomerular filtration rate (GFR) multiplied by the plasma concentration of the substance. The excreted amount of the substance is UV , as just described. Therefore, for the special case of inulin (subscript “in”),

$$(GFR)(P_{\text{in}}) = (U_{\text{in}})(V)$$

By rearranging this equation, we get an equation that looks like the general equation for clearance shown earlier:

$$GFR = \frac{(U_{\text{in}})(V)}{(P_{\text{in}})}$$

In other words, the GFR of a person is equal to the clearance of inulin (UV/P)! If it were necessary to determine the GFR of a person, for example, someone suspected of having kidney disease, a physician would only need to determine the clearance of inulin. **Figure 14.12** shows a mathematical example of the renal handling of inulin. Notice that the GFR is 7.5 L/h, which is 125 mL/min, as described earlier in this section.

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 perfectly meet these criteria, and for technical reasons it is not practical to perform an inulin clearance test in clinical situations. For clinical purposes, the **creatinine clearance** (C_{Cr}) is commonly used to approximate the GFR as follows. Creatinine is a waste product released by muscle cells; it is filtered at the renal corpuscle but does not undergo reabsorption. It does undergo a small amount of secretion, however, so that some peritubular plasma is cleared of its creatinine by secretion. Therefore, C_{Cr} slightly overestimates the GFR but is close enough to be highly useful in most clinical situations. Usually, the concentration of creatinine in the blood is the only measurement necessary because it is assumed that creatinine production by the body is constant and similar between individuals. Therefore, an increase in creatinine concentration in the blood usually indicates a decrease in GFR, one of the hallmarks of kidney disease.

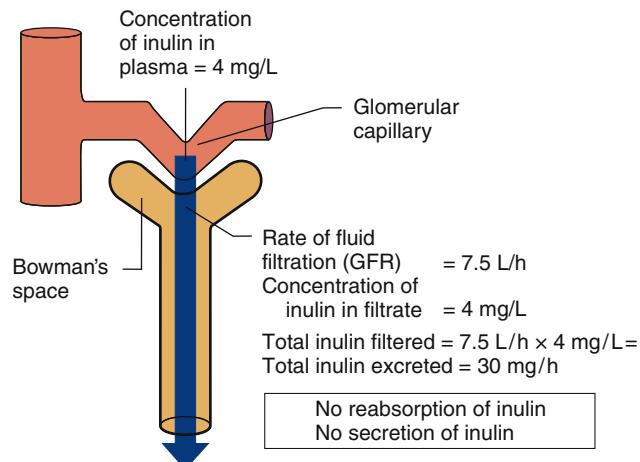


Figure 14.12 Example of renal handling of inulin, a substance that is filtered by the renal corpuscles but is neither reabsorbed nor secreted by the tubule. Therefore, the mass of inulin excreted per unit time is equal to the mass filtered during the same time period. As explained in the text, the clearance of inulin is equal to the glomerular filtration rate.

This leads to an important generalization. When the clearance of any substance is greater than the GFR, that substance must undergo tubular secretion. Look back at our hypothetical substance X (see Figure 14.7): X is filtered, and all the X that escapes filtration is secreted; no X is reabsorbed. Consequently, all the plasma that enters the kidney per unit time is cleared of its X. Therefore, the clearance of X is a measure of **renal plasma flow**. A substance that is handled like X is the organic anion paraaminohippurate (PAH), which is used for this purpose experimentally. (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, that substance must undergo some reabsorption. Performing calculations such as these provides important information about the way in which the kidneys handle a given solute. Suppose a newly developed drug is being tested for its safety and effectiveness. The dose of drug required to achieve a safe and therapeutic effect will depend at least in part on how rapidly it is cleared by the kidneys. Assume that we measure the clearance of the drug and find that it is greater than the GFR as determined by creatinine clearance. This means that the drug is secreted into the nephron tubules and a higher dose of drug than otherwise predicted may be needed to reach an optimal concentration in the blood.

14.5 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 balloonlike 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 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.

The neural controls that influence bladder structures during the phases of filling and micturition are shown in **Figure 14.13**. While the bladder is filling, the parasympathetic input to the detrusor muscle is minimal, and, as a result, the muscle is relaxed. Because of the arrangement of the smooth muscle fibers, when the detrusor muscle is relaxed, the internal urethral sphincter is passively closed. Additionally, there is 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 both the internal and external sphincters are closed during the filling phase.

What happens during micturition? As the bladder fills with urine, the pressure within it increases, which stimulates stretch receptors in the bladder wall. The afferent neurons from these receptors enter the spinal cord and stimulate the parasympathetic neurons, which then cause the detrusor muscle to contract. When the detrusor muscle contracts, the change in shape of the bladder pulls open the internal urethral sphincter. Simultaneously, the afferent input from the stretch receptors reflexively inhibits the sympathetic neurons to the internal urethral sphincter, which further contributes to its opening. In addition, the afferent input also reflexively inhibits the somatic motor neurons to the external urethral

Muscle	Innervation		
	Type	During filling	During micturition
Detrusor (smooth muscle)	Parasympathetic (causes contraction)	Inhibited	Stimulated
Internal urethral sphincter (smooth muscle)	Sympathetic (causes contraction)	Stimulated	Inhibited
External urethral sphincter (skeletal muscle)	Somatic motor (causes contraction)	Stimulated	Inhibited

AP|R **Figure 14.13** Control of the bladder.

sphincter, causing it to relax. Both sphincters are now open, and the contraction of the detrusor muscle can 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 the ability to voluntarily control micturition. 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. Complex interactions in different areas in the brain control micturition. Briefly, there are areas in the brainstem that can both facilitate and inhibit voiding. Furthermore, an area of the midbrain can inhibit voiding, and an area of the posterior hypothalamus can facilitate voiding. Finally, strong inhibitory input from the cerebral cortex, learned during toilet training in early childhood, prevents involuntary urination.

Incontinence

Incontinence is the involuntary release of urine, which can be a disturbing problem both socially and hygienically. The most common types are **stress incontinence** (due to sneezing, coughing, or exercise) and **urge incontinence** (associated with the desire to urinate). Incontinence is more common in women and may occur one to two times per week in more than 25% of women older than 60. It is very common in older women in nursing homes and assisted-living facilities. In women, stress incontinence is usually due to a loss of urethral support provided by the anterior vagina (see Figure 17.17a). Medications (such as estrogen-replacement therapy to improve vaginal tone) can often relieve stress incontinence. Severe cases may require surgery to improve vaginal support of the bladder and urethra. The cause of urge incontinence is often unknown in individual patients. However, any irritation to the bladder or urethra (e.g., with a bacterial infection) can cause urge incontinence. Urge incontinence can be treated with drugs

such as tolterodine or oxybutynin, which antagonize the effects of the parasympathetic nerves on the detrusor muscle. Because these drugs are anticholinergic, they can have side effects such as blurred vision, constipation, and increased heart rate.

SECTION A SUMMARY

Renal Functions

- I. The kidneys regulate the water and ionic composition of the body, excrete waste products, excrete foreign chemicals, produce glucose during prolonged fasting, and release factors and hormones into the blood (renin, 1,25-dihydroxyvitamin D, and erythropoietin). The first three functions are accomplished by continuous processing of the plasma.

Structure of the Kidneys and Urinary System

- I. 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 that the tuft protrudes into.
 - b. The tubule extends from Bowman's capsule and is subdivided 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 by mediated transport.
- Substances to which the tubular epithelium is permeable are reabsorbed by diffusion because water reabsorption creates tubule-interstitium-concentration gradients for them.
 - Active reabsorption of a substance requires the participation of transporters in the apical or basolateral membrane.
 - Tubular reabsorption rates are very high for nutrients, ions, and water, but they are lower for waste products.
 - Many of the mediated-transport systems exhibit transport maximums. 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 the entrance of a substance into the tubule.

The Concept of Renal Clearance

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

Micturition

- In the basic micturition reflex, bladder distension 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.
- 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.
- Incontinence is the involuntary release of urine that occurs most commonly in elderly people (particularly women).

SECTION A REVIEW QUESTIONS

- What are the functions of the kidneys?
- What three hormones/factors do the kidneys secrete into the blood?
- 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?
- What are the three basic renal processes that lead to the formation of urine?
- How does the composition of the glomerular filtrate compare with that of plasma?
- Describe the forces that determine the magnitude of the GFR. What is a normal value of GFR?
- Contrast the mechanisms of reabsorption for glucose and urea. Which one shows a T_m ?
- Diagram the sequence of events leading to micturition.

SECTION B

Regulation of Ion and Water Balance

14.6 Total-Body Balance of Sodium and Water

Chapter 1 explained that water composes about 55% to 60% of the normal body weight, and that water is distributed throughout different compartments of the body (Figure 1.3). Since water is of such obvious importance to homeostasis, the regulation of total-body-water

SECTION A KEY TERMS

14.1 Renal Functions

creatinine	urea
renal	uric acid

14.2 Structure of the Kidneys and Urinary System

afferent arteriole	macula densa
ascending limb	medullary collecting duct
bladder	mesangial cells
Bowman's capsule	nephrons
Bowman's space	papilla
calyx (calyces)	peritubular capillaries
collecting-duct system	podocytes
cortical collecting duct	proximal tubule
cortical	renal artery
descending limb (of Henle's loop)	renal corpuscle
distal convoluted tubule	renal cortex
efferent arteriole	renal medulla
glomerular capillaries	renal pelvis
glomerulus	renal vein
juxtaglomerular apparatus (JGA)	tubule
juxtaglomerular (JG) cells	ureters
juxtamedullary	urethra
loop of Henle	vasa recta

14.3 Basic Renal Processes

apical membrane	glomerular filtration rate (GFR)
basolateral membrane	net glomerular filtration pressure
filtered load	transport maximum (T_m)
glomerular filtrate	tubular reabsorption
glomerular filtration	tubular secretion

14.4 The Concept of Renal Clearance

clearance	inulin
creatinine clearance (C_{Cr})	renal plasma flow

14.5 Micturition

detrusor muscle	internal urethral sphincter
external urethral sphincter	micturition

SECTION A CLINICAL TERMS

14.3 Basic Renal Processes

diabetes mellitus	familial renal glucosuria
diabetic nephropathy	glucosuria

14.5 Micturition

incontinence	urge incontinence
stress incontinence	

balance is critical to survival. This highlights two important general principles of physiology: (1) Homeostasis is essential for health and survival; and (2) controlled exchange of materials—in this case, water—occurs between compartments and across cellular membranes. **Table 14.3** summarizes total-body-water balance. These are average values that are subject to considerable normal variation. There are two sources of body water gain: (1) water produced from

TABLE 14.3

Average Daily Water Gain and Loss in Adults

<i>Intake</i>	
In liquids	1400 mL
In food	1100 mL
Metabolically produced	<u>350 mL</u>
Total	2850 mL
<i>Output</i>	
Insensible loss (skin and lungs)	900 mL
Sweat	50 mL
In feces	100 mL
Urine	<u>1800 mL</u>
Total	2850 mL

the oxidation of organic nutrients, and (2) water ingested in liquids and food (a rare steak is approximately 70% water). Four sites lose water to the external environment: skin, respiratory airways, gastrointestinal 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 the 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 it can be significant with diarrhea and vomiting.

Table 14.4 is a summary of total-body balance for sodium chloride. The excretion of Na^+ and Cl^- via the skin and gastrointestinal tract is normally small but increases markedly during severe sweating, vomiting, or diarrhea. Hemorrhage can also result in the loss of large quantities of both NaCl and water.

Under normal conditions, as Tables 14.3 and 14.4 show, NaCl and water losses equal NaCl and water gains, and no net change in body NaCl and water occurs. This matching of losses and gains is primarily the result of the 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 drinking too much water. The average daily sodium consumption in the US is 3.4 g/day (8.5 gm of sodium chloride shown in Table 14.4), but can be much higher. Current Institute of Medicine guidelines recommend 2.3 g of sodium per day, which is approximately 5.8 g (1 teaspoon) of NaCl (table salt). Healthy kidneys can readily alter the excretion of NaCl over a wide range to balance loss with gain.

TABLE 14.4

Daily Sodium Chloride Intake and Output

<i>Intake</i>	
Food	8.50 g
<i>Output</i>	
Sweat	0.25 g
Feces	0.25 g
Urine	<u>8.00 g</u>
Total	8.50 g

14.7 Basic Renal Processes for Sodium and Water

Both Na^+ and water freely filter from the glomerular capillaries into Bowman's space because they have low molecular weights and circulate in the plasma in the free form (unbound to protein). They both undergo considerable reabsorption—normally more than 99% (see Table 14.2)—but no secretion. Most renal energy utilization is used in this enormous reabsorptive task. The bulk of Na^+ and water reabsorption (about two-thirds) occurs in the proximal tubule, but the major hormonal control of reabsorption is exerted on the distal convoluted tubules and collecting ducts.

The mechanisms of Na^+ and water reabsorption can be summarized in two generalizations: (1) Na^+ 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 osmosis (passive) and is dependent upon Na^+ reabsorption.

Primary Active Na^+ Reabsorption

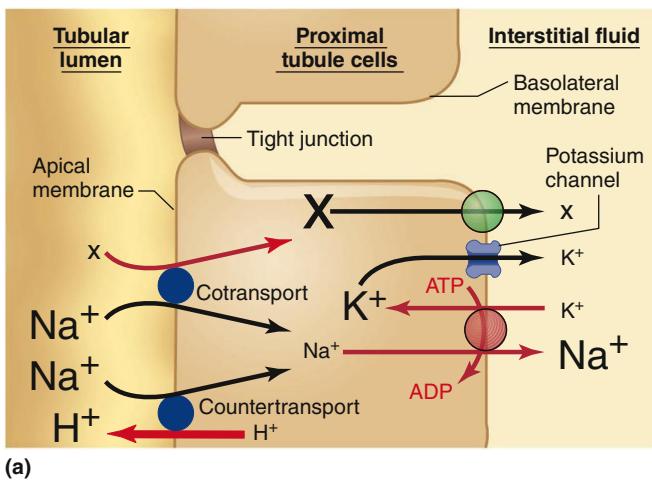
The essential feature underlying Na^+ reabsorption throughout the tubule is the primary active transport of Na^+ out of the cells and into the interstitial fluid, as illustrated for the proximal tubule and cortical collecting duct in **Figure 14.14**. This transport is achieved by Na^+/K^+ -ATPase pumps in the basolateral membrane of the cells. The active transport of Na^+ out of the cell keeps the intracellular concentration of Na^+ low compared to the tubular lumen, so Na^+ moves “downhill” out of the tubular lumen into the tubular epithelial cells.

The mechanism of the downhill Na^+ movement across the apical membrane into the cell varies from segment to segment of the tubule depending on which channels and/or transport proteins are present in their apical membranes. For example, the apical entry step in the proximal tubule cell occurs by cotransport with a variety of organic molecules, such as glucose, or by countertransport with H^+ . In the latter case, H^+ moves out of the cell to the lumen as Na^+ moves into the cell (**Figure 14.14a**). Therefore, in the proximal tubule, Na^+ reabsorption drives the reabsorption of the cotransported substances and the secretion of H^+ . In actuality, the apical membrane of the proximal tubular cell has a brush border composed of numerous microvilli (for clarity, not shown in Figure 14.14a). This greatly increases the surface area for reabsorption. The apical entry step for Na^+ in the cortical collecting duct occurs primarily by diffusion through Na^+ channels (**Figure 14.14b**).

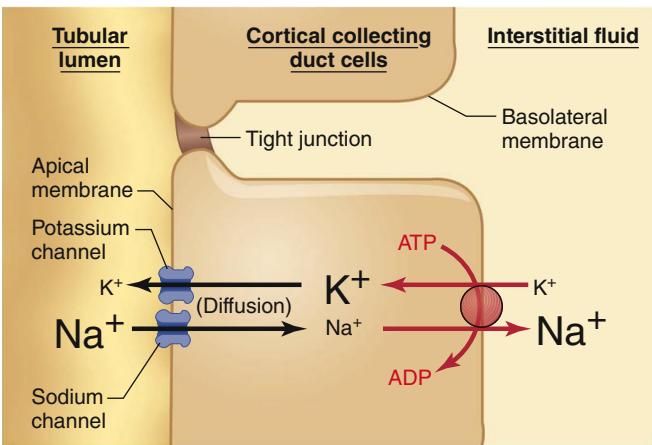
The movement of Na^+ downhill from lumen into cell across the *apical membrane* varies from one segment of the tubule to another. By contrast, the *basolateral membrane* step is the same in all Na^+ -reabsorbing tubular segments—the primary active transport of Na^+ out of the cell is via Na^+/K^+ -ATPase pumps in this membrane. It is this transport process that decreases intracellular Na^+ concentration and thereby makes the downhill apical entry step possible.

Coupling of Water Reabsorption to Na^+ Reabsorption

As Na^+ , Cl^- , and other ions are reabsorbed, water follows passively by osmosis (see Chapter 4). **Figure 14.15** summarizes this coupling of solute and water reabsorption. (1) Na^+ is transported from



(a)



(b)

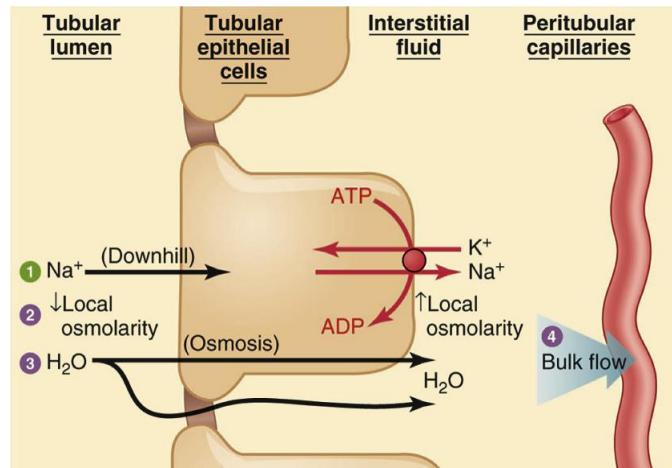
AP|R **Figure 14.14** Mechanism of Na^+ reabsorption in the (a) proximal tubule and (b) cortical collecting duct. (Figure 14.15 shows the movement of the reabsorbed Na^+ from the interstitial fluid into the peritubular capillaries.) The sizes of the letters denote high and low concentrations. “X” represents organic molecules such as glucose and amino acids that are cotransported with Na^+ . The fate of the K^+ that the Na^+/K^+ -ATPase pumps transport is discussed in the later section dealing with renal K^+ handling.

PHYSIOLOGICAL INQUIRY

- Referring to part (b), what would be the effect of a drug that blocks the Na^+ channels in the cortical collecting duct?

Answer can be found at end of chapter.

the tubular lumen to the interstitial fluid across the epithelial cells. Other solutes, such as glucose, amino acids, and HCO_3^- , whose reabsorption depends on Na^+ transport, also contribute to osmosis. (2) The removal of solutes from the tubular lumen decreases the local osmolarity of the tubular fluid adjacent to the cell (i.e., the local water concentration increases). At the same time, the appearance of solute in the interstitial fluid just outside the cell increases the local osmolarity (i.e., the local water concentration decreases). (3) The difference in water concentration between lumen and interstitial fluid causes net diffusion of water from the lumen across the tubular cells’ plasma membranes and/or tight junctions into the



AP|R **Figure 14.15** Coupling of water and Na^+ reabsorption.

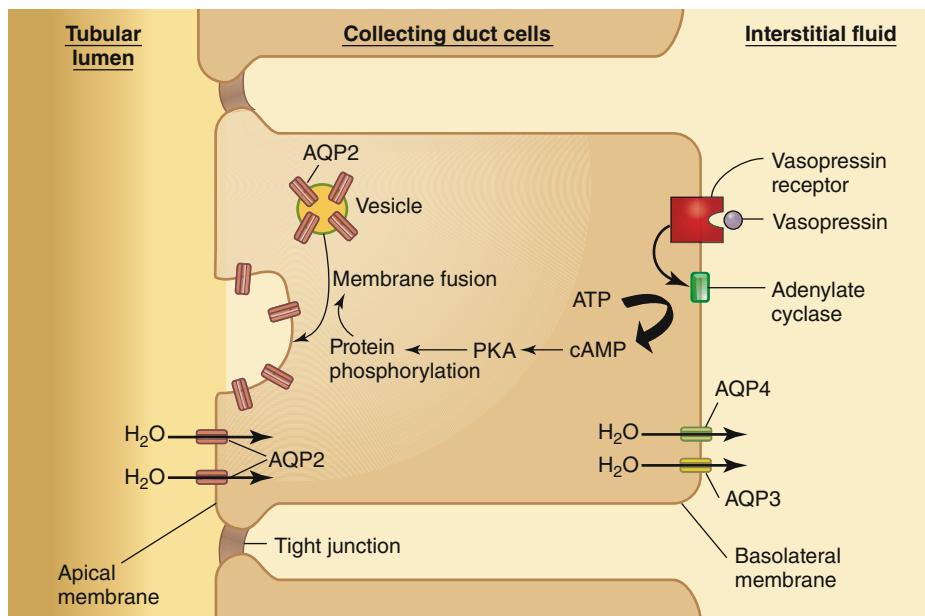
See text for explanation of circled numbers. The reabsorption of solutes other than Na^+ —for example, glucose, amino acids, and HCO_3^- —also contributes to the difference in osmolarity between lumen and interstitial fluid, but the reabsorption of all these substances ultimately depends on direct or indirect cotransport and countertransport with Na^+ (see Figure 14.14a). Therefore, they are not shown in this figure.

interstitial fluid. (4) From there, water, Na^+ , and everything else dissolved in the interstitial fluid move together by bulk flow into peritubular capillaries as the final step in reabsorption.

Water movement across the tubular epithelium can only occur if the epithelium is permeable to water. No matter how large its concentration gradient, water cannot cross an epithelium impermeable to it. Water permeability varies from tubular segment to segment and depends largely on the presence of water channels, called **aquaporins**, in the plasma membranes. The number of aquaporins in the membranes of the epithelial cells of the proximal tubules is always high, so this segment reabsorbs water molecules almost as rapidly as Na^+ . As a result, the proximal tubule reabsorbs large amounts of Na^+ 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 vary greatly due to physiological control. These are the only tubular segments in which water permeability is under such control.

The major determinant of this controlled permeability and, therefore, of passive water reabsorption in the collecting ducts is a peptide hormone secreted by the posterior pituitary gland and known as **vasopressin**, or **antidiuretic hormone (ADH)** (see Chapter 11). Vasopressin stimulates the insertion into the apical membrane of a particular aquaporin water channel made by the collecting-duct cells. More than 10 different aquaporins have been identified throughout the body, and they are identified as AQP1, AQP2, and so on. **Figure 14.16** shows the function of the aquaporin water channels in the cells of the collecting ducts. When vasopressin from the blood enters the interstitial fluid and binds to its receptor on the basolateral membrane, the intracellular production of the second-messenger cAMP is increased. This activates the enzyme cAMP-dependent protein kinase (also called protein kinase A, or PKA), which, in turn, phosphorylates proteins that increase the rate of fusion of vesicles containing AQP2 with the apical membrane. This leads to an increase in the number of



AP|R Figure 14.16 The regulation and function of aquaporins (AQPs) in the collecting-duct cells to increase water reabsorption. Vasopressin binding to its receptor increases intracellular cAMP via activation of a Gs protein (not shown) and subsequent activation of adenylate cyclase. cAMP increases the activity of the enzyme protein kinase A (PKA). PKA increases the phosphorylation of specific proteins that increase the rate of the fusion of vesicles (containing AQP2) with the apical membrane. This leads to an increase in the number of AQP2 channels in the apical membrane. This allows increased passive diffusion of water into the cell. Water exits the cell through AQP3 and AQP4, which are not vasopressin sensitive.

AQPs inserted into the apical membrane from vesicles in the cytosol. This allows an increase in the diffusion of water down its concentration gradient across the apical membrane into the cell. Water then diffuses through AQP3 and AQP4 water channels on the basolateral membrane into the interstitial fluid and then enters the blood. (The basolateral AQPs are constitutively active and are not regulated by vasopressin.) In the presence of a high plasma concentration of vasopressin, the water permeability of the collecting ducts increases dramatically. Therefore, passive water reabsorption is maximal and the final urine volume is small—less than 1% of the filtered water.

Without vasopressin, the water permeability of the collecting ducts is extremely low because the number of AQP2s in the apical membrane is minimal 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 control of vasopressin secretion.

The disease **diabetes insipidus**, which is distinct from the other kind of diabetes (diabetes mellitus, or “sugar diabetes”), illustrates the consequences of disorders of the control of or response to vasopressin. Diabetes insipidus is caused by the failure of the posterior pituitary gland to release vasopressin (**central diabetes insipidus**) or the inability of the kidneys to respond to vasopressin (**nephrogenic diabetes insipidus**). Regardless of the type of diabetes insipidus, the permeability to water of the collecting ducts is low even if the patient

is dehydrated. A constant water diuresis is present that can be as much as 25 L/day; in such extreme cases, it may not be possible to replenish the water that is lost due to the diuresis, and the disease may lead to death due to dehydration and very high plasma osmolarity.

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 Na^+ reabsorption causes both increased Na^+ excretion and increased water excretion, because, as we have seen, water reabsorption is dependent on solute reabsorption. Another example of osmotic diuresis occurs in people with uncontrolled diabetes mellitus; in this case, the glucose that escapes reabsorption because of the huge filtered load retains water in the lumen, causing it to be excreted along with the glucose.

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 necessarily accompanied by equivalent solute loss.

Urine Concentration: The Countercurrent Multiplier System

Before reading this section, you should review several terms presented in Chapter 4—**hyposmotic**, **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 the ability to survive with limited water intake. The human kidney can produce a maximal urinary concentration of 1400 mOsmol/L, almost five times the osmolarity of plasma, which is typically in the range of 285 to 300 mOsmol/L (rounded off to 300 mOsmol/L for convenience). 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 contributes to dehydration when water intake is very low.

Urinary concentration takes place as tubular fluid flows through the *medullary* collecting ducts. The interstitial fluid surrounding these ducts is very hyperosmotic. 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 involves several interrelated factors: (1) the countercurrent anatomy of the loop of Henle of juxtapamedullary nephrons, (2) reabsorption of NaCl in the ascending limbs of those loops of Henle, (3) impermeability to water of those ascending limbs, (4) trapping of urea in the medulla, and (5) hairpin loops of vasa recta to minimize washout of the hyperosmotic medulla. Recall that Henle's loop forms a hairpinlike loop between the proximal tubule and the distal convoluted tubule (see Figure 14.3). 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 are called countercurrent flows, and the entire loop functions as a **countercurrent multiplier system** to create a hyperosmotic medullary interstitial fluid.

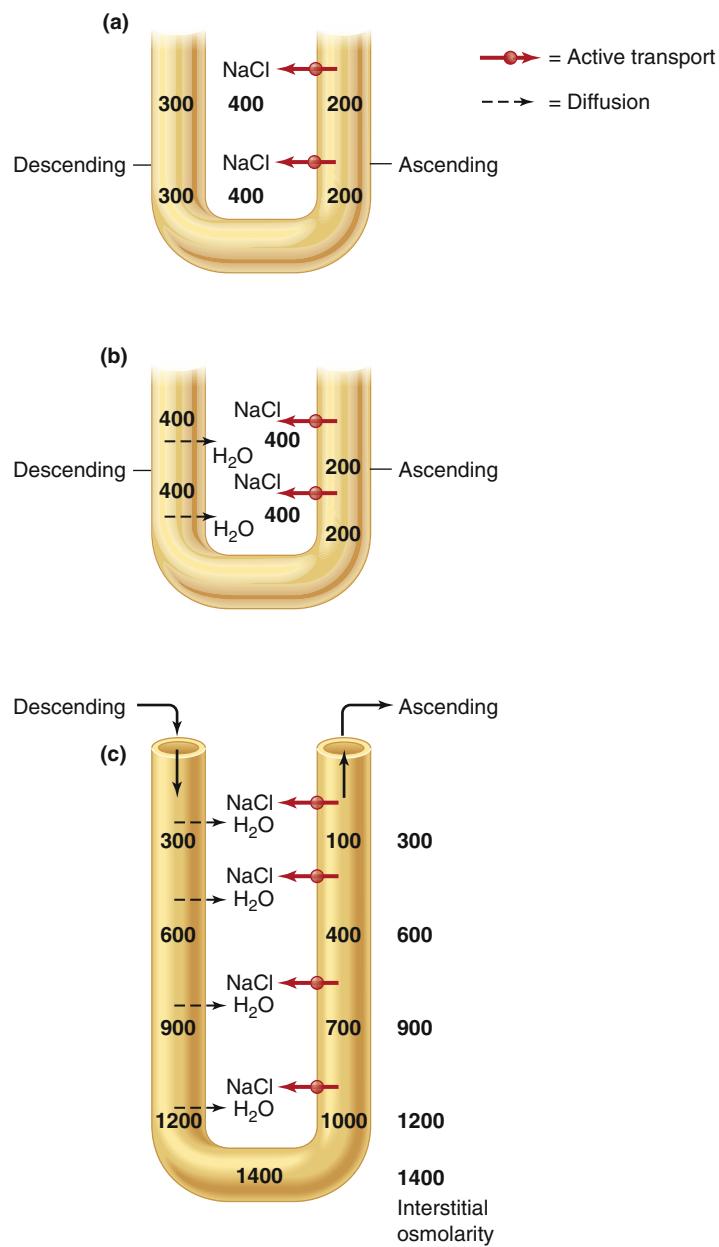
Because the proximal tubule always reabsorbs Na^+ and water in the same proportions, the fluid entering the descending limb of the loop from the proximal tubule has the same osmolarity as plasma—300 mOsmol/L. For the moment, let us skip the descending limb because the events in it can only be understood in the context of what the *ascending* limb is doing. Along the entire length of the ascending limb, Na^+ and Cl^- are reabsorbed from the lumen into the medullary interstitial fluid (Figure 14.17a). In the upper (thick) portion of the ascending limb, this reabsorption is achieved by transporters that actively cotransport Na^+ and Cl^- . Such transporters are not present in the lower (thin) portion of the ascending limb, so the reabsorption there is by simple diffusion. For simplicity in the explanation of the countercurrent multiplier, we shall treat the entire ascending limb as a homogeneous structure that actively reabsorbs Na^+ and Cl^- .

Very importantly, the *ascending limb is relatively impermeable to water*, so 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 because solute is reabsorbed without water.

We now return to the descending limb. This segment, in contrast to the ascending limb, does not reabsorb sodium chloride and is highly permeable to water (Figure 14.17b). Therefore, a net diffusion of water occurs out of the descending limb into the more concentrated interstitial fluid until the osmolalities 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.

Therefore, because of the diffusion of water, the osmolalities 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.

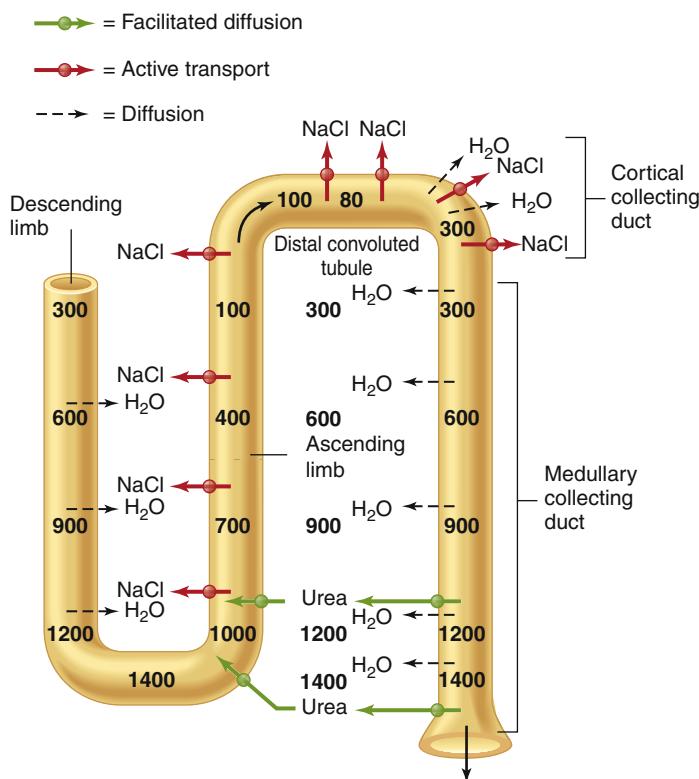
So far, we have been analyzing this system as though the flow through the loop of Henle stops while the ion pumping and water diffusion are occurring. Now, let us see what happens when we allow flow through the entire length of the descending and ascending limbs of the loop of Henle (Figure 14.17c).



AP|R **Figure 14.17** Generating a hyperosmolar medullary renal interstitium. (a) NaCl active transport in ascending limbs (impermeable to H_2O). (b) Passive reabsorption of H_2O in descending limb. (c) Multiplication of osmolarity occurs with fluid flow through the tubular lumen.

The osmolarity difference—200 mOsmol/L—that exists at each horizontal level is “multiplied” as the fluid goes deeper into the medulla. By the time the fluid reaches the bend in the loop, the osmolarity of the tubular fluid and interstitium has been multiplied to a very high osmolarity that can be as high as 1400 mOsmol/L. Keep in mind that the active Na^+ and Cl^- 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 on loop and medullary interstitial osmolarity, which would simply remain 300 mOsmol/L throughout.

Now we have a concentrated medullary interstitial fluid, but we must still follow the fluid within the tubules from the loop of



AP|R **Figure 14.18** Simplified depiction of the generation of an interstitial fluid osmolarity gradient by the renal countercurrent multiplier system and its role in the formation of hyperosmotic urine in the presence of vasopressin. Notice that the hyperosmotic medulla depends on NaCl reabsorption and urea trapping (described in Figure 14.20).

PHYSIOLOGICAL INQUIRY

- Certain types of lung tumors secrete one or more hormones. What would happen to plasma and urine osmolarity and urine volume in a patient with a lung tumor that secretes vasopressin?

Answer can be found at end of chapter.

Henle through the distal convoluted tubule and into the collecting-duct system, using **Figure 14.18** as our guide. Furthermore, urea reabsorption and trapping (described in detail later) contribute to the maximal medullary interstitial osmolarity. The countercurrent multiplier system concentrates the descending-loop fluid but then decreases the osmolarity in the ascending loop so that the fluid entering the distal convoluted tubule is actually more dilute (hypoosmotic)—100 mOsm/L in Figure 14.18—than the plasma. The fluid becomes even more dilute during its passage through the distal convoluted tubule because this tubular segment, like the ascending loop, actively transports Na^+ and Cl^- out of the tubule but is relatively impermeable to water. This hypoosmotic fluid then enters the cortical collecting duct. Because of the significant volume reabsorption, the flow of fluid at the end of the ascending limb is much less than the flow that entered the descending limb.

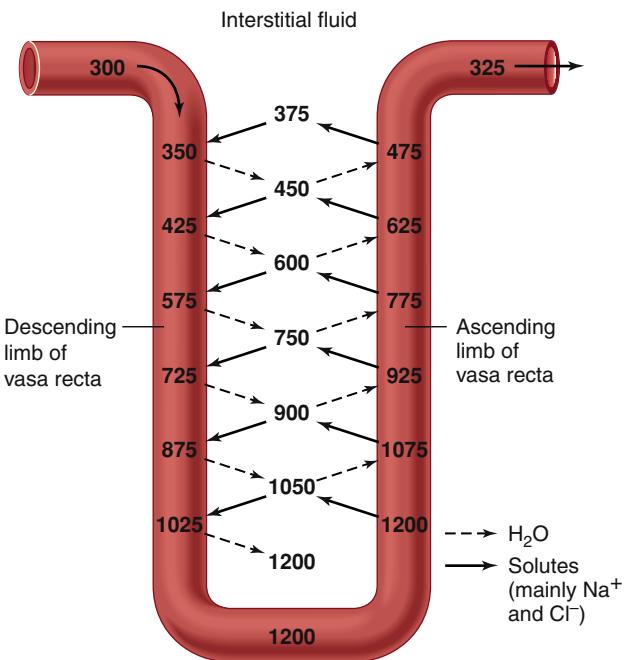
As noted earlier, vasopressin increases tubular permeability to water in both the cortical and medullary collecting ducts. In contrast, vasopressin does not directly influence water reabsorption

in the parts of the tubule prior to the collecting ducts. Therefore, regardless of the plasma concentration of this hormone, the fluid entering the cortical collecting duct is hypoosmotic. From there on, however, vasopressin is crucial. In the presence of high concentrations 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 the interstitial fluid and peritubular plasma of the cortex—that is, until it is once again at 300 mOsm/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 that the loop counter-current multiplier system and urea trapping establish there. 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, 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.

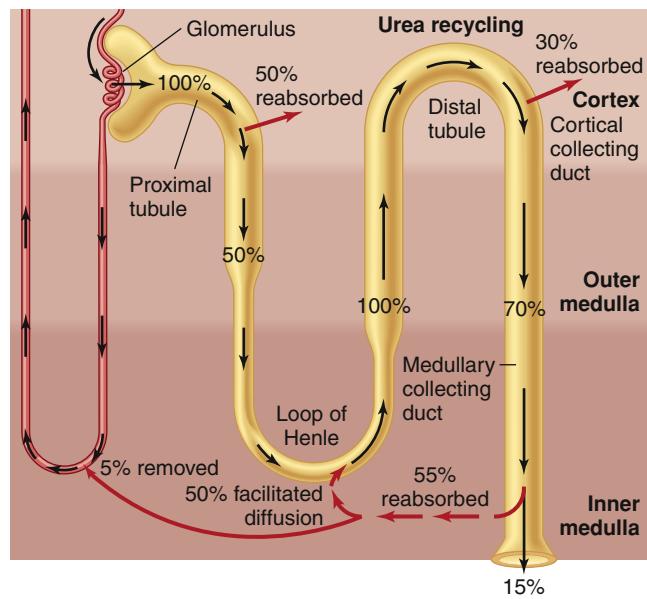
The Medullary Circulation A major question arises with the counter-current system as described previously: Why doesn't the blood flowing through medullary capillaries eliminate the counter-current gradient set up by the loops of Henle? One would think that as plasma with the usual osmolarity of 300 mOsm/L enters the highly concentrated environment of the medulla, there would be massive net diffusion of Na^+ and Cl^- into the capillaries and water out of them and, thus, the interstitial gradient would be "washed away." However, the blood vessels in the medulla (*vasa recta*) form hairpin loops that run parallel to the loops of Henle and medullary collecting ducts. As shown in **Figure 14.19**, 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, Na^+ and Cl^- 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. Therefore, 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. This maintains the steady-state counter-current gradient set up by the loops of Henle. Because of NaCl and water reabsorbed from the loop of Henle and collecting ducts, the amount of blood flow leaving the *vasa recta* is at least twofold higher than the blood flow entering the *vasa recta*. Finally, the total blood flow going through all of the *vasa recta* is a small percentage of the total renal blood flow. This helps to minimize the washout of the hypertonic interstitium of the medulla.



AP|R **Figure 14.19** Function of the vasa recta to maintain the hypertonic interstitial renal medulla. All movements of water and solutes are by diffusion. Not shown is the simultaneously occurring uptake of interstitial fluid by bulk flow.

The Recycling of Urea Helps to Establish a Hypertonic Medullary Interstitium As was just described, the countercurrent multiplier establishes a hypertonic medullary interstitium that the vasa recta help to preserve. We already learned how the reabsorption of water in the proximal tubule mediates the reabsorption of urea by diffusion. As urea passes through the remainder of the nephron, it is reabsorbed, secreted into the tubule, and then reabsorbed again (Figure 14.20). This traps urea, an osmotically active molecule, in the medullary interstitium, thus increasing its osmolarity. In fact, as shown in Figure 14.18, urea contributes to the total osmolarity of the renal medulla.

Urea is freely filtered in the glomerulus. Approximately 50% of the filtered urea is reabsorbed in the proximal tubule, and the remaining 50% enters the loop of Henle. In the thin descending and ascending limbs of the loop of Henle, urea that has accumulated in the medullary interstitium is secreted back into the tubular lumen by facilitated diffusion. Therefore, virtually all of the urea that was originally filtered in the glomerulus is present in the fluid that enters the distal tubule. Some of the original urea is reabsorbed from the distal tubule and cortical collecting duct. Thereafter, about half of the urea is reabsorbed from the *medullary* collecting duct, whereas only 5% diffuses into the vasa recta. The remaining amount is secreted back into the loop of Henle. Fifteen percent of the urea originally filtered remains in the collecting duct and is excreted in the urine. This recycling of urea through the medullary interstitium and minimal uptake by the vasa recta trap urea there and contribute to the high osmolarity shown in Figure 14.18. Of note is that medullary interstitial urea concentration is increased in antidiuretic states and contributes to water reabsorption. This occurs due to vasopressin, which, in addition to its effects on water permeability, also increases the permeability of the inner medullary collecting ducts to urea.



AP|R **Figure 14.20** Urea recycling. The recycling of urea “traps” urea in the inner medulla, which increases osmolarity and helps to establish and maintain hypertonicity.

Summary of Vasopressin Control of Urine Volume and Osmolarity This is a good place to review the reabsorption of water and the role of vasopressin in the generation of a concentrated or dilute urine. Figure 14.21 is a convenient way to do this. First, notice that about 60–70% of the volume reabsorbed in the juxtamedullary nephron is not controlled by vasopressin and occurs isosmotically in the proximal tubule. The direct effect of vasopressin in the collecting ducts participates in the development of increased osmolarity in the renal medullary interstitium. As a result, there is increased water reabsorption from the lumen in the thin descending loop of Henle with a resultant increase in tubular fluid osmolarity even though vasopressin does not have a direct effect on the loop. An interesting aspect of Figure 14.21 that may not seem obvious is why the peak osmolarity in the loop of Henle is lower in the absence of vasopressin. This is because, as previously mentioned, vasopressin stimulates urea reabsorption in the medullary collecting ducts (see Figure 14.20). In the absence of this effect of vasopressin, urea concentration in the medulla decreases. Since urea is responsible for at least half of the solute in the medulla (see Figure 14.18), the maximum osmolarity at the bottom of the loop of Henle (located in the medulla) is decreased.

Note that the tubular fluid osmolarity decreases in the latter half of the loop of Henle under both conditions while there is no change in tubular fluid volume; this reflects the selective reabsorption of solutes from the tubular fluid in these water-impermeable segments of the nephron. Therefore, the ultimate determinant of the volume of urine excreted and the concentration of urine under any set of conditions is vasopressin. In the absence of vasopressin, there is minimal water reabsorption in the collecting ducts so there is little decrease in the volume of the filtrate; this results in a diuresis and hypotonic urine. In the presence of maximum vasopressin during, for example, severe water restriction, most of the water is reabsorbed in the collecting ducts leading to a very small urine volume (antidiuresis) and hypertonic urine. In reality, most humans with access to water have an intermediate vasopressin concentration in the blood.

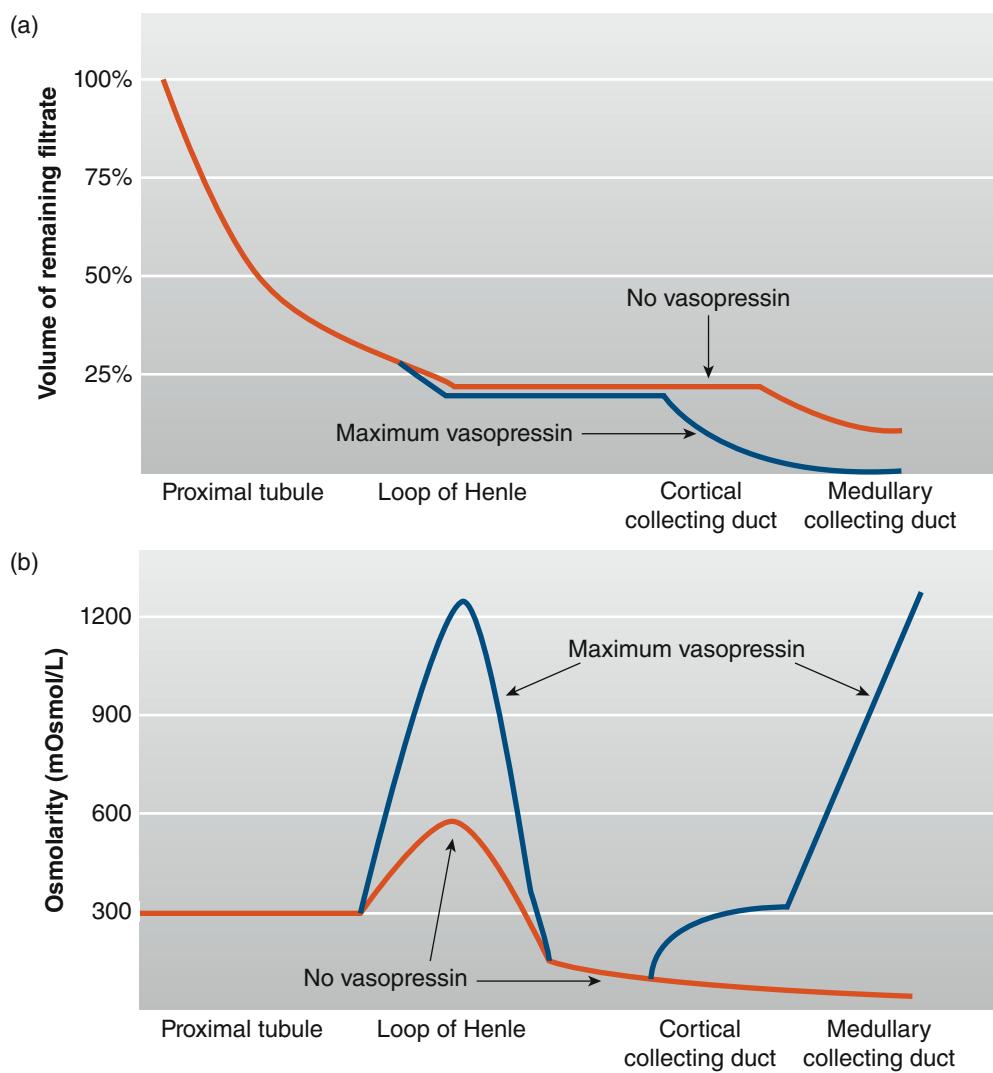


Figure 14.21 The effect of no vasopressin and maximum vasopressin concentration in the blood on (a) the volume remaining in the filtrate in the nephron as well as (b) the osmolarity of the tubular fluid along the length of the nephron.

14.8 Renal Sodium Regulation

In healthy individuals, urinary Na^+ excretion increases when there is an excess of sodium in the body and decreases when there is a sodium deficit. These homeostatic responses are so precise that total-body sodium normally varies by only a few percentage points despite a wide range of sodium intakes and the occasional occurrence of large losses via the skin and gastrointestinal tract.

As we have seen, Na^+ is freely filterable from the glomerular capillaries into Bowman's space and is actively reabsorbed but not secreted. Therefore,

$$\text{Na}^+ \text{ excreted} = \text{Na}^+ \text{ filtered} - \text{Na}^+ \text{ reabsorbed}$$

The kidneys can adjust Na^+ excretion by changing both processes on the right side of the equation. For example, when total-body sodium decreases for any reason, Na^+ excretion decreases below normal levels because Na^+ reabsorption increases.

The first issue in understanding the responses controlling Na^+ reabsorption is to determine what inputs initiate them; that is, what variables are receptors actually sensing? Surprisingly, there are no important receptors capable of detecting the total amount

of sodium in the body. Rather, the responses that regulate urinary Na^+ excretion are initiated mainly by various cardiovascular baroreceptors, such as the carotid sinus, and by sensors in the kidneys that monitor the filtered load of Na^+ .

As described in Chapter 12, baroreceptors respond to pressure changes within the circulatory 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*.

The distribution of water between fluid compartments in the body depends in large part on the concentration of solute in the extracellular fluid. Na^+ is the major extracellular solute constituting, along with associated anions, approximately 90% of these solutes. Therefore, changes in total-body sodium result in similar changes in extracellular volume. Because extracellular volume comprises plasma volume and interstitial volume, plasma volume is also directly related to total-body sodium. We saw in Chapter 12 that plasma volume is an important determinant of 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 a

decrease in cardiovascular pressures. These lower pressures, via baroreceptors, initiate reflexes that influence the renal arterioles and tubules so as to decrease GFR and increase Na^+ reabsorption. These latter events decrease Na^+ excretion, thereby retaining Na^+ (and therefore water) 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 Na^+ in the body determines the extracellular fluid volume, the plasma volume component of which helps determine cardiovascular pressures, which initiate the responses that control Na^+ excretion.

Control of GFR

Figure 14.22 summarizes the major mechanisms by which an example of increased Na^+ and water loss elicits a decrease in GFR. The main direct cause of the decreased GFR is a decreased net glomerular filtration pressure. This occurs both as a consequence of a decreased arterial pressure in the kidneys and, more importantly, as a result of reflexes acting on the renal arterioles. Note that these reflexes are the basic baroreceptor reflexes described in Chapter 12—a decrease in cardiovascular pressures causes neurally mediated reflex vasoconstriction in many areas of the body. As we will see later, the hormones angiotensin II and vasopressin also participate in this renal vasoconstrictor response.

Conversely, an increase in GFR is usually elicited by neural and endocrine inputs when an increased total-body-sodium level increases plasma volume. This increased GFR contributes to the increased renal Na^+ loss that returns extracellular volume to normal.

Control of Na^+ Reabsorption

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

Aldosterone and the Renin–Angiotensin System
The adrenal cortex produces a steroid hormone, **aldosterone**, which stimulates Na^+ reabsorption by the distal convoluted tubule and the cortical collecting ducts. An action affecting these late portions of the tubule is just what one would expect for a fine-tuning input because most of the filtered Na^+ has been reabsorbed by the time the filtrate reaches the distal parts of the nephron. When aldosterone is very low, approximately 2% of the filtered Na^+ (equivalent to 35 g of sodium chloride per day) is not reabsorbed but, rather, is excreted. In contrast, when the plasma concentration of aldosterone is high, essentially all the Na^+ reaching the distal tubule and cortical collecting ducts is reabsorbed. Normally, the plasma concentration of aldosterone and the amount of Na^+ excreted lie somewhere between these extremes.

As opposed to vasopressin, which is a peptide and acts quickly, aldosterone is a steroid and acts more slowly because it induces changes in gene expression and protein synthesis. In the case of the nephron, the proteins participate in Na^+ transport. Look again at Figure 14.14b. Aldosterone induces the synthesis of the ion channels and pumps shown in the cortical collecting duct.

When a person eats a diet high in 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?

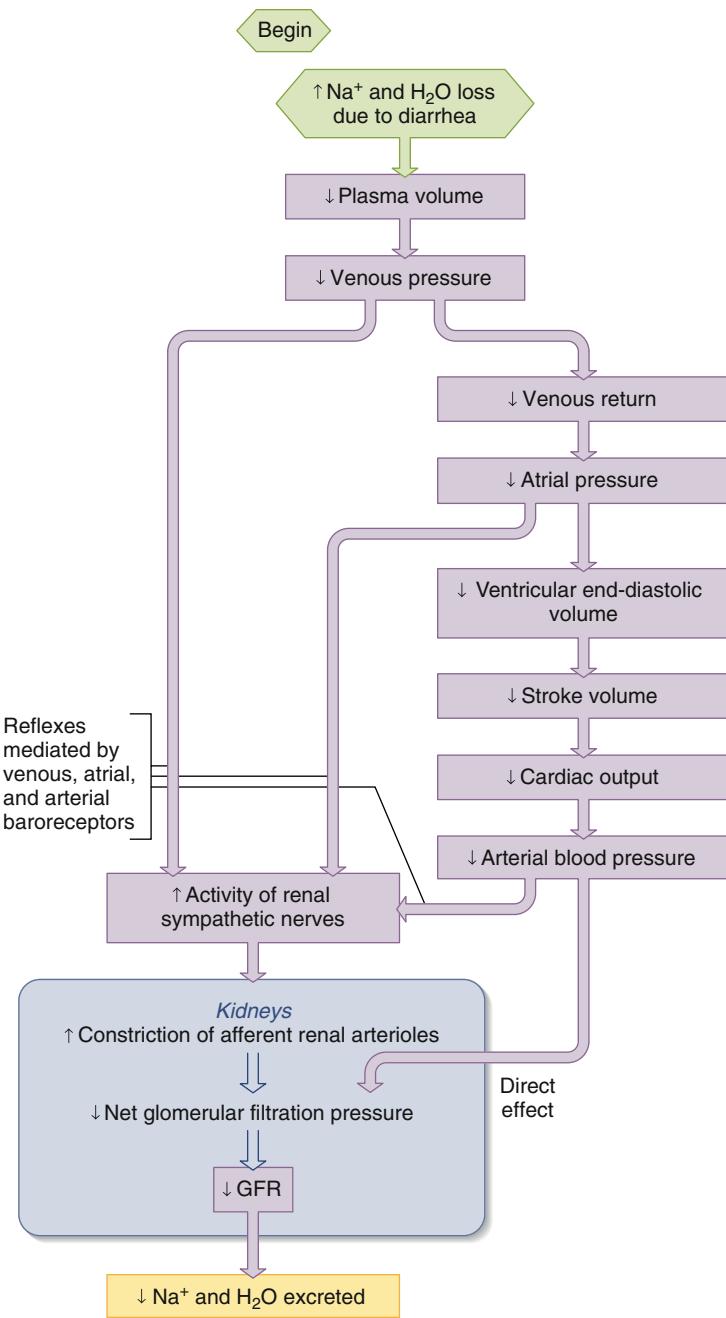


Figure 14.22 Direct and neurally mediated reflex pathways by which the GFR and, thus, Na^+ and water excretion decrease when plasma volume decreases.

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 **renin–angiotensin system**, summarized in **Figure 14.23**. **Renin** (pronounced REE-nin) is an enzyme secreted by the juxtaglomerular cells of the juxtaglomerular apparatuses in the kidneys (refer back to Figures 14.4a and 14.5). 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, a biologically inactive peptide, then undergoes further cleavage to form the active agent of the renin–angiotensin system, angiotensin II. This conversion is mediated by an enzyme known as **angiotensin-converting enzyme (ACE)**, which is found in very high concentration on the apical surface

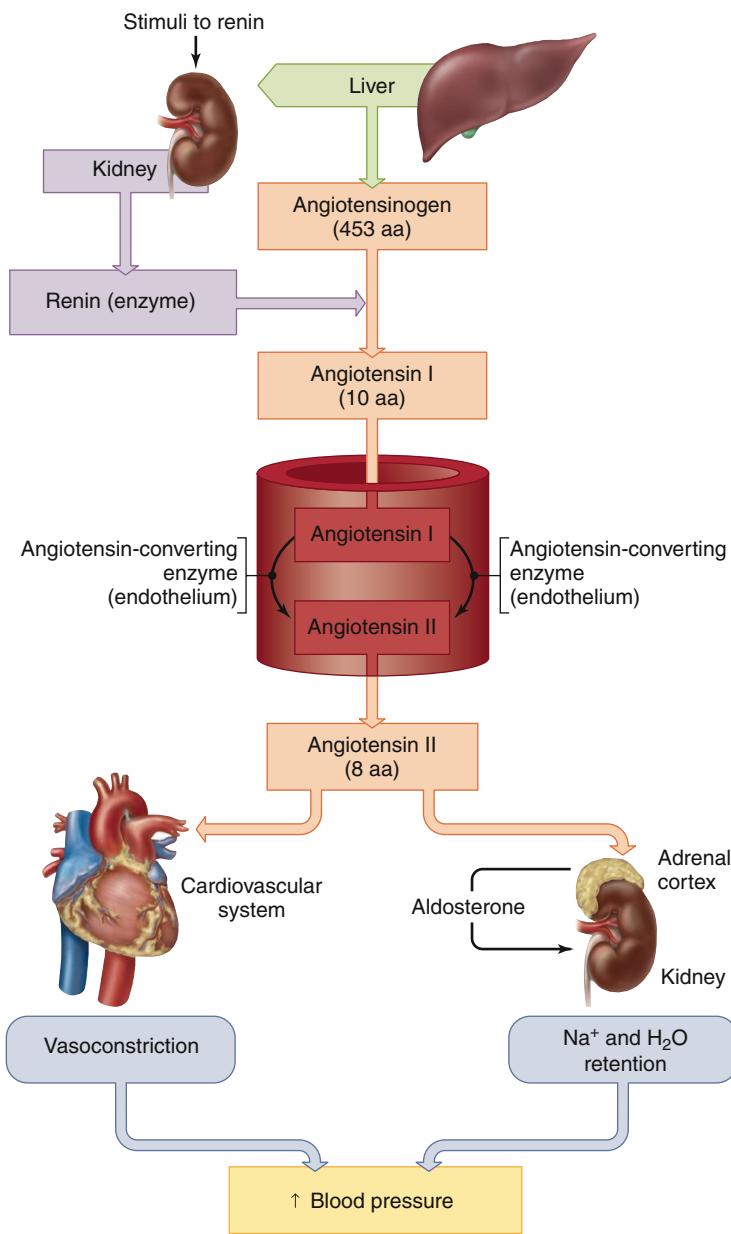


Figure 14.23 Summary of the renin–angiotensin system and the stimulation of aldosterone secretion by angiotensin II. Angiotensin-converting enzyme (ACE) is located on the surface of capillary endothelial cells. The plasma concentration of renin is the rate-limiting factor in the renin–angiotensin system; that is, it is the major determinant of the plasma concentration of angiotensin II. (aa = Amino acids)

PHYSIOLOGICAL INQUIRY

- What effect would an ACE inhibitor have on renin secretion and angiotensin II production? What effect would an angiotensin II receptor blocker (ARB) have on renin secretion and angiotensin II production? (Hint: Also look ahead to Figure 14.24.)

Answers can be found at end of chapter.

of capillary endothelial cells. Angiotensin II exerts many effects, but the most important are the stimulation of the secretion of aldosterone and the constriction of arterioles (described in Chapter 12). Plasma angiotensin II is high during NaCl depletion and low when

NaCl intake is high. It is this change in angiotensin II that brings about the changes in aldosterone secretion.

What causes the changes in plasma angiotensin II concentration with changes in sodium balance? Angiotensinogen and angiotensin-converting enzyme are usually present in excess, so the rate-limiting factor in angiotensin II formation is the plasma renin concentration. Therefore, the chain of events in sodium depletion is increased renin secretion → increased plasma renin concentration → increased plasma angiotensin I concentration → increased plasma angiotensin II concentration → increased aldosterone release → increased plasma aldosterone concentration.

What are the mechanisms by which sodium depletion causes an increase in renin secretion (**Figure 14.24**)? There are at least three distinct inputs to the juxtaglomerular cells: (1) the renal sympathetic

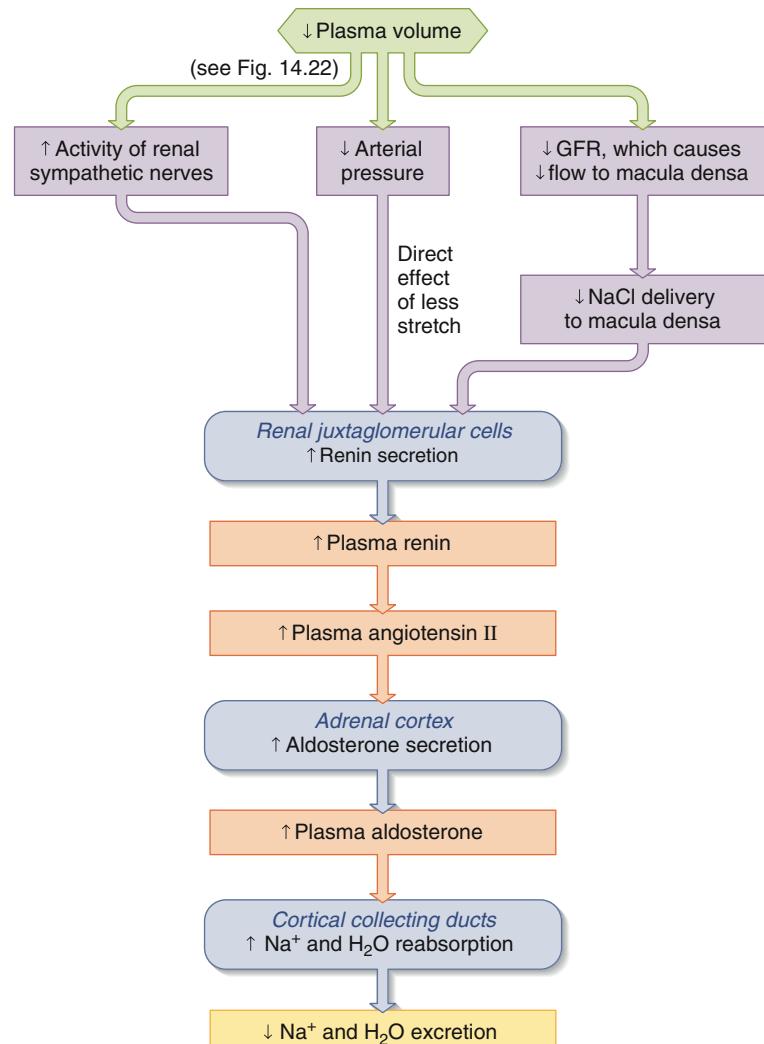


Figure 14.24 Pathways by which decreased plasma volume leads, via the renin–angiotensin system and aldosterone, to increased Na⁺ reabsorption by the cortical collecting ducts and hence to decreased Na⁺ excretion.

PHYSIOLOGICAL INQUIRY

- What would be the effect of denervation (removal of sympathetic neural input) of the kidneys on Na⁺ and water excretion?

Answers can be found at end of chapter.

nerves, (2) intrarenal baroreceptors, and (3) the macula densa (see Figure 14.5). This is an excellent example of the general principle of physiology that most physiological functions (like renin secretion) are controlled by multiple regulatory systems, often working in opposition.

The renal sympathetic nerves directly innervate the juxtaglomerular cells, and an increase in the activity of these nerves stimulates renin secretion. This makes sense because these nerves are reflexively activated via baroreceptors whenever a reduction in body sodium (and, therefore, plasma volume) decreases cardiovascular pressures (see Figure 14.22).

The other two inputs for controlling renin release—intrarenal baroreceptors and the macula densa—are contained within the kidneys and require no external neuroendocrine input (although such input can influence them). As noted earlier, the juxtaglomerular cells are located in the walls of the afferent arterioles. They are sensitive to the pressure within these arterioles and, therefore, function as **intrarenal baroreceptors**. When blood pressure in the kidneys decreases, as occurs when plasma volume is decreased, these cells are stretched less and, therefore, secrete more renin (see Figure 14.24). 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 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 14.2). The macula densa senses the amount of Na^+ in the tubular fluid flowing past it. A decreased Na^+ delivery causes the release of paracrine factors that diffuse from the macula densa to the nearby JG cells, thereby activating them and causing the release of renin. Therefore, in an indirect way, this mechanism is sensitive to changes in sodium intake. If salt intake is low, less Na^+ is filtered and less appears at the macula densa. Conversely, a high salt intake will cause a very low rate of release of renin. If blood pressure is significantly decreased, glomerular filtration rate can decrease. This will decrease the tubular flow rate such that less Na^+ is presented to the macula densa. This input also results in increased renin release at the same time that the sympathetic nerves and intrarenal baroreceptors are doing so (see Figure 14.24).

The importance of this system is highlighted by the considerable redundancy in the control of renin secretion. Furthermore, as illustrated in Figure 14.24, 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 12 that angiotensin II is a potent constrictor of arterioles in many parts of the body and that this effect on peripheral resistance increases arterial pressure.

Drugs have been developed to manipulate the angiotensin II and aldosterone components of the system. ACE inhibitors, such as **lisinopril**, reduce angiotensin II production from angiotensin I by inhibiting angiotensin-converting enzyme. Angiotensin II receptor blockers, such as **losartan**, prevent angiotensin II from binding to its receptor on target tissue (e.g., vascular smooth muscle and the adrenal cortex). Finally, drugs such as **epirenepine** block the binding of aldosterone to its receptor in the kidney. Although these classes of drugs have different mechanisms of action, they

are all effective in the treatment of hypertension. This highlights that many forms of hypertension can be attributed to the failure of the kidneys to adequately excrete Na^+ and water.

Atrial Natriuretic Peptide Another controller is **atrial natriuretic peptide (ANP)**, also known as atrial natriuretic factor (ANF) or atrial natriuretic hormone (ANH). Cells in the cardiac atria synthesize and secrete ANP. ANP acts on several tubular segments to inhibit Na^+ reabsorption. It can also act on the renal blood vessels to increase GFR, which further contributes to increased Na^+ (and water) excretion. An osmotic diuresis that is caused by an increase in Na^+ excretion is called a **natriuresis**. ANP also directly inhibits aldosterone secretion, which leads to an increase in Na^+ excretion. As would be predicted, the secretion of ANP increases when there is an excess of sodium in the body, but the stimulus for this increased secretion is not alterations in Na^+ concentration. Rather, using the same logic (only in reverse) that applies to the control of renin and aldosterone secretion, ANP secretion increases because of the expansion of plasma volume that accompanies an increase in body sodium. The specific stimulus is increased atrial distension (Figure 14.25).

Interaction of Blood Pressure and Renal Function

An important input controlling Na^+ reabsorption is 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 Na^+ reabsorption. Now we are emphasizing that arterial pressure also acts locally on the tubules themselves. Specifically, an *increase* in arterial pressure *inhibits* Na^+ reabsorption and thereby increases Na^+ (and, consequently, water) excretion in a process termed **pressure natriuresis**. The actual transduction mechanism of this direct effect is not established.

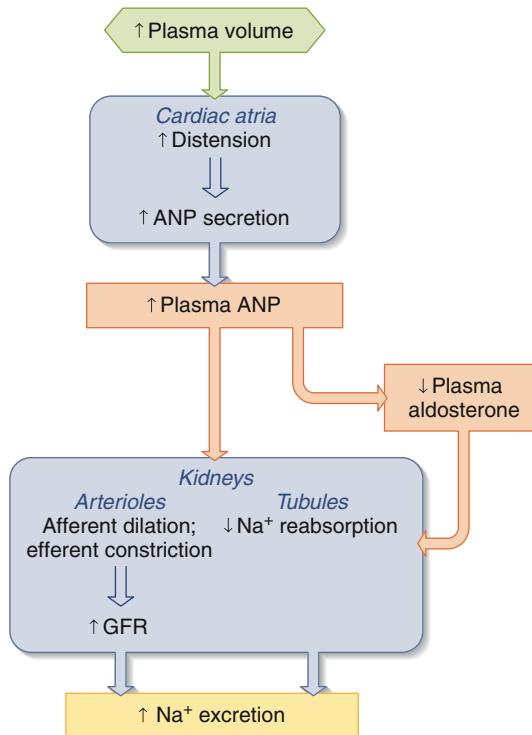


Figure 14.25 Atrial natriuretic peptide (ANP) increases Na^+ excretion.

In summary, an increased blood pressure decreases Na^+ reabsorption by two mechanisms: (1) It inhibits the activity of the renin-angiotensin-aldosterone system, and (2) it also acts locally on the tubules. Conversely, a decreased blood pressure decreases Na^+ excretion by both stimulating the renin-angiotensin-aldosterone system and acting on the tubules to enhance Na^+ reabsorption.

Now is a good time to look back at Figure 12.60, 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 Na^+ excretion is, as Figure 12.60 shows, one of the major links in these relationships. One hypothesis is that many people who develop hypertension do so because their kidneys, for some reason, do not excrete enough Na^+ in response to a normal arterial pressure. Consequently, at this normal pressure, some dietary sodium is retained thereby expanding the plasma volume. This causes the arterial pressure to increase enough to produce adequate Na^+ excretion to balance sodium intake, although at an increased body sodium content. The integrated control of sodium balance is a useful example of the general principles of physiology that the functions of organ systems are coordinated with each other and that controlled exchange of materials occurs between compartments and across cellular membranes.

14.9 Renal Water Regulation

Water excretion is the difference between the volume of water filtered (the GFR) and the volume reabsorbed. The changes in GFR initiated by baroreceptor afferent input described in the previous section tend to have the same effects on water excretion as on Na^+ excretion. As is true for Na^+ , however, the rate of water reabsorption is the most important factor for determining how much water is excreted. As we have seen, this is determined by vasopressin; therefore, total-body water is regulated mainly by reflexes that alter the secretion of this hormone.

As described in Chapter 11, vasopressin is produced by a discrete group of hypothalamic neurons the axons of which terminate on capillaries in the posterior pituitary, where they release vasopressin into the blood. The most important of the inputs to these neurons come from osmoreceptors and baroreceptors.

Osmoreceptor Control of Vasopressin Secretion

We have seen how changes in extracellular volume simultaneously elicit reflex changes in the excretion of *both* Na^+ and water. This is adaptive because the situations causing extracellular volume alterations are very often associated with loss or gain of both Na^+ and water in proportional amounts. In contrast, changes in total-body water with no corresponding change in total-body sodium are compensated for by altering water excretion *without altering Na^+ excretion*.

A crucial point in understanding how such reflexes are initiated is realizing that changes in water alone, in contrast to Na^+ , have relatively little effect on extracellular volume. The reason is that water, unlike Na^+ , distributes throughout all the body fluid compartments, with about two-thirds entering the intracellular compartment rather than simply staying in the extracellular compartment, as Na^+ does. Therefore, cardiovascular pressures and baroreceptors are only slightly affected by pure water gains or losses. In contrast, the major effect of water loss or gain out of

proportion to Na^+ 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 sensory receptors that initiate the reflexes controlling vasopressin secretion are **osmoreceptors** in the hypothalamus. These receptors are responsive to changes in osmolarity.

As an example, imagine that you drink 2 L of water. The excess water decreases the body fluid osmolarity, which results in an inhibition of vasopressin secretion via the hypothalamic osmoreceptors (Figure 14.26). As a result, the water permeability of the collecting ducts decreases dramatically, water reabsorption of these segments is greatly reduced, and a large volume of hypoosmotic urine is excreted. In this manner, the excess water is eliminated and body fluid osmolarity is normalized.

At the other end of the spectrum, when the osmolarity of the body fluids increases because of water deprivation, vasopressin secretion is reflexively increased via the osmoreceptors, water reabsorption by the collecting ducts increases, 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 Na^+ excretion. That is, it requires the kidneys to excrete a urine that, relative to plasma, either contains more water than Na^+ and other solutes (water diuresis) or less water than solute (concentrated urine). This is

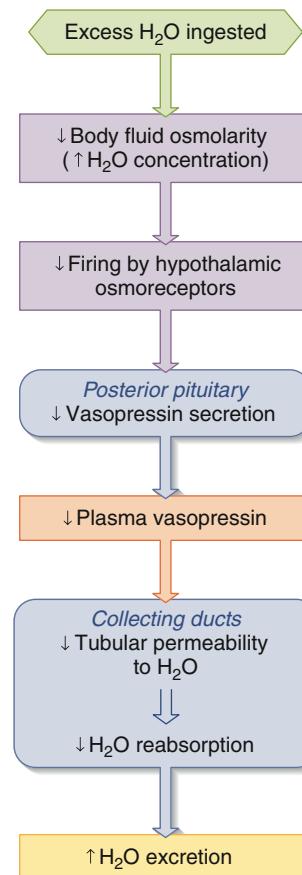


Figure 14.26 Osmoreceptor pathway that decreases vasopressin secretion and increases water excretion when excess water is ingested. The opposite events (an increase in vasopressin secretion) occur when osmolarity increases, as during water deprivation.

made possible by two physiological factors: (1) osmoreceptors and (2) vasopressin-dependent water reabsorption without Na^+ reabsorption in the collecting ducts.

Baroreceptor Control of Vasopressin Secretion

The minute-to-minute control of plasma osmolarity is primarily by the osmoreceptor-mediated vasopressin secretion already described. There are, however, other important controllers of vasopressin secretion. The best understood of these is baroreceptor input to vasopressinergic neurons in the hypothalamus.

A decreased extracellular fluid volume due, for example, to diarrhea or hemorrhage, elicits an increase in aldosterone release via activation of the renin–angiotensin system. However, the decreased extracellular volume also triggers an increase in vasopressin secretion. This increased vasopressin increases the water permeability of the collecting ducts. More water is passively reabsorbed and less is excreted, so water is retained to help stabilize the extracellular volume.

This reflex is initiated by several baroreceptors in the cardiovascular system (Figure 14.27). The baroreceptors decrease their rate of firing when cardiovascular pressures decrease, as occurs when blood volume decreases. Therefore, the baroreceptors transmit fewer impulses 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. The mechanism of this inverse relationship is an inhibitory neurotransmitter released by neurons in the afferent pathway.

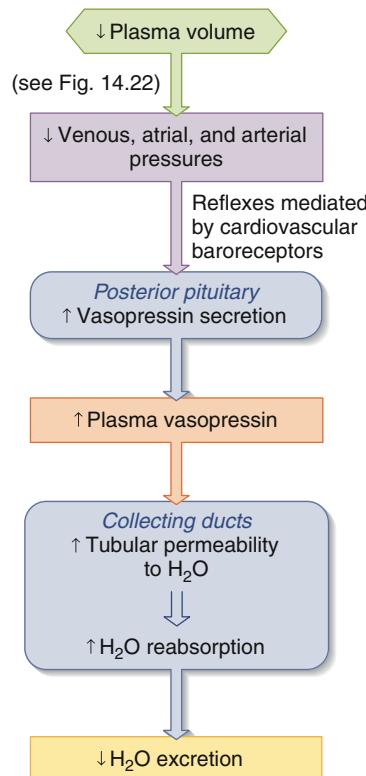


Figure 14.27 Baroreceptor pathway by which vasopressin secretion increases when plasma volume decreases. The opposite events (culminating in a decrease in vasopressin secretion) occur when plasma volume increases.

In addition to its effect on water excretion, vasopressin, like angiotensin II, causes widespread arteriolar constriction. This helps restore arterial blood pressure toward normal (Chapter 12).

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 earlier, has a lesser function under most physiological circumstances, but it can become very important in pathological states, such as hemorrhage.

Other Stimuli to Vasopressin Secretion We have now described two afferent pathways controlling the vasopressin-secreting hypothalamic cells, one from osmoreceptors and the other from baroreceptors. 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, ethanol inhibits vasopressin release, and this may account for the increased urine volume produced following the ingestion of alcohol, a urine volume well in excess of the volume of the beverage consumed. Furthermore, hypoxia alters vasopressin release via afferent input from peripheral arterial chemoreceptors (see Figure 13.33) to the hypothalamus via ascending pathways from the medulla oblongata to the hypothalamus. Nausea is also a very potent stimulus of vasopressin release. The vasoconstrictor effects of vasopressin (see Chapter 12) acting on the blood vessels that perfuse the small intestines help to shift blood flow away from the gastrointestinal tract, thereby decreasing the absorption of ingested toxic substances.

14.10 A Summary Example: The Response to Sweating

Figure 14.28 shows the factors that control renal Na^+ and water excretion in response to severe sweating. You may notice the salty taste of sweat on your upper lip when you exercise. Sweat does contain Na^+ and Cl^- , in addition to water, but is actually hypoosmotic compared to the body fluids from which it is derived. Therefore, sweating causes both a decrease in extracellular volume and an increase in body fluid osmolarity. The renal retention of water and Na^+ minimizes the deviations from normal caused by the loss of water and Na^+ in the sweat.

14.11 Thirst and Salt Appetite

Deficits of salt and water must eventually be compensated for by ingestion of these substances, because the kidneys cannot create new Na^+ or water. The kidneys can only minimize their excretion until ingestion replaces the losses.

The subjective feeling of thirst is stimulated by an increase in plasma osmolarity and by a decrease in extracellular fluid volume (**Figure 14.29**). Plasma osmolarity is the most important stimulus under normal physiological conditions. The increase in plasma osmolarity and the decrease in extracellular fluid are precisely the same two changes that stimulate vasopressin production, and the osmoreceptors and baroreceptors that control vasopressin secretion are similar to those for thirst. The brain centers that receive input from these receptors and that mediate thirst are located in the hypothalamus, very close to those areas that synthesize vasopressin.

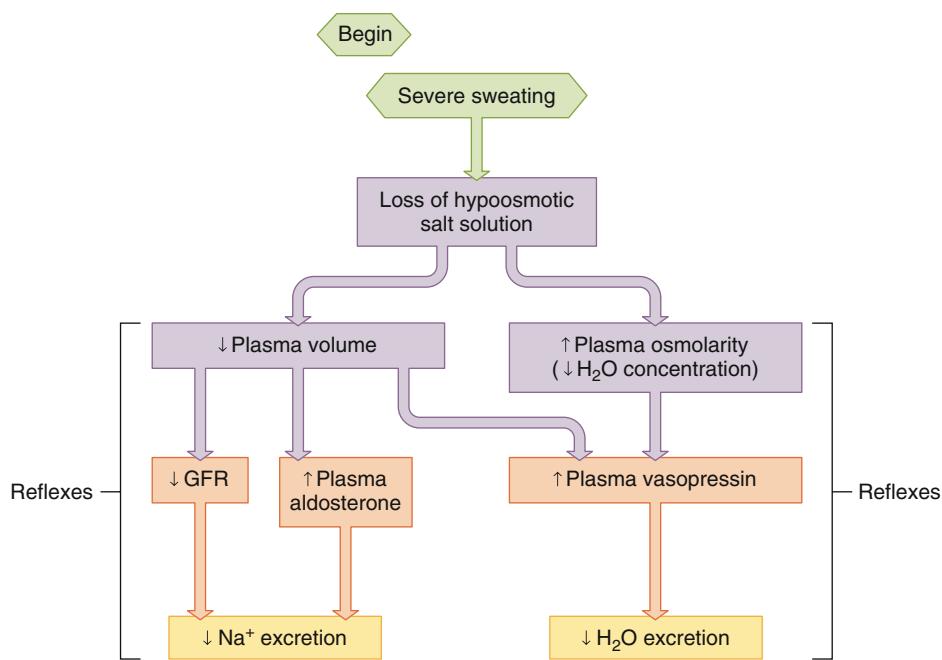


Figure 14.28 Pathways by which Na^+ and water excretion decrease in response to severe sweating. This figure is an amalgamation of Figures 14.22, 14.24, 14.27, and the reverse of Figure 14.26.

PHYSIOLOGICAL INQUIRY

- Explain how this figure illustrates the general principle of physiology described in Chapter 1 that the functions of organ systems are coordinated with each other.

Answer can be found at end of chapter.

There are still other pathways controlling thirst. For example, dryness of the mouth and throat causes thirst, which is relieved by merely moistening them. Some kind of “metering” of water intake by other parts of the gastrointestinal tract also occurs. For example, a thirsty person given access to water stops drinking after replacing the lost water. This occurs well 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. This is probably mediated by afferent sensory nerves from the mouth, throat, and gastrointestinal tract and prevents overhydration.

Salt appetite is an important part of sodium homeostasis and consists of two components, “hedonistic” appetite and “regulatory” appetite. Many mammals “like” salt and eat it whenever they can, regardless of whether they are salt-deficient. Human beings 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, humans have relatively little regulatory salt appetite, at least until a bodily salt deficit becomes extremely large.

14.12 Potassium Regulation

Potassium is the most abundant intracellular ion. Although only 2% of total-body potassium is in the extracellular fluid, the K^+ concentration in this fluid is extremely important for the function of excitable tissues, notably, nerve and muscle. Recall from Chapter 6 that the resting membrane potentials of these tissues largely depend on the concentration gradient of K^+ across the plasma membrane. Consequently, either increases (**hyperkalemia**) or decreases (**hypokalemia**) in extracellular K^+ concentration can cause abnormal rhythms of the heart (**arrhythmias**) and abnormalities of skeletal muscle contraction and neuronal action potential conduction.

A healthy person remains in potassium balance in the steady state by daily excreting an amount of K^+ in the urine equal to the amount ingested minus the amounts eliminated in feces and sweat. Like Na^+ losses, K^+ 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 K^+ excretion is the major mechanism regulating body potassium.

Renal Regulation of K^+

K^+ is freely filterable in the glomerulus. Normally, the tubules reabsorb most of this filtered K^+ so that very little of the filtered K^+ appears in the urine. However, the cortical collecting ducts can secrete K^+ and changes in K^+ excretion are due mainly to changes in K^+ secretion by this tubular segment (Figure 14.30).

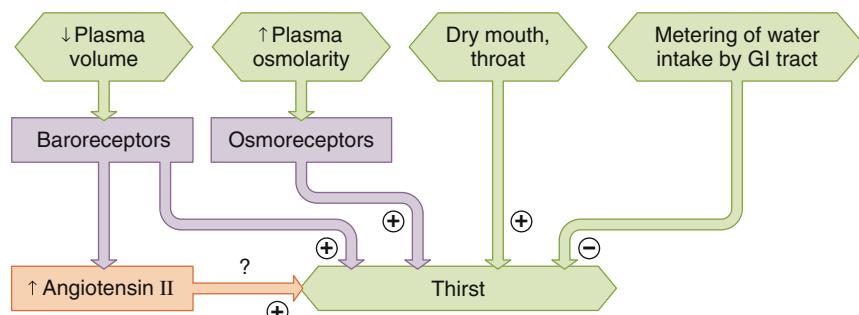
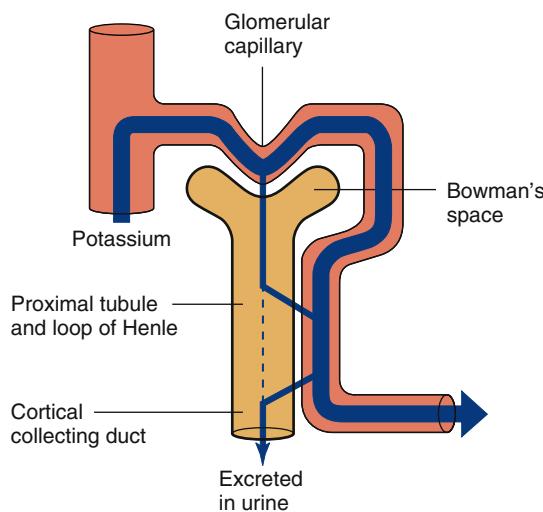


Figure 14.29 Inputs controlling thirst. The osmoreceptor input is the single most important stimulus under most physiological conditions. Psychological factors and conditioned responses are not shown. The question mark (?) indicates that evidence for the effects of angiotensin II on thirst comes primarily from experimental animals.



AP|R **Figure 14.30** Simplified model of the basic renal processing of potassium.

During potassium depletion, when the homeostatic response is to minimize K^+ loss, there is no K^+ secretion by the cortical collecting ducts. Only the small amount of filtered K^+ that escapes tubular reabsorption is excreted. With normal fluctuations in potassium intake, a variable amount of K^+ is added to the small amount filtered and not reabsorbed. This maintains total-body potassium balance.

Figure 14.14b illustrated the mechanism of K^+ secretion by the cortical collecting ducts. 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 apical membrane. Therefore, the secretion of K^+ by the cortical collecting duct is associated with the reabsorption of Na^+ by this tubular segment. K^+ secretion does not occur in other Na^+ -reabsorbing tubular segments because there are few K^+ channels in the apical membranes of their cells. Rather, in these segments, the K^+ pumped into the cell by Na^+/K^+ -ATPase simply diffuses back across the basolateral membrane through K^+ channels located there (see Figure 14.14a).

What factors influence K^+ 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 14.31), plasma K^+ concentration increases, though very slightly, and this directly drives enhanced basolateral uptake via the Na^+/K^+ -ATPase pumps. Thus, there is an enhanced K^+ secretion. Conversely, a low-potassium diet or a negative potassium balance, such as results from diarrhea, directly decreases basolateral K^+ uptake. This reduces K^+ secretion and excretion, thereby helping to reestablish potassium balance.

A second important factor linking K^+ secretion to potassium balance is the hormone aldosterone (see Figure 14.31). Besides stimulating tubular Na^+ reabsorption by the cortical collecting ducts, aldosterone simultaneously enhances K^+ secretion by this tubular segment.

The homeostatic mechanism by which an excess or deficit of potassium controls aldosterone production (see Figure 14.31) is different from the mechanism described earlier involving the renin–angiotensin system. The aldosterone-secreting cells of the adrenal cortex are sensitive to the K^+ concentration of the

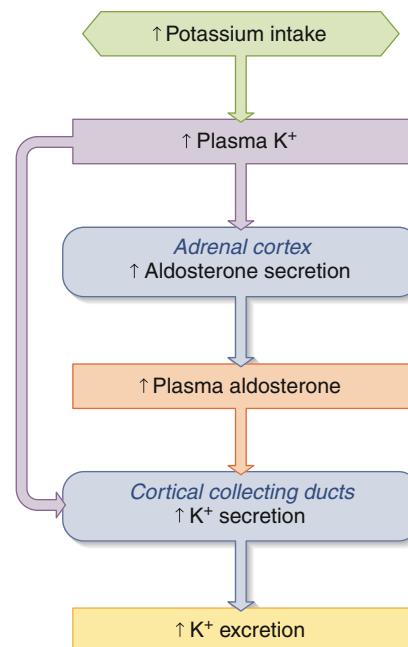


Figure 14.31 Pathways by which an increased potassium intake induces greater K^+ excretion.

PHYSIOLOGICAL INQUIRY

- How does this figure highlight the general principle of physiology introduced in Chapter 1 that physiological processes require the transfer and balance of matter and energy?

Answer can be found at end of chapter.

extracellular fluid. In this way, an increased intake of potassium leads to an increased extracellular K^+ concentration, which in turn directly stimulates the adrenal cortex to produce aldosterone. The increased plasma aldosterone concentration increases K^+ secretion and thereby eliminates the excess potassium from the body.

Conversely, a decreased extracellular K^+ concentration decreases aldosterone production and thereby reduces K^+ secretion. Less K^+ than usual is excreted in the urine, thereby helping to restore the normal extracellular concentration.

Figure 14.32 summarizes the control and major renal tubular effects of aldosterone. The fact that a single hormone regulates both Na^+ and K^+ excretion raises the question of potential conflicts between homeostasis of the two ions. For example, if a person was sodium-deficient and therefore secreting large amounts of aldosterone, the K^+ -secreting effects of this hormone would tend to cause some K^+ loss even though potassium balance was normal to start with. Usually, such conflicts cause only minor imbalances because there are a variety of other counteracting controls of Na^+ and K^+ excretion.

14.13 Renal Regulation of Calcium and Phosphate Ions

Calcium and phosphate balance are controlled primarily by parathyroid hormone and $1,25-(OH)_2D$, as described in detail in Chapter 11. Approximately 60% of plasma calcium is available for filtration in the kidney. The remaining plasma calcium is protein-bound or complexed with anions. Because calcium is so important

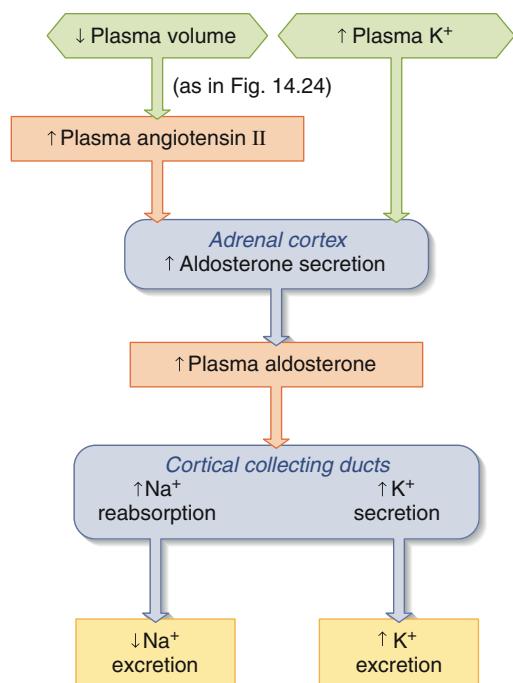


Figure 14.32 Summary of the control of aldosterone and its effects on Na^+ reabsorption and K^+ secretion.

in the function of every cell in the body, the kidneys have very effective mechanisms to reabsorb calcium ion from the tubular fluid. More than 60% of calcium ion reabsorption is not under hormonal control and occurs in the proximal tubule. The hormonal control of calcium ion reabsorption occurs mainly in the distal convoluted tubule and early in the cortical collecting duct. When plasma calcium is low, the secretion of parathyroid hormone (PTH) from the parathyroid glands increases. PTH stimulates the opening of calcium channels in these parts of the nephron, thereby increasing calcium ion reabsorption. As discussed in Chapter 11,

another important action of PTH in the kidneys is to increase the activity of the 1-hydroxylase enzyme, thus activating $25(\text{OH})\text{-D}$ to $1,25-(\text{OH})_2\text{D}$, which then goes on to increase calcium and phosphate ion absorption in the gastrointestinal tract.

About half of the plasma phosphate is ionized and is filterable. Like calcium, most of the phosphate ion that is filtered is reabsorbed in the proximal tubule. Unlike calcium ion, phosphate ion reabsorption is decreased by PTH, thereby increasing the excretion of phosphate ion. Therefore, when plasma calcium is low, and PTH and calcium ion reabsorption are increased as a result, phosphate ion excretion is increased.

14.14 Summary—Division of Labor

Table 14.5 summarizes the division of labor of renal function along the renal tubule. So far, we have discussed all of these processes except the transport of acids and bases, which Section C of this chapter will cover.

14.15 Diuretics

Drugs used clinically to increase the volume of urine excreted are known as **diuretics**. Most act on the tubules to inhibit the reabsorption of Na^+ , along with Cl^- and/or HCO_3^- , resulting in increased excretion of these ions. Because water reabsorption is dependent upon solute (particularly Na^+) 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 Na^+ reabsorption. For example, **loop diuretics**, such as **furosemide**, act on the ascending limb of the loop of Henle to inhibit the first step in Na^+ reabsorption in this segment—cotransport of Na^+ and Cl^- across the apical membrane into the cell.

Loop diuretics can have the unwanted side-effect of causing low plasma K^+ . Due to increased Na^+ delivery to the distal nephrons,

TABLE 14.5 Summary of “Division of Labor” in the Renal Tubules

Tubular Segment	Major Functions	Controlling Factors
Glomerulus/Bowman's capsule	Forms ultrafiltrate of plasma	Starling forces (P_{GC} , P_{BS} , π_{GC})
Proximal tubule	Bulk reabsorption of solutes and water Secretion of solutes (except K^+) and organic acids and bases	Active transport of solutes with passive water reabsorption Parathyroid hormone inhibits phosphate ion reabsorption
Loop of Henle	Establishes medullary osmotic gradient (juxamedullary nephrons) Secretion of urea	
Descending limb	Bulk reabsorption of water	Passive water reabsorption
Ascending limb	Reabsorption of Na^+ and Cl^-	Active transport
Distal tubule and cortical collecting ducts	Fine-tuning of the reabsorption/secretion of small quantities of useful solutes remaining	Aldosterone stimulates Na^+ reabsorption and K^+ secretion Parathyroid hormone stimulates calcium ion reabsorption
Cortical and medullary collecting ducts	Fine-tuning of water reabsorption Reabsorption of urea	Vasopressin increases passive reabsorption of water

K^+ secretion can increase in the cortical collecting ducts (see Figures 14.14b and 14.32). This can lead to the loss of K^+ in the urine in addition to the desired effect of losing Na^+ and water.

In contrast to loop diuretics, **potassium-sparing diuretics** inhibit Na^+ reabsorption in the cortical collecting duct, without increasing K^+ secretion there. Potassium-sparing diuretics either block the action of aldosterone (e.g., *spironolactone* or *eplerenone*) or block the epithelial Na^+ channel in the cortical collecting duct (e.g., *triamterene* or *amiloride*). This explains why they do not cause increased K^+ excretion. **Osmotic diuretics** such as **mannitol** are filtered but not reabsorbed, thus retaining water in the urine. This is the same reason that uncontrolled diabetes mellitus and its associated glucosuria can cause excessive water loss and dehydration (see Figure 16.21).

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, the regulation of blood pressure normally produces stability of total-body-sodium mass and extracellular volume because of the close correlation between these variables. In contrast, in several types of disease, this correlation is disrupted and the reflexes that maintain blood pressure can cause renal retention of Na^+ . Sodium excretion may decrease to almost nothing despite continued sodium ingestion, leading to abnormal expansion of the extracellular fluid (**edema**). Diuretics are used to prevent or reverse this renal retention of Na^+ and water.

The most common example of this phenomenon is **congestive heart failure** (Chapter 12). A person with a failing heart manifests a decreased GFR and increased aldosterone secretion, both of which contribute to extremely low Na^+ in the urine. The net result is extracellular volume expansion and edema. The Na^+ -retaining responses are triggered by the lower cardiac output (a result of cardiac failure) and the decrease in arterial blood pressure that results directly from this decrease in cardiac output.

Another disease in which diuretics are often used is hypertension (Chapter 12). The decrease in body sodium and water resulting from the diuretic-induced excretion of these substances brings about arteriolar dilation and a lowering of the blood pressure. The precise mechanism by which decreased body sodium causes arteriolar dilation is not known.

SECTION B SUMMARY

Total-Body Balance of Sodium and Water

- I. The body gains water via ingestion and internal production, and it loses water via urine, the gastrointestinal tract, and evaporation from the skin and respiratory tract (as insensible loss and sweat).
- II. The body gains Na^+ and Cl^- by ingestion and loses them via the skin (in sweat), the gastrointestinal tract, and urine.
- III. For both water and Na^+ , the major homeostatic control point for maintaining stable balance is renal excretion.

Basic Renal Processes for Sodium and Water

- I. Na^+ is freely filterable at the glomerulus, and its reabsorption is a primary active process dependent upon Na^+/K^+ -ATPase pumps in the basolateral membranes of the tubular epithelium. Na^+ is not secreted.
- II. Na^+ entry into the cell from the tubular lumen is always passive. Depending on the tubular segment, it is either through ion channels or by cotransport or countertransport with other substances.
- III. Na^+ reabsorption creates an osmotic difference across the tubule, which drives water reabsorption, largely through water channels (aquaporins).

IV. Water reabsorption is independent of the posterior pituitary hormone vasopressin until it reaches the collecting-duct system, where vasopressin increases water permeability. A large volume of dilute urine is produced when plasma vasopressin concentration and, hence, water reabsorption by the collecting ducts are low.

V. A small volume of concentrated urine is produced by the renal countercurrent multiplier system when plasma vasopressin concentration is high.

- a. The active transport of sodium chloride by the ascending loop of Henle causes increased osmolarity of the interstitial fluid of the medulla but a dilution of the luminal fluid.
- b. Vasopressin increases the permeability to water of the cortical collecting ducts by increasing the number of AQP2 water channels inserted into the apical membrane. Water is reabsorbed by this segment until the luminal fluid is isoosmotic to plasma in the cortical peritubular capillaries.
- 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. Na^+ excretion is the difference between the amount of Na^+ filtered and the amount reabsorbed.
- II. GFR and, hence, the filtered load of Na^+ are 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 Na^+ reabsorption is the adrenal cortical hormone aldosterone, which stimulates Na^+ 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:
 - a. Stimulation of the renal sympathetic nerves to the juxtaglomerular cells by extrarenal baroreceptor reflexes;
 - b. Pressure decreases sensed by the juxtaglomerular cells, themselves acting as intrarenal baroreceptors; and
 - c. A signal generated by low Na^+ or Cl^- concentration in the lumen of the macula densa.
- V. Many other factors influence Na^+ reabsorption. One of these, atrial natriuretic peptide, is secreted by cells in the atria in response to atrial distension; it inhibits Na^+ reabsorption, and it also increases GFR.
- VI. Arterial pressure acts locally on the renal tubules to influence Na^+ reabsorption; an increased pressure causes 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 contributes to the regulation of water excretion, but the major control is via vasopressin-mediated control of water reabsorption.
- III. Vasopressin secretion by the posterior pituitary is controlled by osmoreceptors and by non-osmotic sensors such as cardiovascular baroreceptors in the hypothalamus.
 - a. Via the osmoreceptors, a high body fluid osmolarity stimulates vasopressin secretion and a low osmolarity inhibits it.
 - b. A low extracellular volume stimulates vasopressin secretion via the baroreceptor reflexes, and a high extracellular volume inhibits it.

A Summary Example: The Response to Sweating

- I. Severe sweating can lead to a decrease in plasma volume and an increase in plasma osmolarity.
- II. This will result in a decrease in GFR and an increase in aldosterone, which together decrease Na^+ excretion, and an increase in vasopressin, which decreases H_2O excretion.
- III. The net result of the renal retention of Na^+ and H_2O is to minimize hypovolemia and maintain plasma osmolarity.

Thirst and Salt Appetite

- I. Thirst is stimulated by a variety of inputs, including baroreceptors, osmoreceptors, and possibly 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 feces and sweat.
- II. K^+ is freely filterable at the renal corpuscle and undergoes both reabsorption and secretion, the latter occurring in the cortical collecting ducts and serving as the major controlled variable determining K^+ excretion.
- III. When body potassium increases, extracellular potassium concentration also increases. This increase acts directly on the cortical collecting ducts to increase K^+ secretion and also stimulates aldosterone secretion. The increased plasma aldosterone then also stimulates K^+ secretion.
- IV. The most common cause of hyperaldosteronism (too much aldosterone in the blood) is a noncancerous adrenal tumor (adenoma) that secretes aldosterone in the absence of stimulation from angiotensin II. The excess aldosterone causes increased renal K^+ secretion and Na^+ reabsorption, and fluid retention. Hyperaldosteronism is a common cause of endocrine hypertension.

Renal Regulation of Calcium and Phosphate Ions

- I. About half of the plasma calcium and phosphate is ionized and filterable.
- II. Most calcium and phosphate ion reabsorption occurs in the proximal tubule.
- III. PTH increases calcium ion absorption in the distal convoluted tubule and early cortical collecting duct. PTH decreases phosphate ion reabsorption in the proximal tubule.

Summary—Division of Labor

- I. Each segment of the nephron is responsible for a different function.
- II. The proximal tubule is responsible for the bulk reabsorption of solute and water.
- III. The loop of Henle generates the medullary osmotic gradient that allows for the passive reabsorption of water in the collecting ducts.
- IV. The distal tubules and collecting ducts are the site of most regulation (fine-tuning) of the excretion of solutes and water.

Diuretics

- I. Most diuretics inhibit reabsorption of Na^+ and water, thereby enhancing the excretion of these substances. Different diuretics act on different nephron segments.

SECTION B REVIEW QUESTIONS

1. What are the sources of water gain and loss in the body? What are the sources of Na^+ gain and loss?
2. Describe the distribution of water and Na^+ between the intracellular and extracellular fluids.
3. What is the relationship between body sodium and extracellular fluid volume?

4. What is the mechanism of Na^+ 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 Na^+ 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 Na^+ , Cl^- , 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 Na^+ is excreted per unit time?
10. Diagram the sequence of events in 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 K^+ excretion.
17. What are the two major controls of aldosterone secretion, and what are this hormone's major actions?
18. Contrast the control of calcium and phosphate ion excretion by PTH.
19. List the different types of diuretics and briefly summarize their mechanisms of action.
20. List several diseases that diuretics can be used to treat.

SECTION B KEY TERMS

14.6 Total-Body Balance of Sodium and Water

insensible water loss

14.7 Basic Renal Processes for Sodium and Water

antidiuretic hormone (ADH)	isoosmotic
aquaporins	obligatory water loss
countercurrent multiplier system	osmotic diuresis
diuresis	vasopressin
hyperosmotic	water diuresis
hypoosmotic	

14.8 Renal Sodium Regulation

aldosterone	atrial natriuretic peptide (ANP)
angiotensin-converting enzyme (ACE)	intrarenal baroreceptors
angiotensin I	natriuresis
angiotensin II	pressure natriuresis
angiotensinogen	renin
	renin–angiotensin system

14.9 Renal Water Regulation

osmoreceptors

14.11 Thirst and Salt Appetite

salt appetite

SECTION B CLINICAL TERMS

14.7 Basic Renal Processes for Sodium and Water

central diabetes insipidus nephrogenic diabetes insipidus
diabetes insipidus

14.8 Renal Sodium Regulation

eplerenone losartan
lisinopril

14.12 Potassium Regulation

arrhythmias hypokalemia
hyperkalemia

14.15 Diuretics

amiloride	mannitol
congestive heart failure	osmotic diuretics
diuretics	potassium-sparing diuretics
edema	spironolactone
furosemide	triaterene
loop diuretics	

SECTION C

Hydrogen Ion Regulation

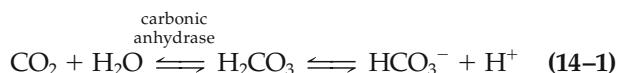
The understanding of the regulation of acid–base balance requires appreciation of a general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. Metabolic reactions are highly sensitive to the H⁺ concentration of the fluid in which they occur. This sensitivity is due to the influence that H⁺ has on the tertiary structures of proteins, such as enzymes, such that their function can be altered (see Figure 2.17). Not surprisingly, then, the H⁺ concentration of the extracellular fluid is tightly regulated. At this point, the reader should review the section on H⁺, 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 matching gains and losses. When loss exceeds gain, the arterial plasma H⁺ concentration decreases and pH exceeds 7.4. This is termed **alkalosis**. When gain exceeds loss, the arterial plasma H⁺ concentration increases and the pH is less than 7.4. This is termed **acidosis**.

14.16 Sources of Hydrogen Ion Gain or Loss

Table 14.6 summarizes the major routes for gains and losses of H⁺. As described in Chapter 13, a huge quantity of CO₂—about 20,000 mmol—is generated daily as the result of oxidative

metabolism. These CO₂ molecules participate in the generation of H⁺ during the passage of blood through peripheral tissues via the following reactions:



This source does not normally constitute a net gain of H⁺. This is because the H⁺ generated via these reactions is reincorporated into water when the reactions are reversed during the passage of blood through the lungs (see Chapter 13). Net retention of CO₂ does occur in hypoventilation or respiratory disease and in such cases causes a net gain of H⁺. Conversely, net loss of CO₂ occurs in hyperventilation, and this causes net elimination of H⁺.

The body also produces both organic and inorganic acids 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 of these acids yields anions and H⁺. Simultaneously, however, the metabolism of a variety of organic anions utilizes H⁺ and produces HCO₃⁻. Therefore, the metabolism of nonvolatile solutes both generates and utilizes H⁺. With the high-protein diet typical in the United States, the generation of nonvolatile acids predominates in most people, with an average net production of 40 to 80 mmol of H⁺ per day.

A third potential source of the net gain or loss of H⁺ in the body occurs when gastrointestinal secretions leave the body. Vomitus contains a high concentration of H⁺ and so constitutes a source of net loss. In contrast, the other gastrointestinal secretions are alkaline. They contain very little H⁺, but their concentration of HCO₃⁻ is higher than in plasma. Loss of these fluids, as in diarrhea, in essence constitutes a *gain* of H⁺. Given the mass-action relationship shown in equation 14–1, *when HCO₃⁻ is lost from the body, it is the same as if the body had gained H⁺*. This is because loss of the HCO₃⁻ causes the reactions shown in equation 14–1 to be driven to the right, thereby generating H⁺ within the body. Similarly, when the body gains HCO₃⁻, it is the same as if the body had lost H⁺, as the reactions of equation 14–1 are driven to the left.

Finally, the kidneys constitute the fourth source of net H⁺ gain or loss. That is, the kidneys can either remove H⁺ from the plasma or add it.

TABLE 14.6 Sources of Hydrogen Ion Gain or Loss

Gain

- Generation of H⁺ from CO₂
- Production of nonvolatile acids from the metabolism of proteins and other organic molecules
- Gain of H⁺ due to loss of HCO₃⁻ in diarrhea or other nongastric GI fluids
- Gain of H⁺ due to loss of HCO₃⁻ in the urine

Loss

- Utilization of H⁺ in the metabolism of various organic anions
- Loss of H⁺ in vomitus
- Loss of H⁺ (primarily in the form of H₂PO₄⁻ and NH₄⁺) in the urine
- Hyperventilation

14.17 Buffering of Hydrogen Ion in the Body

Any substance that can reversibly bind H⁺ is called a **buffer**. Most H⁺ is bound 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 nmol/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 body fluid hydrogen ion concentration.

The general form of buffering reactions is



Recall the law of mass action described in Chapter 3, which governs the net direction of the reaction in equation 14–2. 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 any 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 H⁺ combines 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 H⁺ or the addition of alkali, equation 14–2 proceeds to the left and H⁺ is released from HBuffer. In this manner, buffers stabilize H⁺ concentration against changes in either direction.

The major extracellular buffer is the CO₂/HCO₃[−] system summarized in equation 14–1. This system also contributes to buffering within cells, but the major intracellular buffers are phosphates and proteins. An example of an intracellular protein buffer is hemoglobin, as described in Chapter 13.

This buffering does not eliminate H⁺ from the body or add it to the body; it only keeps the H⁺ “locked up” until balance can be restored. How balance is achieved is the subject of the rest of our description of hydrogen ion regulation.

14.18 Integration of Homeostatic Controls

The kidneys are ultimately responsible for balancing hydrogen ion gains and losses so as to maintain plasma hydrogen ion concentration within a narrow range. The kidneys normally excrete the excess H⁺ from nonvolatile acids generated from metabolism—that is, all acids other than carbonic acid. An additional net gain of H⁺ can occur with increased production of these nonvolatile acids, with hypoventilation or respiratory malfunction, or with the loss of alkaline gastrointestinal secretions. When this occurs, the kidneys increase the elimination of H⁺ from the body to restore balance. Alternatively, if there is a net loss of H⁺ from the body due to hyperventilation or vomiting, the kidneys replenish this H⁺.

Although the kidneys are the ultimate hydrogen ion balancers, the respiratory system also has a very important homeostatic function. 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 reflexively altered

so as to help compensate for the imbalance. We described this phenomenon in Chapter 13 (see Figure 13.38). An increased arterial H⁺ concentration stimulates ventilation, which lowers arterial P_{CO₂} that, by mass action, reduces H⁺ concentration. Alternatively, a decreased plasma H⁺ concentration inhibits ventilation, thereby increasing arterial P_{CO₂} and the H⁺ concentration.

In this way, the respiratory system and kidneys work together. The respiratory response to altered plasma H⁺ 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. If the respiratory system is the actual cause of the H⁺ imbalance, then the kidneys are the sole homeostatic responder. Conversely, malfunctioning kidneys can create a H⁺ imbalance by eliminating too little or too much H⁺ from the body, and then the respiratory response is the only one in control. As you can see, the control of acid–base balance requires that the functions of organ systems be coordinated with each other—another general principle of physiology highlighted in this book.

14.19 Renal Mechanisms

The kidneys eliminate or replenish H⁺ from the body by altering plasma HCO₃[−] concentration. The key to understanding how altering plasma HCO₃[−] concentration eliminates or replenishes H⁺ was stated earlier. That is, the excretion of HCO₃[−] in the urine increases the plasma H⁺ concentration just as if a H⁺ had been added to the plasma. Similarly, the addition of HCO₃[−] to the plasma decreases the plasma H⁺ concentration just as if a H⁺ had been removed from the plasma.

When the plasma H⁺ ion concentration decreases (alkalosis) for whatever reason, the kidneys' homeostatic response is to excrete large quantities of HCO₃[−]. This increases plasma H⁺ concentration toward normal. In contrast, when plasma H⁺ concentration increases (acidosis), the kidneys do not excrete HCO₃[−] in the urine. Rather, kidney tubular cells produce new HCO₃[−] and add it to the plasma. This decreases the H⁺ ion concentration toward normal.

HCO₃[−] Handling

HCO₃[−] is completely filterable at the renal corpuscles and undergoes significant tubular reabsorption in the proximal tubule, ascending loop of Henle, and cortical collecting ducts. It 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 HCO₃[−] because it is always much less than tubular reabsorption, and we will treat HCO₃[−] excretion as the difference between filtration and reabsorption.

HCO₃[−] reabsorption is an active process, but it is not accomplished in the conventional manner of simply having an active pump for HCO₃[−] at the apical or basolateral membrane of the tubular cells. Instead, HCO₃[−] reabsorption depends on the tubular secretion of H⁺, which combines in the lumen with filtered HCO₃[−].

Figure 14.33 illustrates the sequence of events. Begin this figure inside the cell with the combination of CO₂ and H₂O to

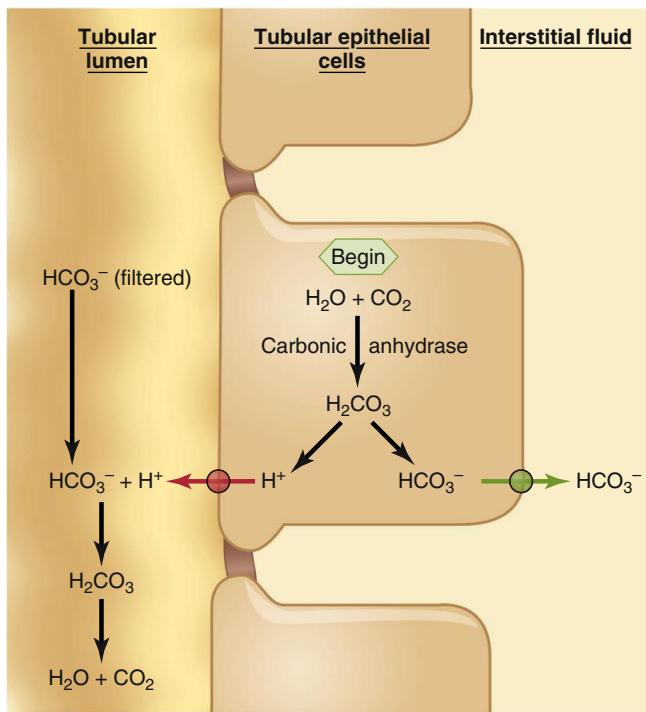


Figure 14.33 General model of the reabsorption of HCO_3^- in the proximal tubule and cortical collecting duct. Begin looking at this figure inside the cell, with the combination of CO_2 and H_2O to form H_2CO_3 . As shown in the figure, active H^+ -ATPase pumps are involved in the movement of H^+ out of the cell across the apical membrane; in several tubular segments, this transport step is also mediated by Na^+/H^+ countertransporters and/or H^+/K^+ -ATPase pumps.

form H_2CO_3 , a reaction catalyzed by the enzyme carbonic anhydrase. The H_2CO_3 immediately dissociates to yield H^+ and HCO_3^- . The HCO_3^- moves down its concentration gradient via facilitated diffusion 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.

The secreted H^+ , however, is not excreted. Instead, it combines in the lumen with a filtered HCO_3^- and generates CO_2 and H_2O , both of which can diffuse into the cell and be available for another cycle of H^+ generation. The overall result is that the HCO_3^- filtered from the plasma at the renal corpuscle has disappeared, but its place in the plasma has been taken by the HCO_3^- that was produced inside the cell. In this manner, no net change in plasma HCO_3^- concentration has occurred. It may seem inaccurate to refer to this process as HCO_3^- “reabsorption” because the HCO_3^- that appears in the peritubular plasma is not the same HCO_3^- that was filtered. Yet, the overall result is the same as if the filtered HCO_3^- had been reabsorbed in the conventional manner like Na^+ or K^+ .

Except in response to alkalosis, discussed in Section 14.20 the kidneys normally reabsorb all filtered HCO_3^- , thereby preventing the loss of HCO_3^- in the urine.

Addition of New HCO_3^- to the Plasma

An essential concept shown in Figure 14.33 is that as long as there are still significant amounts of filtered HCO_3^- in the lumen, almost all secreted H^+ will combine with it. But what happens to

any secreted H^+ once almost all the HCO_3^- has been reabsorbed and is no longer available in the lumen to combine with the H^+ ?

The answer, illustrated in **Figure 14.34**, is that the extra secreted H^+ combines in the lumen with a filtered nonbicarbonate buffer, the most important of which is HPO_4^{2-} . The H^+ is then excreted in the urine as part of H_2PO_4^- . Now for the critical point: Note in Figure 14.34 that, under these conditions, the HCO_3^- generated within the tubular cell by the carbonic anhydrase reaction and entering the plasma constitutes a *net gain* of HCO_3^- by the plasma, not merely a replacement for filtered HCO_3^- . Therefore, when secreted H^+ combines in the lumen with a buffer other than HCO_3^- , the overall effect is not merely one of HCO_3^- conservation, as in Figure 14.33, but, rather, of addition to the plasma of *new* HCO_3^- . This increases the HCO_3^- concentration of the plasma and alkalinizes it.

To repeat, significant amounts of H^+ combine with filtered nonbicarbonate buffers like HPO_4^{2-} only after the filtered HCO_3^- has virtually all been reabsorbed. The main reason is that there is such a large load of filtered HCO_3^- —25 times more than the load of filtered nonbicarbonate buffers—competing for the secreted H^+ .

There is a second mechanism by which the tubules contribute new HCO_3^- to the plasma that involves not H^+ secretion but, rather, the renal production and secretion of ammonium ion (NH_4^+) (**Figure 14.35**). Tubular cells, mainly those of the proximal tubule, take up glutamine from both the glomerular filtrate and peritubular plasma and metabolize it. In the process,

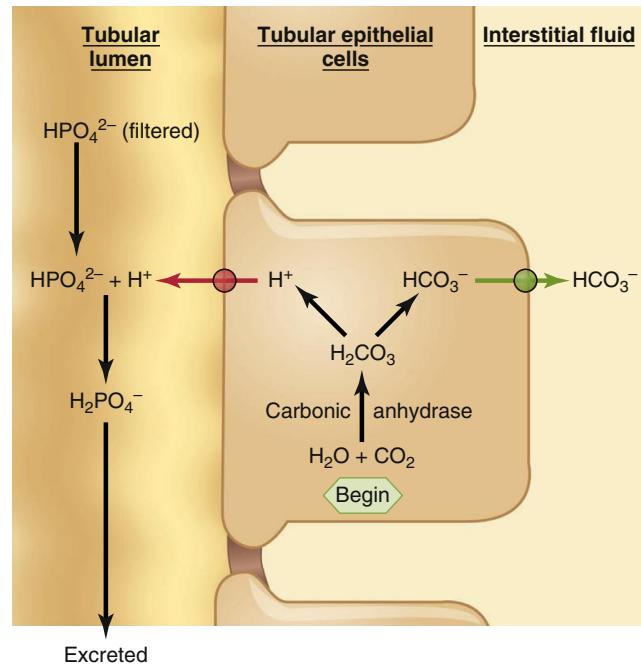


Figure 14.34 Renal contribution of new HCO_3^- to the plasma as achieved by tubular secretion of H^+ . The process of intracellular H^+ and HCO_3^- generation, with H^+ moving into the lumen and HCO_3^- into the plasma, is identical to that shown in Figure 14.33. Once in the lumen of the proximal tubule, however, the H^+ combines with filtered phosphate ion (HPO_4^{2-}) rather than filtered HCO_3^- and is excreted as H_2PO_4^- . As described in the legend for Figure 14.33, the transport of H^+ into the lumen is accomplished not only by H^+ -ATPase pumps but, in several tubular segments, by Na^+/H^+ countertransporters and/or H^+/K^+ -ATPase pumps as well.

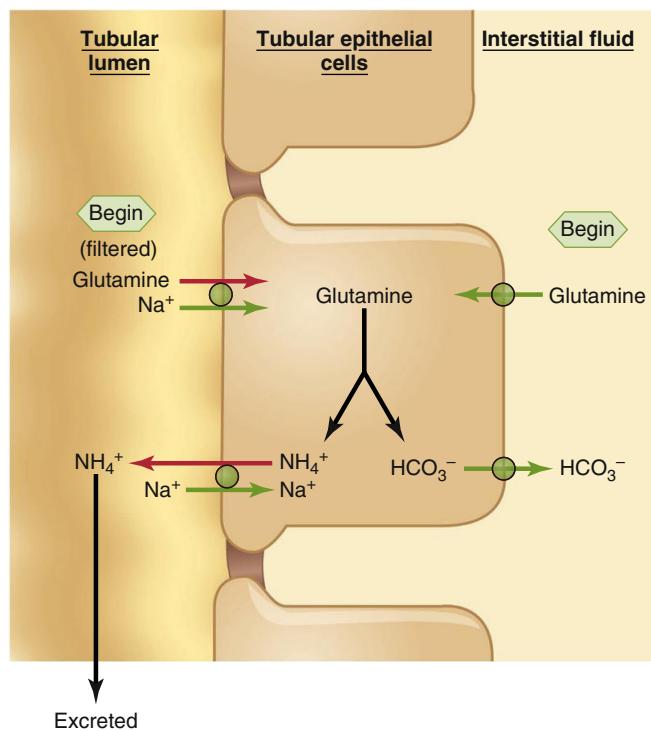


Figure 14.35 Renal contribution of new HCO_3^- to the plasma as achieved by renal metabolism of glutamine and excretion of ammonium (NH_4^+). Compare this figure to Figure 14.34. This process occurs mainly in the proximal tubule.

both NH_4^+ and HCO_3^- are formed inside the cells. The NH_4^+ is actively secreted via $\text{Na}^+/\text{NH}_4^+$ countertransport into the lumen and excreted, while the HCO_3^- moves into the peritubular capillaries and constitutes new plasma HCO_3^- .

A comparison of Figures 14.34 and 14.35 demonstrates that the overall result—renal contribution of new HCO_3^- to the plasma—is the same regardless of whether it is achieved (1) by H^+ secretion and excretion on nonbicarbonate buffers such as phosphate (see Figure 14.34) or (2) by glutamine metabolism with excretion (see Figure 14.35). It is convenient, therefore, to view the latter as representing H^+ excretion “bound” to NH_3 , just as the former case constitutes H^+ excretion bound to nonbicarbonate buffers. Thus, the amount of H^+ excreted in the urine in these two forms is a measure of the amount of new HCO_3^- added to the plasma by the kidneys. Indeed, “urinary H^+ excretion” and “renal contribution of new HCO_3^- to the plasma” are really two sides of the same coin.

The kidneys normally contribute enough new HCO_3^- to the blood by excreting H^+ to compensate for the H^+ from nonvolatile acids generated in the body.

14.20 Classification of Acidosis and Alkalosis

The renal responses to the presence of acidosis or alkalosis are summarized in **Table 14.7**. To repeat, acidosis refers to any situation in which the H^+ concentration of arterial plasma is increased above normal whereas alkalosis denotes a decrease. All such situations fit into two distinct categories (**Table 14.8**): (1) *respiratory acidosis or alkalosis* and (2) *metabolic acidosis or alkalosis*.

As its name implies, respiratory acidosis results from altered alveolar ventilation. Respiratory acidosis occurs when the respiratory

TABLE 14.7 Renal Responses to Acidosis and Alkalosis

Responses to acidosis

- Sufficient H^+ is secreted to reabsorb all the filtered HCO_3^- .
- Still more H^+ is secreted, and this contributes new HCO_3^- to the plasma as the H^+ is excreted bound to nonbicarbonate urinary buffers such as HPO_4^{2-} .
- Tubular glutamine metabolism and ammonium excretion are enhanced, which also contributes new HCO_3^- to the plasma.

Net result: More new HCO_3^- than usual is added to the blood, and plasma HCO_3^- is increased, thereby compensating for the acidosis. The urine is highly acidic (lowest attainable pH = 4.4).

Responses to alkalosis

- Rate of H^+ secretion is inadequate to reabsorb all the filtered HCO_3^- , so significant amounts of HCO_3^- are excreted in the urine, and there is little or no excretion of H^+ on nonbicarbonate urinary buffers.
- Tubular glutamine metabolism and ammonium excretion are decreased so that little or no new HCO_3^- is contributed to the plasma from this source.

Net result: Plasma HCO_3^- concentration is decreased, thereby compensating for the alkalosis. The urine is alkaline (pH > 7.4).

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 H^+ concentrations in such cases is completely explainable in terms of mass action. The hallmark of respiratory acidosis is an increase in both arterial P_{CO_2} and H^+ concentration, whereas that of respiratory alkalosis is a decrease 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 the Clinical Case Study of Chapter 16). Metabolic acidosis can also result from excessive loss of HCO_3^- , as in diarrhea. A cause of metabolic alkalosis is persistent vomiting, with its associated loss of H^+ as HCl from the stomach.

What is the arterial P_{CO_2} in metabolic acidosis or alkalosis? By definition, metabolic acidosis and alkalosis must be due to something other than excess retention or loss of carbon dioxide, so you might have predicted that arterial P_{CO_2} would be unchanged, but this is not the case. As emphasized earlier in this chapter, the increased H^+ concentration associated with metabolic acidosis reflexively stimulates ventilation and decreases arterial P_{CO_2} . By mass action, this helps restore the H^+ concentration toward normal. Conversely, a person with metabolic alkalosis will reflexively have ventilation inhibited. The result is an increase in arterial P_{CO_2} and, by mass action, an associated restoration of H^+ concentration toward normal.

To reiterate, the plasma P_{CO_2} changes in metabolic acidosis and alkalosis are not the *cause* of the acidosis or alkalosis but

TABLE 14.8 Changes in the Arterial Concentrations of H^+ , HCO_3^- , and Carbon Dioxide in Acid–Base Disorders

Primary Disorder	H^+	HCO_3^-	CO_2	Cause of HCO_3^- Change	Cause of CO_2 Change
Respiratory acidosis	↑	↑	↑	Renal compensation	Primary abnormality
Respiratory alkalosis	↓	↓	↓		
Metabolic acidosis	↑	↓	↓	Primary abnormality	Reflex ventilatory compensation
Metabolic alkalosis	↓	↑	↑		

PHYSIOLOGICAL INQUIRY

- A patient has an arterial P_{O_2} of 50 mmHg, an arterial P_{CO_2} of 60 mmHg, and an arterial pH of 7.36. Classify the acid–base disturbance and hypothesize a cause.

Answer can be found at end of chapter.

the result of compensatory reflexive responses to nonrespiratory abnormalities. Thus, in metabolic as opposed to respiratory conditions, the arterial plasma P_{CO_2} and H^+ concentration move in opposite directions, as summarized in Table 14.8. ■

SECTION C SUMMARY

Sources of Hydrogen Ion Gain or Loss

- Total-body balance of H^+ 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 14.6).
- A stable balance is achieved by regulation of urinary losses.

Buffering of Hydrogen Ion in the Body

- Buffering is a means of minimizing changes in H^+ concentration by combining these ions reversibly with anions such as HCO_3^- and intracellular proteins.
- 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

- The kidneys and the respiratory system are the homeostatic regulators of plasma H^+ concentration.
- The kidneys are the organs that achieve body H^+ balance.
- A decrease in arterial plasma H^+ concentration causes reflex hypoventilation, which increases arterial P_{CO_2} and, hence, increases plasma H^+ concentration toward normal. An increase in plasma H^+ concentration causes reflexive hyperventilation, which decreases arterial P_{CO_2} and, hence, decreases H^+ concentration toward normal.

Renal Mechanisms

- The kidneys maintain a stable plasma H^+ concentration by regulating plasma HCO_3^- concentration. They can either excrete HCO_3^- or contribute new HCO_3^- to the blood.
- HCO_3^- is reabsorbed when H^+ , generated in the tubular cells by a process catalyzed by carbonic anhydrase, is secreted into the lumen and combine with filtered HCO_3^- . The secreted H^+ is not excreted in this situation.
- In contrast, when the secreted H^+ combines in the lumen with filtered phosphate ion or other nonbicarbonate buffer, it is excreted, and the kidneys have contributed new HCO_3^- to the blood.
- The kidneys also contribute new HCO_3^- to the blood when they produce and excrete ammonium.

Classification of Acidosis and Alkalosis

- Acid–base disorders are categorized as respiratory or metabolic.
 - Respiratory acidosis is due to retention of carbon dioxide, and respiratory alkalosis is due to excessive elimination of carbon dioxide.
 - All other causes of acidosis or alkalosis are termed *metabolic* and reflect gain or loss, respectively, of H^+ from a source other than carbon dioxide.

SECTION C REVIEW QUESTIONS

- What are the sources of gain and loss of H^+ in the body?
- List the body's major buffer systems.
- Describe the role of the respiratory system in the regulation of H^+ concentration.
- How does the tubular secretion of H^+ occur, and how does it achieve HCO_3^- reabsorption?
- How does H^+ secretion contribute to the renal addition of new HCO_3^- to the blood? What determines whether secreted H^+ will achieve these results or will instead cause HCO_3^- reabsorption?
- How does the metabolism of glutamine by the tubular cells contribute new HCO_3^- to the blood and ammonium to the urine?
- What two quantities make up “ H^+ excretion”? Why can this term be equated with “contribution of new HCO_3^- to the plasma”?
- How do the kidneys respond to the presence of acidosis or alkalosis?
- Classify the four types of acid–base disorders according to plasma H^+ concentration, HCO_3^- concentration, and P_{CO_2} .
- Explain how overuse of certain diuretics can lead to metabolic alkalosis.

SECTION C KEY TERMS

14.16 Sources of Hydrogen Ion Gain or Loss

nonvolatile acids

14.17 Buffering of Hydrogen Ion in the Body

buffer

SECTION C CLINICAL TERMS

acidosis

alkalosis

14.20 Classification of Acidosis and Alkalosis

metabolic acidosis
metabolic alkalosis

respiratory acidosis
respiratory alkalosis

Clinical Case Study: Severe Kidney Disease in a Woman with Diabetes Mellitus



A patient with poorly controlled, long-standing type 2 diabetes mellitus has been feeling progressively weaker over the past few months. She has also been feeling generally ill and has been gaining weight although she has not changed her eating habits. During a routine visit to her family doctor, some standard blood and urine tests are ordered as an initial evaluation. In addition, her previously diagnosed mild high blood pressure has gotten significantly worse. The physician is concerned when the testing shows an increase in creatinine in her blood and a significant amount of protein in her urine. The patient is referred to a nephrologist (kidney-disease expert) who makes the diagnosis of diabetic kidney disease (diabetic nephropathy).

Many diseases affect the kidneys. Potential causes of kidney damage include congenital and inherited defects, metabolic disorders, infection, inflammation, trauma, vascular problems, and certain forms of cancer. Obstruction of the urethra or a ureter may cause injury from the buildup of pressure and may predispose the kidneys to bacterial infection. A common cause of renal failure is poorly controlled diabetes mellitus. The increase in blood glucose interferes with normal renal filtration and tubular function (see Section 14.13 of this chapter and Chapter 16), and high blood pressure common to patients with type 2 diabetes mellitus causes vascular damage in the kidney.

One of the earliest signs of a decrease in kidney function is an increase in creatinine in the blood, which was found to be the case in our patient. As described in Section 14.3 of this chapter, creatinine is a waste product of muscle metabolism that is filtered in the glomerulus and not reabsorbed. Although a small amount of creatinine is secreted in the renal tubule, creatinine clearance is a good estimate of glomerular filtration rate (GFR). Because a decrease in GFR occurs early in kidney disease, and because creatinine production is fairly constant, an increase in creatinine in the blood is a useful warning sign that creatinine clearance is decreasing and that kidney failure is occurring.

Reflect and Review #1

- Loss of lean body (muscle) mass can be a normal consequence of aging. Since most of the creatinine production in the body is from skeletal muscle, how would the decrease in lean body mass in elderly individuals affect the interpretation of plasma creatinine concentration as an index of GFR? (*Hint:* See Section 14.4.)

Another frequent sign of kidney disease, which was also observed in our patient, is the appearance of protein in the urine. In normal kidneys, there is a tiny amount of protein in the glomerular filtrate because the filtration barrier 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, in diabetic nephropathy, the

filtration barrier 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 appears in the urine. The loss of protein in the urine leads to a decrease in the amount of protein in the blood. This results in a decrease in the osmotic force retaining fluid in the blood and subsequently the formation of edema throughout the body (see Chapter 12). In our patient, this resulted in an increase in body weight.

Although many diseases of the kidneys are self-limited and produce no permanent damage, others worsen if untreated. The symptoms of profound renal malfunction are relatively independent of the damaging agent and are collectively known as **uremia**, literally, “urea in the blood.”

The severity of uremia depends upon how well the impaired kidneys can 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 K^+ 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 fails to add enough new HCO_3^- to the blood to compensate for the daily metabolic production of nonvolatile 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% to 30% of the nephrons are functioning. This is because these remaining nephrons undergo alterations in function—filtration, reabsorption, and secretion—to compensate for the missing nephrons. For example, each remaining nephron increases its rate of K^+ secretion, so that the total amount of K^+ the kidneys excrete is maintained at normal levels. The limits of regulation are restricted, however. To use K^+ 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 K^+ to prevent potassium retention.

Other problems arise in uremia because of abnormal secretion of the hormones the kidneys produce. For example, decreased secretion of erythropoietin results in anemia (see Chapter 12). Decreased ability to form $1,25-(OH)_2D$ results in deficient absorption of calcium ion from the gastrointestinal tract, with a resulting decrease in plasma calcium, increase in PTH, and inadequate bone calcification (secondary hyperparathyroidism). Erythropoietin and $1,25-(OH)_2D$ (calcitriol) can be administered to patients with uremia to improve hematocrit and calcium balance.

Reflect and Review #2

- Why do patients on long-term hemodialysis often have increased plasma concentrations of phosphorus? (*Hint:* See Section 14.13, Table 14.5, and look back at Section F of Chapter 11.)

(continued)

In the case of the secreted enzyme renin, there is rarely too little secretion; rather, there is too much secretion by the juxtaglomerular cells of the damaged kidneys. The main reason for the increase in renin is decreased perfusion of affected nephrons (intrarenal baroreceptor mechanism). The result is increased plasma angiotensin II concentration and the development of ***renal hypertension***. ACE inhibitors and angiotensin II receptor blockers can be used to decrease blood pressure and improve sodium and water balance. Our patient was counseled to more carefully and aggressively control her blood glucose and blood pressure with diet, exercise, and medications. She was also started on an ACE inhibitor. Unfortunately, her blood creatinine and proteinuria continued to worsen to the point of end-stage renal disease requiring hemodialysis.

Hemodialysis, Peritoneal Dialysis, and Transplantation

Failing kidneys may 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 help minimize but not eliminate these problems. For example, decreasing potassium intake reduces the amount of K^+ to be excreted. The clinical techniques used to perform the kidneys' excretory functions are hemodialysis and peritoneal dialysis. The general term ***dialysis*** means to separate substances using a permeable membrane.

The artificial kidney is an apparatus that utilizes a process termed ***hemodialysis*** to remove wastes and excess substances from the blood (Figure 14.36). 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 dialysis 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 renal capillaries. The dialysis fluid contains solutes 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 K^+ concentration of the patient is above normal, K^+ 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 like the woman in our case with chronic irreversible renal failure require treatment for the rest of their lives, however, unless they receive a kidney transplant. Such patients undergo hemodialysis several times a week.

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 an indwelling plastic tube 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

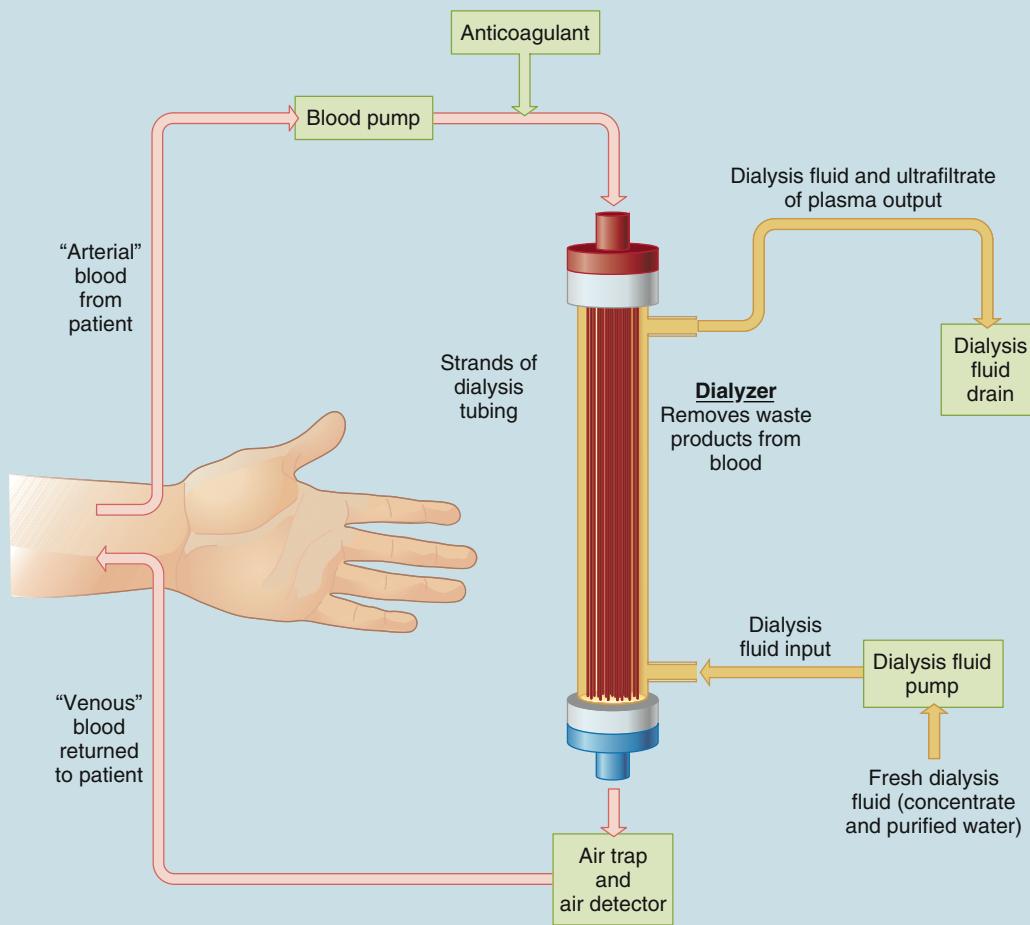


Figure 14.36 Simplified diagram of hemodialysis. Note that blood and dialysis fluid flow in opposite directions through the dialyzer (countercurrent). The blood flow can be 400 mL/min, and the dialysis fluid flow rate can be 1000 mL/min! During a 3 to 4 h dialysis session, approximately 72 to 96 L of blood and 3000 to 4000 L of dialysis fluid pass through the dialyzer. The dialyzer is composed of many strands of very thin dialysis tubing. Blood flows inside each tube, and dialysis fluid bathes the outside of the dialysis tubing. This provides a large surface area for diffusion of waste products out of the blood and into the dialysis fluid.

dialysis fluid is then removed and replaced with new fluid. This procedure can be performed several times daily by a patient who is simultaneously doing normal activities.

The long-term 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, but great strides have been made in reducing the frequency of rejection (see Chapter 18). Many people who could benefit from a transplant, however, do not receive one. Currently, the major source of kidneys for transplantation is recently deceased persons. Recently, donation from a living, related donor has become more common. Because of the large safety factor, the donor can function normally with one kidney. In 2013, approximately 101,000 people in the United States were waiting for a kidney transplant. There were approximately

11,000 deceased donor and 6000 living donor kidney transplants in 2013, highlighting the shortage of transplantable kidneys. It is hoped that improved public understanding will lead to many more individuals giving permission in advance to have their kidneys and other organs used following their death. Our patient continued on hemodialysis three times a week for several years waiting for a kidney transplant. It was determined that her older brother was a compatible organ match, and he donated his kidney to our patient, allowing her to stop hemodialysis treatments. She continues to aggressively control her blood glucose and blood pressure.

Clinical terms: dialysis, hemodialysis, peritoneal dialysis, renal hypertension, uremia

See Chapter 19 for complete, integrative case studies.

CHAPTER 14 TEST QUESTIONS Recall and Comprehend

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Which of the following will lead to an increase in glomerular fluid filtration in the kidneys?
 - a. an increase in the protein concentration in the plasma
 - b. an increase in the fluid pressure in Bowman's space
 - c. an increase in the glomerular capillary blood pressure
 - d. a decrease in the glomerular capillary blood pressure
 - e. constriction of the afferent arteriole
2. Which of the following is true about renal clearance?
 - a. It is the amount of a substance excreted per unit time.
 - b. A substance with clearance > GFR undergoes only filtration.
 - c. A substance with clearance > GFR undergoes filtration and secretion.
 - d. It can be calculated knowing only the filtered load of a substance and the rate of urine production.
 - e. Creatinine clearance approximates renal plasma flow.
3. Which of the following will *not* lead to a diuresis?
 - a. excessive sweating
 - b. central diabetes insipidus
 - c. nephrogenic diabetes insipidus
 - d. excessive water intake
 - e. uncontrolled diabetes mellitus
4. Which of the following contributes directly to the generation of a hypertonic medullary interstitium in the kidney?
 - a. active Na^+ transport in the descending limb of Henle's loop
 - b. active water reabsorption in the ascending limb of Henle's loop
 - c. active Na^+ reabsorption in the distal convoluted tubule
 - d. water reabsorption in the cortical collecting duct
 - e. secretion of urea into Henle's loop
5. An increase in renin is caused by
 - a. a decrease in sodium intake.
 - b. a decrease in renal sympathetic nerve activity.
 - c. an increase in blood pressure in the renal artery.
 - d. an aldosterone-secreting adrenal tumor.
 - e. essential hypertension.
6. An increase in parathyroid hormone will
 - a. increase plasma $25(\text{OH})\text{D}$.
 - b. decrease plasma $1,25-(\text{OH})_2\text{D}$.
 - c. decrease calcium ion excretion.
 - d. increase phosphate ion reabsorption.
 - e. increase calcium ion reabsorption in the proximal tubule.
7. Which of the following is a component of the renal response to metabolic acidosis?
 - a. reabsorption of H^+
 - b. secretion of HCO_3^- into the tubular lumen
 - c. secretion of ammonium into the tubular lumen
 - d. secretion of glutamine into the interstitial fluid
 - e. carbonic anhydrase-mediated production of HPO_4^{2-}
8. Which of the following is consistent with respiratory alkalosis?
 - a. an increase in alveolar ventilation during mild exercise
 - b. hyperventilation
 - c. an increase in plasma HCO_3^-
 - d. an increase in arterial CO_2
 - e. urine pH < 5.0
9. Which is *true* about the difference between cortical and juxtamedullary nephrons?
 - a. Most nephrons are juxtamedullary.
 - b. The efferent arterioles of cortical nephrons give rise to most of the vasa recta.
 - c. The afferent arterioles of the juxtamedullary nephrons give rise to most of the vasa recta.
 - d. All cortical nephrons have a loop of Henle.
 - e. Juxtamedullary nephrons generate a hyperosmotic medullary interstitium.
10. Which of the following is consistent with untreated chronic renal failure?
 - a. proteinuria
 - b. hypokalemia
 - c. increased plasma $1,25-(\text{OH})_2\text{D}$
 - d. increased plasma erythropoietin
 - e. increased plasma HCO_3^-

CHAPTER 14 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. Substance T is present in the urine. Does this prove that it is filterable at the glomerulus? Hint: See Figure 14.6 and remember the different routes for a substance to enter the tubular fluid.
2. Substance V is not normally present in the urine. Does this prove that it is neither filtered nor secreted? Hint: See Figure 14.7 and remember the third process in renal function.
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? Hint: See Figure 14.12.
4. A person is excreting abnormally large amounts of a particular amino acid. Just from the theoretical description of T_m -limited reabsorptive mechanisms in the text, list several possible causes. Hint: See Figure 14.11.
5. The concentration of urea in urine is always much higher than the concentration in plasma. Does this mean that urea is secreted? Hint: See Figure 14.20 and remember that concentration is a ratio.
6. If a person takes a drug that blocks the reabsorption of Na^+ , what will happen to the reabsorption of water, urea, Cl^- , glucose, and amino acids and to the secretion of H^+ ? Hint: See Figure 14.14.
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. Hint: See Figure 14.24.
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? Hint: See Figure 14.23.
9. In the steady state, what is the amount of sodium chloride excreted daily in the urine of a normal person ingesting 12 g of sodium chloride per day: (a) 12 g/day, or (b) less than 12 g/day? Explain. Hint: See Figure 14.28 and ask yourself whether the kidney is the only organ that can lose sodium chloride.
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? Hint: See Figure 14.29 and remember the main stimulus to vasopressin and thirst.
11. A patient has a tumor in the adrenal cortex that continuously secretes large amounts of aldosterone. What is this condition called, and what effects does this have on the total amount of sodium and potassium in her body? Hint: See Figure 14.32.
12. A person is taking a drug that inhibits the tubular secretion of H^+ . What effect does this drug have on the body's balance of sodium, water, and H^+ ? Hint: See Figures 14.14, 14.33, and 14.34. Remember that Na^+ reabsorption by the proximal tubule is achieved by Na^+/H^+ countertransport.
13. How can the overuse of diuretics lead to metabolic alkalosis? Hint: See Figures 14.24, 14.33, 14.34, and 14.35. Remember that overuse of diuretics can lead to an increase in plasma aldosterone concentration and to potassium depletion.

CHAPTER 14 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. A general principle of physiology is that *structure is a determinant of—and has coevolved with—function*. How does the anatomy of the renal corpuscle and associated structures determine function?
2. *Physiological processes are dictated by the laws of chemistry and physics.* Give one example each of how a law of chemistry and a law of physics are important in understanding the regulation of renal function.
3. How does the control of vasopressin secretion highlight the general principle of physiology that *most physiological functions are controlled by multiple regulatory systems, often working in opposition*?

CHAPTER 14 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 14.4 The glomerular filtration rate would be greatly decreased. This would result in a decrease in the removal of toxic substances from the blood. As you will learn, kidney disease is a common and troubling consequence of long-term untreated diabetes mellitus.

Figure 14.8 GFR will decrease because the increase in plasma osmotic force from albumin will oppose filtration.

Figure 14.9 A blood clot occluding the afferent arteriole would decrease blood flow to that glomerulus and greatly decrease GFR in that individual glomerulus. A blood clot in the efferent arteriole would increase P_{GC} and, therefore, GFR. If this only occurred in a few glomeruli, it would not have a significant effect on renal function because of the large number of total glomeruli in the two kidneys providing a safety factor.

Figure 14.11 Filtered load = GFR \times Plasma glucose concentration.
Excretion rate = Urine glucose concentration \times Urine flow rate.

Figure 14.14 It would decrease sodium reabsorption from the tubular fluid. This will result in an increase in urinary sodium excretion. The osmotic force of sodium will carry water with it, thus increasing urine output. Examples of such diuretics are triamterene and amiloride.

Figure 14.18 The increased vasopressin would cause maximal water reabsorption. Urine volume would be low (antidiuresis) and urine

osmolarity would remain high. The continuous water reabsorption would cause a decrease in plasma sodium concentration (hyponatremia) due to dilution of sodium. Consequently, the plasma would have very low osmolarity. The decreased plasma osmolarity would not inhibit vasopressin secretion from the tumor because it is not controlled by the hypothalamic osmoreceptors. This is called the *syndrome of inappropriate antidiuretic hormone (SIADH)* and is one of several possible causes of hyponatremia in humans.

Figure 14.23 An ACE inhibitor will decrease angiotensin II production. The resultant increase in Na^+ and water excretion would decrease blood pressure, leading to a reflexive increase in renin secretion. An ARB would also decrease blood pressure and therefore increase renin secretion. However, with an ARB, angiotensin II would increase because angiotensin-converting-enzyme activity would be normal.

Figure 14.24 Under normal conditions, the redundant control of renin release, as indicated in this figure, as well as the participation of vasopressin (see Figure 14.27), would allow the maintenance of normal sodium and water balance even with denervated kidneys. However, during severe decreases in plasma volume, like in dehydration, the denervated kidney may not produce sufficient renin to maximally decrease Na^+ excretion.

Figure 14.28 The adaptation to a hot environment depends on the ability to lose heat from the body by sweating (see Figure 16.17). The ability to detect a decrease in plasma volume by low-pressure baroreceptors in the heart (see Chapter 12) and an increase in osmolarity by osmoreceptors in the brain sets in motion a coordinated response to minimize the loss of body water and ions including Na^+ . This includes a decrease in GFR in the kidneys and an increase in secretion of aldosterone from the adrenal cortex. The decreased GFR decreases the amount of water and ions entering the filtrate in the kidneys, thereby decreasing losses in the urine. The increased concentration of plasma aldosterone increases renal Na^+ reabsorption. The increased synthesis of vasopressin in the hypothalamus and its release from axons in the posterior pituitary leads to an increase in vasopressin in the blood that signals the kidneys to increase water reabsorption. Therefore, the coordination of organs from the nervous system (the brain), endocrine system (posterior pituitary), circulatory system (heart), and urinary system (kidneys) minimizes the loss of water and Na^+ during sweating until the deficits of both can be replaced by increased ingestion and absorption in the gastrointestinal tract.

Figure 14.31 The concept of mass balance is one of the most important in homeostasis (see Figure 1.11). As described in Chapter 1, when the gain of a substance exceeds its loss, one is in a positive balance for that substance.

Although you have learned that K^+ is extremely important in the normal function of excitable cells (see Chapter 6 and Section 12.4 of Chapter 12), too much K^+ is dangerous because of its effects on the membrane potential. For that reason, precise homeostatic control mechanisms exist to maintain whole-body K^+ balance. Small increases in plasma K^+ have a direct effect in the kidneys to increase K^+ secretion. Furthermore, small increases in plasma K^+ stimulate the release of aldosterone from the adrenal cortex, which, in turn, stimulates K^+ secretion in the kidneys. The direct effect of increased K^+ and the renal effect of aldosterone act to normalize K^+ balance. The failure of the adrenal cortex to produce adequate aldosterone in response to an increase in plasma K^+ (as in primary adrenal insufficiency, see Section 11.15 of Chapter 11) can lead to life-threatening hyperkalemia.

Table 14.8 The patient has respiratory acidosis with renal compensation (hypercapnia with a normalization of arterial pH). The patient is hypoxic, which, with normal lung function, usually leads to hyperventilation and respiratory alkalosis. Therefore, the patient is likely to have chronic lung disease resulting in hypoxemia and retention of carbon dioxide (hypercapnia). We know it is chronic because the kidneys have had time to compensate for the acidosis by increasing the HCO_3^- added to the blood, thus restoring arterial pH almost to normal (see Figures 14.33 to 14.35).

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