CHAPTER 24

The Regulation of Fluid and Electrolyte Balance

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CHAPTER OUTLINE

KEY CONCEPTS

1. Total body water is distributed in two major compartments: intracellular water and extracellular water. In an average young adult man, total body water, intracellular water, and extracellular water amount to 60%, 40%, and 20% of body weight, respectively. The corresponding figures for an average young adult woman are 50%, 30%, and 20% of body weight.
2. The volumes of body fluid compartments are determined by using the indicator dilution method and this equation is: Volume = Amount of indicator≡Concentration of indicator at equilibrium.
3. Electrical neutrality is present in solutions of electrolytes; that is, the sum of the cations is equal to the sum of the anions (both expressed in milliequivalents).
4. Sodium (Na^+) is the major osmotically active solute in extracellular fluid (ECF), and potassium (K^+) has the same role in the intracellular fluid (ICF) compartment. Cells are typically in osmotic equilibrium with their external environment. The amount of water in (and, hence, the volume of) cells depends on the amount of K^+ they contain and, similarly, the amount of water in (and, hence, the volume of) the ECF is determined by its Na^+ content.
5. Plasma osmolality is closely regulated by arginine vasopressin (AVP), which governs renal excretion of water, and by habit and thirst, which govern water intake.
6. AVP is synthesized in the hypothalamus, released from the posterior pituitary gland, and acts on the collecting ducts of the kidney to increase their water permeability. The major stimuli for the release of AVP are an increase in effective plasma osmolality (detected by osmoreceptors in the anterior hypothalamus) and a decrease in blood volume (detected by stretch receptors in the left atrium, carotid sinuses, and aortic arch).
7. The kidneys are the primary site of control of Na^+ excretion. Only a small percentage (usually about 1%) of the filtered Na^+ is excreted in the urine, but this amount is of critical importance in overall Na^+ balance.
8. Multiple factors affect Na^+ excretion, including glomerular filtration rate, angiotensin II and aldosterone, intrarenal physical forces, natriuretic hormones and factors such as atrial natriuretic peptide, and renal sympathetic nerves. Changes in these factors may account for altered Na^+ excretion in response to excess Na^+ or Na^+ depletion. Estrogens, glucocorticoids, osmotic diuretics, poorly reabsorbed anions in the urine, and diuretic drugs also affect renal Na^+ excretion.
9. The effective arterial blood volume (EABV) depends on the degree of filling of the arterial system and determines the perfusion of the body's tissues. A decrease in EABV leads to Na^+ retention by the kidneys and contributes to the development of generalized edema in pathophysiological conditions, such as congestive heart failure.
10. The kidneys play a major role in the control of K^+ balance. K^+ is reabsorbed by the proximal convoluted tubule and the loop of Henle and is secreted by cortical collecting duct principal cells. Inadequate renal K^+ excretion produces hyperkalemia and excessive K^+ excretion produces hypokalemia.
11. Calcium balance is regulated on both input and output sides. The absorption of Ca^{2+} from the small intestine is controlled by $1,25(OH)_2$ vitamin D_3, and the excretion of Ca^{2+} by the kidneys is controlled by parathyroid hormone (PTH).
12. Magnesium in the body is mostly in bone, but it is also an important intracellular ion. The kidneys regulate the plasma $[Mg^{2+}]$.
13. Filtered phosphate usually exceeds the maximal reabsorptive capacity of the kidney tubules for phosphate (Tm_{PO_4}), and about 5 to 20% of filtered phosphate is usually excreted. Phosphate reabsorption occurs mainly in the proximal tubules and is inhibited by PTH. Phosphate is an important pH buffer in the urine. Hyperphosphatemia is a significant problem in chronic renal failure.
14. The urinary bladder stores urine until it can be conveniently emptied. Micturition is a complex act involving both autonomic and somatic nerves.

A major function of the kidneys is to regulate the volume, composition, and osmolality of the body fluids. The fluid surrounding our body cells (the ECF) is constantly renewed and replenished by the circulating blood plasma. The kidneys constantly process the plasma; they filter, reabsorb, and secrete substances and, in health, maintain the internal environment within narrow limits. In this chapter, we begin with a discussion of the fluid compartments of the body—their location, magnitude, and composition. Then we consider water, sodium, potassium, calcium, magnesium, and phosphate balance, with special emphasis on the role of the kidneys in maintaining our fluid and electrolyte balance. Finally, we consider the role of the ureters, urinary bladder, and urethra in the transport, storage, and elimination of urine.

FLUID COMPARTMENTS OF THE BODY

Water is the major constituent of all body fluid compartments. **Total body water** averages about 60% of body weight in young adult men and about 50% of body weight in young adult women (Table 24.1). The percentage of body weight water occupies depends on the amount of adipose tissue (fat) a person has. A lean person has a high percentage and an obese individual a low percentage of body weight that is water because adipose tissue contains a low percentage of water (about 10%), whereas most other tissues have a much higher percentage of water. For example, muscle is about 75% water. Newborns have a low percentage of body weight as water because of a relatively large ECF volume and little fat (see Table 24.1). Adult women have relatively less water than men because, on average, they have more subcutaneous fat and less muscle mass. As people age, they tend to lose muscle and add adipose tissue; hence, water content declines with age.

Body Water Is Distributed in Several Fluid Compartments

Total body water can be divided into two compartments or spaces: **intracellular fluid** (ICF) and **extracellular fluid** (ECF). The ICF is comprised of the fluid within the trillions of cells in our body. The ECF is comprised of fluid outside of the cells. In a young adult man, two thirds of the body water is in the ICF, and one third is in the ECF (Fig. 24.1). These two fluids differ strikingly in terms of their electrolyte composition. However, their total solute concentrations (osmolalities) are normally equal, because of the high water permeability of most cell membranes, so that an osmotic difference between cells and ECF rapidly disappears.

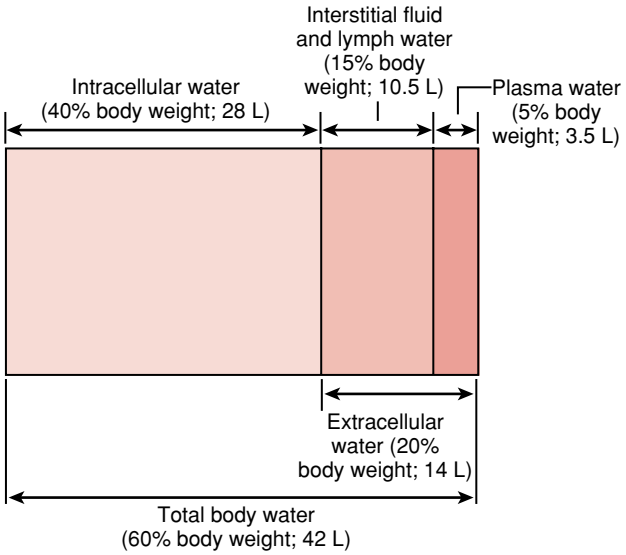

FIGURE 24.1 **Water distribution in the body.** This diagram is for an average young adult man weighing 70 kg. In an average young adult woman, total body water is 50% of body weight, intracellular water is 30% of body weight, and extracellular water is 20% of body weight.

The ECF can be further subdivided into two major subcompartments, which are separated from each other by the endothelium of blood vessels. The **blood plasma** is the ECF found within the vascular system; it is the fluid portion of the blood in which blood cells and platelets are suspended. The blood plasma water comprises about one fourth of the ECF or about 3.5 L for an average 70-kg man (see Fig. 24.1). The interstitial fluid and lymph are considered together because they cannot be easily separated. The water of the **interstitial fluid** and **lymph** comprises three fourths of the ECF. The interstitial fluid directly bathes most body cells, and the lymph is the fluid within lymphatic vessels. The blood plasma, interstitial fluid, and lymph are nearly identical in composition, except for the higher protein concentration in the plasma.

An additional ECF compartment (not shown in Fig. 24.1), the **transcellular fluid**, is small but physiologically important. Transcellular fluid amounts to about 1 to 3% of body weight. Transcellular fluids include cerebrospinal fluid, aqueous humor of the eye, secretions of the digestive tract and associated organs (saliva, bile, pancreatic juice), renal tubular fluid and bladder urine, synovial fluid, and sweat. In these cases, the fluid is separated from the blood plasma by an epithelial cell layer in addition to a capillary endothelium. The epithelial layer modifies the electrolyte composition of the fluid, so that transcellular fluids are not plasma ultrafiltrates (as is interstitial fluid and lymph); they have a distinct ionic composition. There is a constant turnover of transcellular fluids; they are continuously formed and absorbed or removed. Impaired for-

TABLE 24.1 **Average Total Body Water as a Percentage of Body Weight**

Age	Men	Both Sexes	Women
0–1 month		76	
1–12 months		65	
1–10 years		62	
10–16 years	59		57
17–39 years	61		50
40–59 years	55		52
60 years and older	52		46

From Edelman IS, Leibman J. Anatomy of body water and electrolytes. Am J Med 1959;27:256–277.

mation, abnormal loss from the body, or blockage of fluid removal can have serious consequences.

The Indicator Dilution Method Measures Fluid Compartment Size

The indicator dilution method can be used to determine the size of body fluid compartments (see Chapter 14). A known amount of a substance (the indicator), which should be confined to the compartment of interest, is administered. After allowing sufficient time for uniform distribution of the indicator throughout the compartment, a plasma sample is collected. The concentration of the indicator in the plasma at equilibrium is measured, and the distribution volume is calculated from this formula

$$\text{Volume} = \text{Amount of indicator} / \text{Concentration of indicator} \quad (1)$$

If there was loss of indicator from the fluid compartment, the amount lost is subtracted from the amount administered.

To measure total body water, heavy water (deuterium oxide), tritiated water (HTO), or antipyrene (a drug that distributes throughout all of the body water) is used as an indicator. For example, suppose we want to measure total body water in a 60-kg woman. We inject 30 mL of deuterium oxide (D_2O) as an isotonic saline solution into an arm vein. After a 2-hr equilibration period, a blood sample is withdrawn, and the plasma is separated and analyzed for D_2O. A concentration of 0.001 mL D_2O/mL plasma water is found. Suppose during the equilibration period, urinary, respiratory, and cutaneous losses of D_2O are 0.12 mL. Substituting these values into the indicator dilution equation, we get

$$\text{Total body water} = (30 - 0.12 \text{ mL } D_2O) \times 0.001 \text{ mL } D_2O/\text{mL water} = 29{,}880 \text{ mL or } 30 \text{ L} \quad (2)$$

Therefore, total body water as a percentage of body weight equals 50% in this woman.

To measure extracellular water volume, the ideal indicator should distribute rapidly and uniformly outside the cells and should not enter the cell compartment. Unfortunately, there is no such ideal indicator, so the exact volume of the ECF cannot be measured. A reasonable estimate, however, can be obtained using two different classes of substances: impermeant ions and inert sugars. ECF volume has been determined from the volume of distribution of these ions: radioactive Na^+, radioactive Cl^-, radioactive sulfate, thiocyanate (SCN^-), and thiosulfate ($S_2O_3^{2-}$); radioactive sulfate ($^{35}SO_4^{2-}$) is probably the most accurate. However, ions are not completely impermeant; they slowly enter the cell compartment, so measurements tend to lead to an overestimate of ECF volume. Measurements with inert sugars (such as mannitol, sucrose, and inulin) tend to lead to an underestimate of ECF volume because they are excluded from some of the extracellular water—for example, the water in dense connective tissue and cartilage. Special techniques are required when using these sugars because they are rapidly filtered and excreted by the kidneys after their intravenous injection.

Cellular water cannot be determined directly with any indicator. It can, however, be calculated from the difference between measurements of total body water and extracellular water.

Plasma water is determined by using Evans blue dye, which avidly binds serum albumin or radioiodinated serum albumin (RISA), and by collecting and analyzing a blood plasma sample. In effect, the plasma volume is measured from the distribution volume of serum albumin. The assumption is that serum albumin is completely confined to the vascular compartment, but this is not entirely true. Indeed, serum albumin is slowly (3 to 4% per hour) lost from the blood by diffusive and convective transport through capillary walls. To correct for this loss, repeated blood samples can be collected at timed intervals, and the concentration of albumin at time zero (the time at which no loss would have occurred) can be determined by extrapolation. Alternatively, the plasma concentration of indicator 10 minutes after injection can be used; this value is usually close to the extrapolated value. If plasma volume and hematocrit are known, total circulating blood volume can be calculated (see Chapter 11).

Interstitial fluid and lymph volume cannot be determined directly. It can be calculated as the difference between ECF and plasma volumes.

Body Fluids Differ in Electrolyte Composition

Body fluids contain many uncharged molecules (e.g., glucose and urea), but quantitatively speaking, **electrolytes** (ionized substances) contribute most to the total solute concentration (or osmolality) of body fluids. Osmolality is of prime importance in determining the distribution of water between intracellular and ECF compartments.

The importance of ions (particularly Na^+) in determining the plasma osmolality (P_{osm}) is exemplified by an equation that is of value in the clinic:

$$P_{osm} = 2 \times [Na^+] + \frac{[\text{glucose}] \text{ in mg/dL}}{18} + \frac{[\text{blood urea nitrogen}] \text{ in mg/dL}}{2.8} \quad (3)$$

If the plasma $[Na^+]$ is 140 mmol/L, blood glucose is 100 mg/dL (5.6 mmol/L), and blood urea nitrogen is 10 mg/dL (3.6 mmol/L), the calculated osmolality is 289 mOsm/kg H_2O. The equation indicates that Na^+ and its accompanying anions (mainly Cl^- and HCO_3^-) normally account for more than 95% of the plasma osmolality. In some special circumstances (e.g., alcohol intoxication), plasma osmolality calculated from the above equation may be much lower than the true, measured osmolality as a result of the presence of unmeasured osmotically active solutes (e.g., ethanol).

The concentrations of various electrolytes in plasma, interstitial fluid, and ICF are summarized in Table 24.2. The ICF values are based on determinations made in skeletal muscle cells. These cells account for about two thirds of the cell mass in the human body. Concentrations are expressed in terms of milliequivalents per liter or per kg H_2O.

An **equivalent** contains one mole of univalent ions, and a **milliequivalent** (mEq) is 1/1,000th of an equivalent. Equiv-

TABLE 24.2 Electrolyte Composition of the Body Fluids

	Plasma Electrolyte (mEq/L)	Plasma Water (mEq/kg H_2O)	Interstitial Fluid (mEq/kg H_2O)	Intracellular Fluid[a] (mEq/kg H_2O)
Cations				
Na^+	42	153	145	10
K^+	4	4.3	4	159
Ca^{2+}	5	5.4	3	1
Mg^{2+}	2	2.2	2	40
Total	153	165	154	210
Anions				
Cl^-	103	111	117	3
HCO_3^-	25	27	28	7
Protein	17	18	—	45
Others	8	9	9	155
Total	153	165	154	210

[a] Skeletal muscle cells.

alents are calculated as the product of moles times valence and represent the concentration of charged species. For singly charged (univalent) ions, such as Na^+, K^+, Cl^-, or HCO_3^-, 1 mmol is equal to 1 mEq. For doubly charged (divalent) ions, such as Ca^{2+}, Mg^{2+}, or SO_4^{2-}, 1 mmol is equal to 2 mEq. Some electrolytes, such as proteins, are polyvalent, so there are several mEq/mmol. The usefulness of expressing concentrations in terms of mEq/L is based on the fact that in solutions, we have electrical neutrality; that is

$$3 \text{ cations} = 3 \text{ anions} \quad (4)$$

If we know the total concentration (mEq/L) of all cations in a solution and know only some of the anions, we can easily calculate the concentration of the remaining anions. This was done in Table 24.2 for the anions labeled "Others." Plasma concentrations are listed in the first column of Table 24.2. Na^+ is the major cation in plasma, and Cl^- and HCO_3^- are the major anions. The plasma proteins (mainly serum albumin) bear net negative charges at physiological pH. The electrolytes are actually dissolved in the plasma water, so the second column in Table 24.2 expresses concentrations per kg H_2O. The water content of plasma is usually about 93%; about 7% of plasma volume is occupied by solutes, mainly the plasma proteins. To convert concentration in plasma to concentration in plasma water, we divided the plasma concentration by the plasma water content (0.93 L H_2O/L plasma). Therefore, 142 mEq Na^+/L plasma becomes 153 mEq/L H_2O or 153 mEq/kg H_2O (since 1 L of water weighs 1 kg).

Interstitial fluid (Column 3 of Table 24.2) is an ultrafiltrate of plasma. It contains all of the small electrolytes in essentially the same concentration as in plasma, but little protein. The proteins are largely confined to the plasma because of their large molecular size. Differences in small ion concentrations between plasma and interstitial fluid (compare Columns 2 and 3) occur because of the different protein concentrations in these two compartments. Two factors are involved. The first is an electrostatic effect: Because the plasma proteins are negatively charged, they cause a redistribution of small ions, so that the concentrations of diffusible cations (such as Na^+) are lower in interstitial fluid than in plasma and the concentrations of diffusible anions (such as Cl^-) are higher in interstitial fluid than in plasma. Second, Ca^{2+} and Mg^{2+} are bound to some extent (about 40% and 30%, respectively) by plasma proteins, and it is only the unbound ions that can diffuse through capillary walls. Hence, the total plasma Ca^{2+} and Mg^{2+} concentrations are higher than in interstitial fluid.

ICF composition (Table 24.2, Column 4) is different from ECF composition. The cells have a higher K^+, Mg^{2+}, and protein concentration than in the surrounding interstitial fluid. The intracellular Na^+, Ca^{2+}, Cl^-, and HCO_3^- levels are lower than outside the cell. The anions in skeletal muscle cells labeled "Others" are mainly organic phosphate compounds important in cell energy metabolism, such as creatine phosphate, ATP, and ADP. As described in Chapter 2, the high intracellular [K^+] and low intracellular [Na^+] are a consequence of plasma membrane Na^+/K^+-ATPase activity; this enzyme extrudes Na^+ from the cell and takes up K^+. The low intracellular [Cl^-] and [HCO_3^-] in skeletal muscle cells are primarily a consequence of the inside negative membrane potential (−90 mV), which favors the outward movement of these small, negatively charged ions. The intracellular [Mg^{2+}] is high; most is not free, but is bound to cell proteins. Intracellular [Ca^{2+}] is low; as discussed in Chapter 1, the cytosolic [Ca^{2+}] in resting cells is about 10^{-7} M (0.0002 mEq/L). Most of the cell Ca^{2+} is sequestered in organelles, such as the sarcoplasmic reticulum in skeletal muscle.

Intracellular and Extracellular Fluids Are Normally in Osmotic Equilibrium

Despite the different compositions of ICF and ECF, the total solute concentration (osmolality) of these two fluid compartments is normally the same. ICF and ECF are in osmotic equilibrium because of the high water permeability of cell membranes, which does not permit an osmolality difference to be sustained. If the osmolality changes in one compartment, water moves to restore a new osmotic equilibrium (see Chapter 2).

The volumes of ICF and ECF depend primarily on the

volume of water present in these compartments. But the latter depends on the amount of solute present and the osmolality. This fact follows from the definition of the term *concentration*: concentration = amount/volume; hence, volume = amount/concentration. The main osmotically active solute in cells is K^+; therefore, a loss of cell K^+ will cause cells to lose water and shrink (see Chapter 2). The main osmotically active solute in the ECF is Na^+; therefore, a gain or loss of Na^+ from the body will cause the ECF volume to swell or shrink, respectively.

The distribution of water between intracellular and extracellular compartments changes in a variety of circumstances. Figure 24.2 provides some examples. Total body water is divided into the two major compartments, ICF and ECF. The y-axis represents total solute concentration and the x-axis the volume; the area of a box (concentration times volume) gives the amount of solute present in a compartment. Note that the height of the boxes is always equal, since osmotic equilibrium (equal osmolalities) is achieved.

In the normal situation (shown in Figure 24.2A), two thirds (28 L for a 70-kg man) of total body water is in the ICF, and one third (14 L) is in the ECF. The osmolality of both fluids is 285 mOsm/kg H_2O. Hence, the cell compartment contains 7,980 mOsm and the ECF contains 3,990 mOsm.

In Figure 24.2B, 2.0 L of pure water were added to the ECF (e.g., by drinking water). Plasma osmolality is lowered, and water moves into the cell compartment along the osmotic gradient. The entry of water into the cells causes them to swell, and intracellular osmolality falls until a new equilibrium (solid lines) is achieved. Since 2 L of water were added to an original total body water volume of 42 L, the new total body water volume is 44 L. No solute was added, so the new osmolality at equilibrium is (7,980 + 3,990 mOsm)/44 kg = 272 mOsm/kg H_2O. The volume of the ICF at equilibrium, calculated by solving the equation, 272 mOsm/kg H_2O × volume = 7,980 mOsm, is 29.3 L The volume of the ECF at equilibrium is 14.7 L. From these calculations, we conclude that two thirds of the added water ends up in the cell compartment and one third stays in the ECF. This description of events is artificial because, in reality, the kidneys would excrete the added water over the course of a few hours, minimizing the fall in plasma osmolality and cell swelling.

In Figure 24.2C, 2.0 L of isotonic saline (0.9% NaCl solution) were added to the ECF. Isotonic saline is isosmotic to plasma or ECF and, by definition, causes no change in cell volume. Therefore, all of the isotonic saline is retained in the ECF and there is no change in osmolality.

Figure 24.2D shows the effect of infusing intravenously 1.0 L of a 5% NaCl solution (osmolality about 1,580 mOsm/kg H_2O). All the salt stays in the ECF. The cells are exposed to a hypertonic environment, and water leaves the cells. Solutes left behind in the cells become more concentrated as water leaves. A new equilibrium will be established, with the final osmolality higher than normal but equal inside and outside the cells. The final osmolality can be calculated from the amount of solute present (7,980 + 3,990 + 1,580 mOsm) divided by the final volume (28 + 14 + 1 L); it is equal to 315 mOsm/kg H_2O. The final volume of the ICF equals 7,980 mOsm divided by 315 mOsm/kg H_2O or 25.3 L, which is 2.7 L less than the initial volume. The final

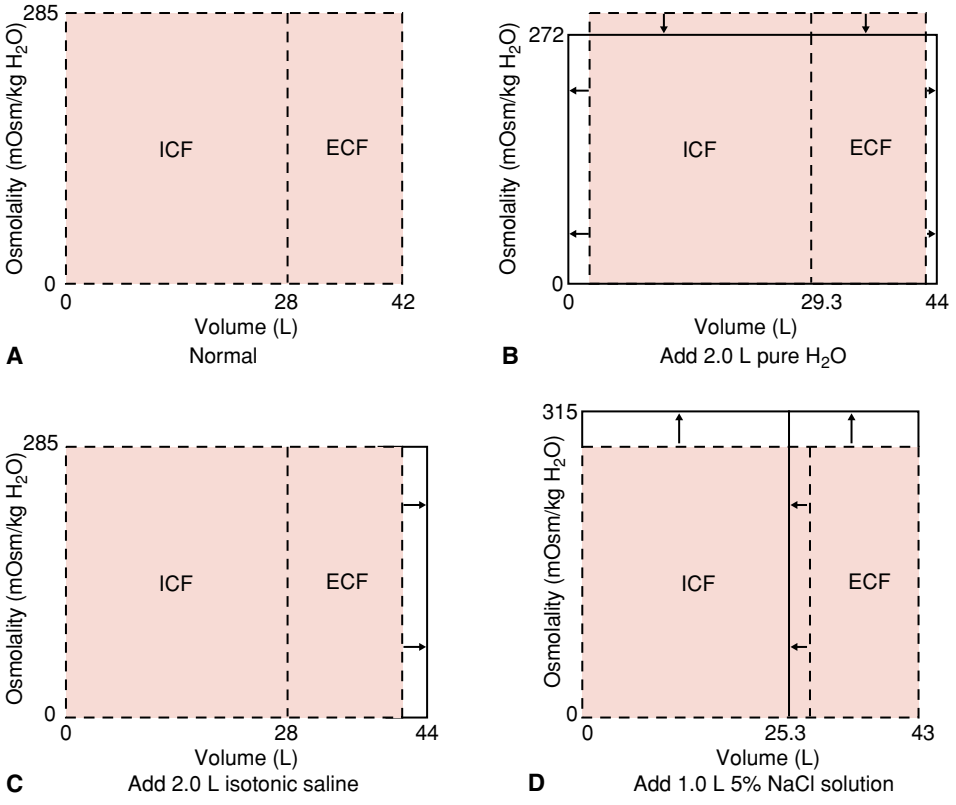

FIGURE 24.2 Effects of various disturbances on the osmolalities and volumes of intracellular fluid (ICF) and extracellular fluid (ECF). The dashed lines indicate the normal condition; the solid lines, the situation after a new osmotic equilibrium has been attained. (See text for details.)

volume of the ECF is 17.7 L, which is 3.7 L more than its initial value. The addition of hypertonic saline to the ECF, therefore, led to its considerable expansion mostly because of loss of water from the cell compartment.

WATER BALANCE

People normally stay in a stable water balance; that is, water input and output are equal. There are three major aspects to the control of water balance: arginine vasopressin, excretion of water by the kidneys, and habit and thirst.

Water Input and Output Are Equal

A balance chart for water for an average 70-kg man is presented in Table 24.3. The person is in a stable balance (or steady state) because the total input and total output of water from the body are equal (2,500 mL/day). On the input side, water is found in the beverages we drink and in the foods we eat. Solid foods, which consist of animal or vegetable matter, are, like our own bodies, mostly water. Water of oxidation is produced during metabolism; for example, when 1 mol of glucose is oxidized, 6 mol of water are produced. In a hospital setting, the input of water as a result of intravenous infusions would also need to be considered. On the output side, losses of water occur via the skin, lungs, gastrointestinal tract, and kidneys. We always lose water by simple evaporation from the skin and lungs; this is called **insensible water loss**.

Appreciable water loss from the skin, in the form of sweat, occurs at high temperatures or with heavy exercise. As much as 4 L of water per hour can be lost in sweat. Sweat, which is a hypoosmotic fluid, contains NaCl; excessive sweating can lead to significant losses of salt. Gastrointestinal losses of water are normally small (see Table 24.3), but with diarrhea, vomiting, or drainage of gastrointestinal secretions, massive quantities of water and electrolytes may be lost from the body.

The kidneys are the sites of adjustment of water output from the body. Renal water excretion changes to maintain balance. If there is a water deficiency, the kidneys diminish the excretion of water and urine output falls. If there is water excess, the kidneys increase water excretion and urine flow to remove the extra water. The renal excretion of water is controlled by arginine vasopressin.

The water needs of an infant or young child, per kg body weight, are several times higher than that of an adult. Children have, for their body weight, a larger body surface area and higher metabolic rate. They are much more susceptible to volume depletion.

TABLE 24.3 Daily Water Balance in an Average 70-kg Man

	Input		Output
Water in beverages	1,000 mL	Skin and lungs	900 mL
Water in food	1,200 mL	Gastrointestinal tract (feces)	100 mL
Water of oxidation	300 mL	Kidneys (urine)	1,500 mL
Total	2,500 mL	Total	2,500 mL

Arginine Vasopressin Is Critical in the Control of Renal Water Output and Plasma Osmolality

Arginine vasopressin (AVP), also known as **antidiuretic hormone** (ADH), is a nonapeptide synthesized in the body of nerve cells located in the supraoptic and paraventricular nuclei of the anterior hypothalamus (Fig. 24.3) (see Chapter 32). The hormone travels by axoplasmic flow down the hypothalamic-neurohypophyseal tract and is stored in vesicles in nerve terminals in the median eminence and, mostly, the posterior pituitary. When the cells are brought to threshold, they rapidly fire action potentials, Ca^{2+} enters the nerve terminals, the AVP-containing vesicles release their contents into the interstitial fluid surrounding the nerve terminals, and AVP diffuses into nearby capillaries. The hormone is carried by the blood stream to its target tissue, the collecting ducts of the kidneys, where it increases water reabsorption (see Chapter 23).

Factors Affecting AVP Release. Many factors influence the release of AVP, including pain, trauma, emotional stress, nausea, fainting, most anesthetics, nicotine, morphine, and angiotensin II. These conditions or agents produce a decline in urine output and more concentrated urine. Ethanol and atrial natriuretic peptide inhibit AVP release, leading to the excretion of a large volume of dilute urine.

The main factor controlling AVP release under ordinary circumstances is a change in plasma osmolality. Figure 24.4 shows how plasma AVP concentrations vary as a function of plasma osmolality. When plasma osmolality rises, neurons called **osmoreceptor cells**, located in the anterior hypothalamus, shrink. This stimulates the nearby neurons in

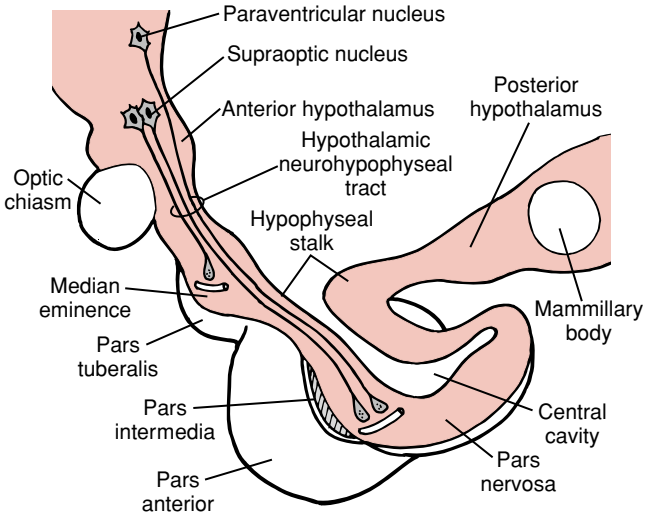

FIGURE 24.3 The pituitary and hypothalamus. AVP is synthesized primarily in the supraoptic nucleus and to a lesser extent in the paraventricular nuclei in the anterior hypothalamus. It is then transported down the hypothalamic neurohypophyseal tract and stored in vesicles in the median eminence and posterior pituitary, where it can be released into the blood.

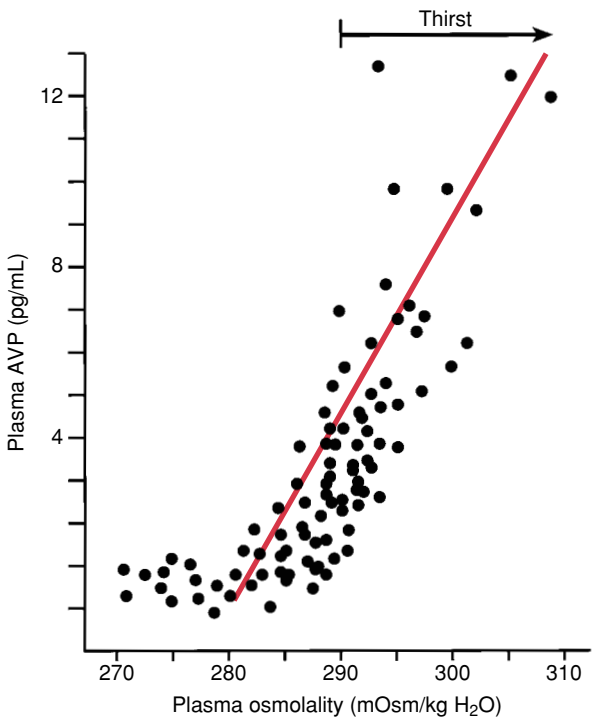

FIGURE 24.4 The relationship between plasma AVP level and plasma osmolality in healthy people. Decreases in plasma osmolality were produced by drinking water and increases by fluid restriction. Plasma AVP levels were measured by radioimmunoassay. At plasma osmolalities below 280 mOsm/kg H_2O, plasma AVP is decreased to low or undetectable levels. Above this threshold, plasma AVP increases linearly with plasma osmolality. Normal plasma osmolality is about 285 to 287 mOsm/kg H_2O, so we live above the threshold for AVP release. The thirst threshold is attained at a plasma osmolality of 290 mOsm/kg H_2O, so the thirst mechanism "kicks in" only when there is an appreciable water deficit. Changes in plasma AVP and consequent changes in renal water excretion are normally capable of maintaining a normal plasma osmolality below the thirst threshold. (From Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982;72:339–353.)

the paraventricular and supraoptic nuclei to release AVP, and plasma AVP concentration rises. The result is the formation of osmotically concentrated urine. Not all solutes are equally effective in stimulating the osmoreceptor cells; for example, urea, which can enter these cells and, therefore, does not cause the osmotic withdrawal of water, is ineffective. Extracellular NaCl, however, is an effective stimulus for AVP release. When plasma osmolality falls in response to the addition of excess water, the osmoreceptor cells swell, AVP release is inhibited, and plasma AVP levels fall. In this situation, the collecting ducts express their intrinsically low water permeability, less water is reabsorbed, a dilute urine is excreted, and plasma osmolality can be restored to normal by elimination of the excess water. Figure 24.5 shows that the entire range of urine osmolalities, from dilute to concentrated urines, is a linear function of plasma AVP in healthy people.

A second important factor controlling AVP release is the blood volume—more precisely, the effective arterial blood volume. An increased blood volume inhibits AVP release, whereas a decreased blood volume (hypovolemia) stimulates AVP release. Intuitively, this makes sense, since with excess volume, a low plasma AVP level would promote the excretion of water by the kidneys. With hypovolemia, a high plasma AVP level would promote conservation of water by the kidneys.

The receptors for blood volume include stretch receptors in the left atrium of the heart and in the pulmonary veins within the pericardium. More stretch results in more impulses transmitted to the brain via vagal afferents and inhibition of AVP release. The common experiences of producing a large volume of dilute urine, a **water diuresis**—when lying down in bed at night, when exposed to cold weather, or when immersed in a pool during the summer—may be related to activation of this pathway. In all of these situations, the atria are stretched by an increased central blood volume. Arterial baroreceptors in the carotid sinuses and aortic arch also reflexly change AVP release; a fall in pressure at these sites stimulates AVP release. Finally, a decrease in renal blood flow stimulates renin release, which leads to increased angiotensin II production. Angiotensin II stimulates AVP release by acting on the brain.

Relatively large blood losses (more than 10% of blood volume) are required to increase AVP release (Fig. 24.6). With a loss of 15 to 20% of blood volume, however, large increases in plasma AVP are observed. Plasma levels of AVP may rise to levels much higher (e.g., 50 pg/mL) than are needed to concentrate the urine maximally (e.g., 5 pg/mL). (Compare Figures 24.5 and 24.6.) With severe hemorrhage, high circulating levels of AVP exert a significant vasoconstrictor effect, which helps compensate by raising the blood pressure.

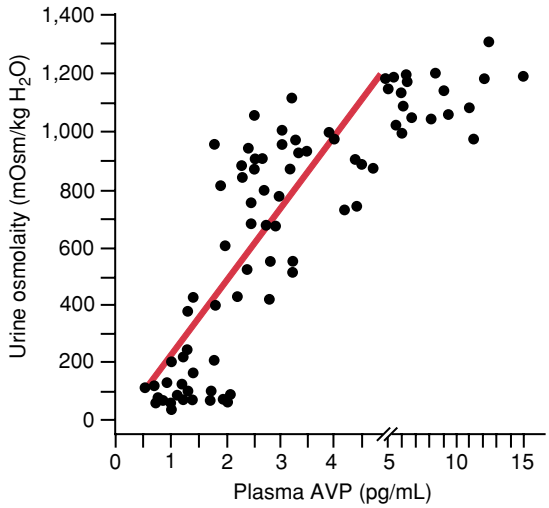

FIGURE 24.5 The relationship between urine osmolality and plasma AVP levels. With low plasma AVP levels, a hypoosmotic (compared to plasma) urine is excreted and, with high plasma AVP levels, a hyperosmotic urine is excreted. Note that maximally concentrated urine (1,200 to 1,400 mOsm/kg H_2O) is produced when the plasma AVP level is about 5 pg/mL. (From Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982;72:339–353.)

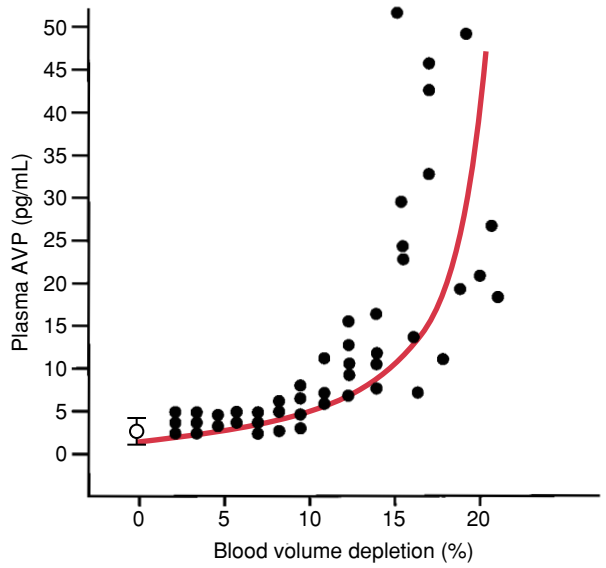

FIGURE 24.6 The relationship between plasma AVP and blood volume depletion in the rat. Note that severe hemorrhage (a loss of 20% of blood volume) causes a striking increase in plasma AVP. In this situation, the vasoconstrictor effect of AVP becomes significant and counteracts the low blood pressure. (From Dunn FL, Brennan TJ, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973;52:3212–3219)

Interaction Between Stimuli Affecting AVP Release. The two stimuli, plasma osmolality and blood volume, most often work synergistically to increase or decrease AVP release. For example, a great excess of water intake in a healthy person will inhibit AVP release because of both the fall in plasma osmolality and increase in blood volume. In certain important clinical circumstances, however, there is a conflict between these two inputs. For example, severe congestive heart failure is characterized by a decrease in the effective arterial blood volume, even though total blood volume is greater than normal. This condition results because the heart does not pump sufficient blood into the arterial system to maintain adequate tissue perfusion. The arterial baroreceptors signal less volume, and AVP release is stimulated. The patient will produce osmotically concentrated urine and will also be thirsty from the decreased effective arterial blood volume, with consequent increased water intake. The combination of decreased renal water excretion and increased water intake leads to hypoosmolality of the body fluids, which is reflected in a low plasma [Na^+] or **hyponatremia**. Despite the hypoosmolality, plasma AVP levels remain elevated and thirst persists. It appears that maintaining an effective arterial blood volume is of overriding importance, so osmolality may be sacrificed in this condition. The hypoosmolality creates new problems, such as the swelling of brain cells. Hyponatremia is discussed in Clinical Focus Box 24.1.

Clinical AVP Disorders. **Neurogenic diabetes insipidus** (central, hypothalamic, pituitary) is a condition characterized by a deficient production or release of AVP. Plasma AVP levels are low, and a large volume of dilute urine (up to 20 L/day) is excreted. In **nephrogenic diabetes insipidus**, the collecting ducts are partially or completely unresponsive to AVP. Urine output is increased, but the plasma AVP level is usually higher than normal (secondary to excessive loss of dilute fluid from the body). Nephrogenic diabetes insipidus may be acquired (e.g., via drugs such as lithium) or inherited. Mutations in the collecting duct AVP receptor gene or in the water channel (aquaporin-2) gene have now been identified in some families. In the **syndrome of inappropriate secretion of ADH** (SIADH), plasma AVP levels are inappropriately high for the existing osmolality. Plasma osmolality is low because the kidneys form concentrated urine and save water. This condition is sometimes caused by a bronchogenic tumor that produces AVP in an uncontrolled fashion.

Habit and Thirst Govern Water Intake

People drink water largely from habit, and this water intake normally covers an individual's water needs. Most of the time, we operate below the threshold for thirst. **Thirst**, a conscious desire to drink water, is mainly an emergency mechanism that comes into play when there is a perceived water deficit. Its function is obviously to encourage water intake to repair the water deficit. The **thirst center** is located in the anterior hypothalamus, close to the neurons that produce and control AVP release. This center relays impulses to the cerebral cortex, so that thirst becomes a conscious sensation.

Several factors affect the thirst sensation (Fig. 24.7). The major stimulus is an increase in osmolality of the blood, which is detected by osmoreceptor cells in the hypothalamus. These cells are distinct from those that affect AVP release. Ethanol and urea are not effective stimuli for the osmoreceptors because they readily penetrate these cells and do not cause them to shrink. NaCl is an effective stimulus. An increase in plasma osmolality of 1 to 2% (i.e., about 3 to 6 mOsm/kg H_2O) is needed to reach the thirst threshold.

Hypovolemia or a decrease in the effective arterial blood volume stimulates thirst. Blood volume loss must be considerable for the thirst threshold to be reached; most blood donors do not become thirsty after donating 500 mL of blood (10% of blood volume). A larger blood loss (15 to 20% of blood volume), however, evokes intense thirst. A decrease in effective arterial blood volume as a result of severe diarrhea, vomiting, or congestive heart failure may also provoke thirst.

The receptors for blood volume that stimulate thirst include the arterial baroreceptors in the carotid sinuses and aortic arch and stretch receptors in the cardiac atria and great veins in the thorax. The kidneys may also act as volume receptors. When blood volume is decreased, the kidneys release renin into the circulation. This results in production of angiotensin II, which acts on neurons near the third ventricle of the brain to stimulate thirst.

The thirst sensation is reinforced by dryness of the mouth and throat, which is caused by a reflex decrease in secretion by salivary and buccal glands in a water-deprived person. The gastrointestinal tract also monitors water intake. Moistening of the mouth or distension of the stomach,

CLINICAL FOCUS BOX 24.1

Hyponatremia

Hyponatremia, defined as a plasma [Na^+] < 135 mEq/L, is the most common disorder of body fluid and electrolyte balance in hospitalized patients. Most often it reflects too much water, not too little Na^+, in the plasma. Since Na^+ is the major solute in the plasma, it is not surprising that hyponatremia is usually associated with hypoosmolality. Hyponatremia, however, may also occur with a normal or even elevated plasma osmolality.

Drinking large quantities of water (20 L/day) rarely causes frank hyponatremia because of the large capacity of the kidneys to excrete dilute urine. If, however, plasma AVP is not decreased when plasma osmolality is decreased or if the ability of the kidneys to dilute the urine is impaired, hyponatremia may develop even with a normal water intake.

Hyponatremia with hypoosmolality can occur in the presence of a decreased, normal, or even increased total body Na^+. Hyponatremia and decreased body Na^+ content may be seen with increased Na^+ loss, such as with vomiting, diarrhea, and diuretic therapy. In these instances, the decrease in ECF volume stimulates thirst and AVP release. More water is ingested, but the kidneys form osmotically concentrated urine and plasma hypoosmolality and hyponatremia result. Hyponatremia and a normal body Na^+ content are seen in hypothyroidism, cortisol deficiency, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). SIADH occurs with neurological disease, severe pain, certain drugs (such as hypoglycemic agents), and with some tumors. For example, a bronchogenic tumor may secrete AVP without control by plasma osmolality. The result is renal conservation of water. Hyponatremia and increased total body Na^+ are seen in edematous states, such as congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. The decrease in effective arterial blood volume stimulates thirst and AVP release. Excretion of a dilute urine may also be impaired because of decreased delivery of fluid to diluting sites along the nephron and collecting ducts. Although Na^+ and water are retained by the kidneys in the edematous states, relatively more water is conserved, leading to a dilutional hyponatremia.

Hyponatremia and hypoosmolality can cause a variety of symptoms, including muscle cramps, lethargy, fatigue, disorientation, headache, anorexia, nausea, agitation, hypothermia, seizures, and coma. These symptoms, mainly neurological, are a consequence of the swelling of brain cells as plasma osmolality falls. Excessive brain swelling may be fatal or may cause permanent damage. Treatment requires identifying and treating the underlying cause. If Na^+ loss is responsible for the hyponatremia, isotonic or hypertonic saline or NaCl by mouth is usually given. If the blood volume is normal or the patient is edematous, water restriction is recommended. Hyponatremia should be corrected slowly and with constant monitoring because too rapid correction can be harmful.

Hyponatremia in the presence of increased plasma osmolality is seen in hyperglycemic patients with uncontrolled diabetes mellitus. In this condition, the high plasma [glucose] causes the osmotic withdrawal of water from cells, and the extra water in the ECF space leads to hyponatremia. Plasma [Na^+] falls by 1.6 mEq/L for each 100 mg/dL rise in plasma glucose.

Hyponatremia and a normal plasma osmolality are seen with so-called **pseudohyponatremia**. This occurs when plasma lipids or proteins are greatly elevated. These molecules do not significantly elevate plasma osmolality. They do, however, occupy a significant volume of the plasma, and because the Na^+ is dissolved only in the plasma water, the [Na^+] measured in the entire plasma is low.

for example, inhibit thirst, preventing excessive water intake. For example, if a dog is deprived of water for some time and is then presented with water, it will commence drinking but will stop before all of the ingested water has been absorbed by the small intestine. Monitoring of water intake by the mouth and stomach in this situation limits water intake, preventing a dip in plasma osmolality below normal.

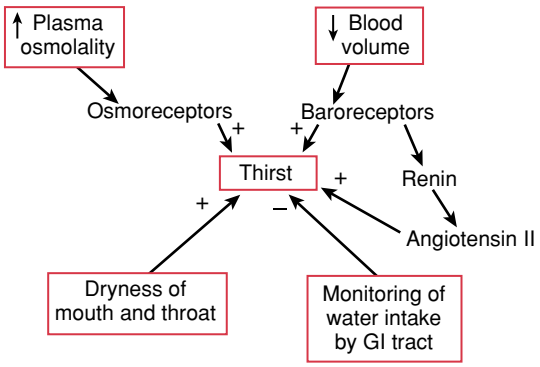

FIGURE 24.7 **Factors affecting the thirst sensation.** A plus sign indicates stimulation of thirst, the minus sign indicates an inhibitory influence.

SODIUM BALANCE

Na^+ is the most abundant cation in the ECF and, with its accompanying anions Cl^- and HCO_3^-, largely determines the osmolality of the ECF. Because the osmolality of the ECF is closely regulated by AVP, the kidneys, and thirst, the amount of water in (and, hence, the volume of) the ECF compartment is mainly determined by its Na^+ content. The kidneys are primarily involved in the regulation of Na^+ balance. We consider first the renal mechanisms involved in Na^+ excretion and then overall Na^+ balance.

The Kidneys Excrete Only a Small Percentage of the Filtered Na^+ Load

Table 24.4 shows the magnitude of filtration, reabsorption, and excretion of ions and water for a healthy adult man on an average American diet. The amount of Na^+ filtered was calculated from the product of the plasma [Na^+] and

TABLE 24.4 Magnitude of Daily Filtration, Reabsorption, and Excretion of Ions and Water in a Healthy Young Man on a Typical American Diet

	[Plasma] (mEq/L)	GFR (L/day)	Filtered (mEq/day)	Excreted (mEq/day)	Reabsorbed (mEq/day)	% Reabsorbed
Sodium	140	180	25,200	100	25,100	99.6
Chloride	105	180	18,900	100	18,800	99.5
Bicarbonate	24	180	4,320	2	4318	99.9
Potassium	4	180	720 L/day	100 L/day	620 L/day	86.1
Water	0.93[a]	180	167	1.5	165.5	99.1

[a] Plasma contains about 0.93 L H_2O per L.

glomerular filtration rate (GFR). The quantity of Na^+ reabsorbed was calculated from the difference between filtered and excreted amounts. Note that 99.6% (25,100≡25,200) of the filtered Na^+ was reabsorbed or, in other words, percentage excretion of Na^+ was only 0.4% of the filtered load. In terms of overall Na^+ balance for the body, the quantity of Na^+ excreted by the kidneys is of key importance because ordinarily about 95% of the Na^+ we consume is excreted by way of the kidneys. Tubular reabsorption of Na^+ must be finely regulated to keep us in Na^+ balance.

Figure 24.8 shows the percentage of filtered Na^+ reabsorbed in different parts of the nephron. Seventy percent of filtered Na^+, together with the same percentage of filtered water, is reabsorbed in the proximal convoluted tubule. The loop of Henle reabsorbs about 20% of filtered Na^+, but only 10% of filtered water. The distal convoluted tubule reabsorbs about 6% of filtered Na^+ (and no water), and the collecting ducts reabsorb about 3% of the filtered Na^+ (and 19% of the filtered water). Only about 1% of the filtered Na^+ (and water) is usually excreted. The distal nephron (distal convoluted tubule, connecting tubule, and collecting duct) has a lower capacity for Na^+ transport than more proximal segments and can be overwhelmed if too much Na^+ fails to be reabsorbed in proximal segments. The distal nephron is of critical importance in determining the final excretion of Na^+.

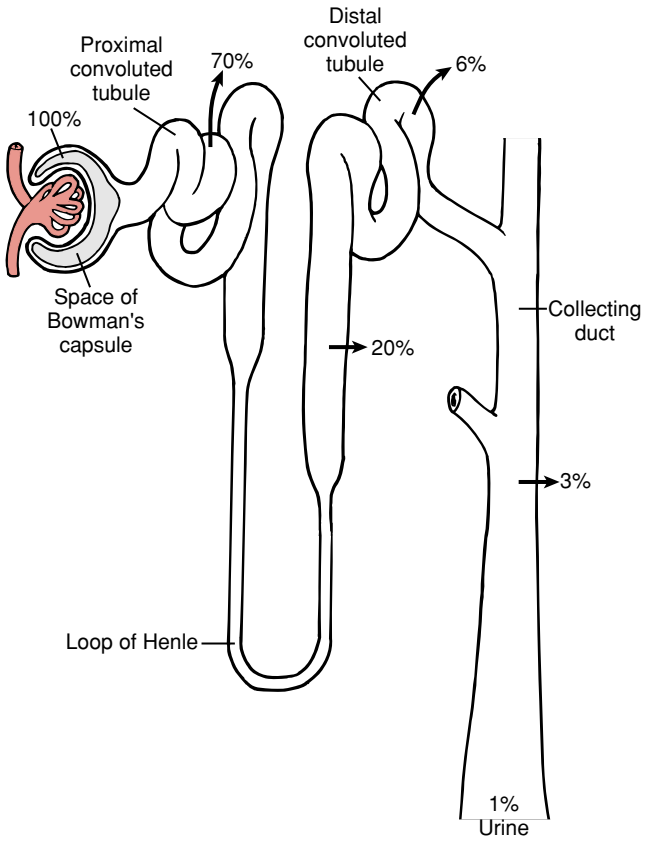

FIGURE 24.8 **The percentage of the filtered load of Na^+** reabsorbed along the nephron. About 1% of the filtered Na^+ is usually excreted.

Many Factors Affect Renal Na^+ Excretion

Multiple factors affect renal Na^+ excretion; these are discussed below. A factor may promote Na^+ excretion either by increasing the amount of Na^+ filtered by the glomeruli or by decreasing the amount of Na^+ reabsorbed by the kidney tubules or, in some cases, by affecting both processes.

Glomerular Filtration Rate. Na^+ excretion tends to change in the same direction as GFR. If GFR rises—for example, from an expanded ECF volume—the tubules reabsorb the increased filtered load less completely, and Na^+ excretion increases. If GFR falls—for example, as a result of blood loss—the tubules can reabsorb the reduced filtered Na^+ load more completely, and Na^+ excretion falls. These changes are of obvious benefit in restoring a normal ECF volume.

Small changes in GFR could potentially lead to massive changes in Na^+ excretion, if it were not for a phenomenon called **glomerulotubular balance** (Table 24.5). There is a balance between the amount of Na^+ filtered and the amount of Na^+ reabsorbed by the tubules, so the tubules increase the rate of Na^+ reabsorption when GFR is increased and decrease the rate of Na^+ reabsorption when GFR is decreased. This adjustment is a function of the proximal convoluted tubule and the loop of Henle, and it reduces the impact of changes in GFR on Na^+ excretion.

The Renin-Angiotensin-Aldosterone System. **Renin** is a proteolytic enzyme produced by granular cells, which are located in afferent arterioles in the kidneys (see Fig. 23.4). There are three main stimuli for renin release:

TABLE 24.5 Glomerulotubular Balance[a]

	Filtered Na^+	− Reabsorbed Na^+	= Excreted Na^+
Period	(mEq/min)	(mEq/min)	(mEq/min)
1	6.00	5.95	0.05
Increase GFR by one third			
2	8.00	7.90	0.10

[a] Results from an experiment performed on a 10-kg dog. Note that in response to an increase in GFR (produced by infusing a drug that dilated afferent arterioles), tubular reabsorption of Na^+ increased, so that only a modest increase in Na^+ excretion occurred. If there had been no glomerulotubular balance and if tubular Na^+ reabsorption had stayed at 5.95 mEq/min, the kidneys would have excreted 2.05 mEq/min in period 2. If we assume that the ECF volume in the dog is 2 L (20% of body weight) and if plasma [Na^+] is 140 mEq/L, an excretion rate of 2.05 mEq/min would result in excretion of the entire ECF Na^+ (280 mEq) in a little more than 2 hours. The dog would have been dead long before this could happen, which underscores the importance of glomerulotubular balance.

1) A decrease in pressure in the afferent arteriole, with the granular cells being sensitive to stretch and function as an **intrarenal baroreceptor**

2) Stimulation of sympathetic nerve fibers to the kidneys via β_2-adrenergic receptors on the granular cells

3) A decrease in fluid delivery to the macula densa region of the nephron, resulting, for example, from a decrease in GFR

All three of these pathways are activated and reinforce each other when there is a decrease in the effective arterial blood volume—for example, following hemorrhage, transudation of fluid out of the vascular system, diarrhea, severe sweating, or a low salt intake. Conversely, an increase in the effective arterial blood volume inhibits renin release. Long-term stimulation causes vascular smooth muscle cells in the afferent arteriole to differentiate into granular cells and leads to further increases in renin supply. Renin in the blood plasma acts on a plasma α_2-globulin produced by the liver, called **angiotensinogen** (or renin substrate) and splits off the decapeptide **angiotensin I** (Fig. 24.9). Angiotensin I is converted to the octapeptide **angiotensin II** as the blood courses through the lungs. This reaction is catalyzed by the **angiotensin-converting enzyme** (ACE), which is present on the surface of endothelial cells. All the components of this system (renin, angiotensinogen, angiotensin-converting enzyme) are present in some organs (e.g., the kidneys and brain), so that angiotensin II may also be formed and act locally.

The **renin-angiotensin-aldosterone system** (RAAS) is a salt-conserving system. Angiotensin II has several actions related to Na^+ and water balance:

1) It stimulates the production and secretion of the **aldosterone** from the zona glomerulosa of the adrenal cortex (see Chapter 36). This mineralocorticoid hormone then acts on the distal nephron to increase Na^+ reabsorption.

2) Angiotensin II directly stimulates tubular Na^+ reabsorption.

3) Angiotensin stimulates thirst and the release of AVP by the posterior pituitary.

Angiotensin II is also a potent vasoconstrictor of both resistance and capacitance vessels; increased plasma levels following hemorrhage, for example, help sustain blood pressure. Inhibiting angiotensin II production by giving an ACE inhibitor lowers blood pressure and is used in the treatment of hypertension.

The RAAS plays an important role in the day-to-day control of Na^+ excretion. It favors Na^+ conservation by the kidneys when there is a Na^+ or volume deficit in the body. When there is an excess of Na^+ or volume, diminished RAAS activity permits enhanced Na^+ excretion. In the absence of aldosterone (e.g., in an adrenalectomized individual) or in a person with adrenal cortical insufficiency—**Addison's disease**—excessive amounts of Na^+ are lost in the urine. Percentage reabsorption of Na^+ may decrease from a normal value of about 99.6% to a value of 98%. This change (1.6% of the filtered Na^+ load) may not seem like much, but if the kidneys filter 25,200 mEq/day (see Table 24.4) and excrete an extra $0.016 \times 25{,}200 = 403$ mEq/day, this is the amount of Na^+ in almost 3 L of ECF (assuming a [Na^+] of 140 mEq/L). Such a loss of Na^+ would lead to a decrease in plasma and blood volume, circulatory collapse, and even death.

When there is an extra need for Na^+, people and many animals display a **sodium appetite**, an urge for salt intake, which can be viewed as a brain mechanism, much like thirst, that helps compensate for a deficit. Patients with Addison's disease often show a well-developed sodium appetite, which helps keep them alive.

Large doses of a potent mineralocorticoid will cause a person to retain about 200 to 300 mEq Na^+ (equivalent to about 1.4 to 2 L of ECF), and the person will "escape" from the salt-retaining action of the steroid. Retention of this amount of fluid is not sufficient to produce obvious edema. The fact that the person will not continue to accumulate Na^+ and water is due to the existence of numerous factors that are called into play when ECF volume is expanded; these factors promote renal Na^+ excretion and overpower the salt-retaining action of aldosterone. This phenomenon is called **mineralocorticoid escape**.

Intrarenal Physical Forces (Peritubular Capillary Starling Forces). An increase in the hydrostatic pressure or a decrease in the colloid osmotic pressure in peritubular capillaries (the so-called "physical" or Starling forces) results in reduced fluid uptake by the capillaries. In turn, an accumulation of the reabsorbed fluid in the kidney interstitial spaces results. The increased interstitial pressure causes a widening of the tight junctions between proximal tubule cells, and the epithelium becomes even more leaky than normal. The result is increased back-leak of salt and water into the tubule lumen and an overall reduction in net reabsorption. These changes occur, for example, if a large volume of isotonic saline is infused intravenously. They also occur if the **filtration fraction** (GFR/RPF) is lowered from the dilation of efferent arterioles, for example. In this case, the protein concentration (or colloid osmotic pressure) in efferent arteriolar blood and peritubular capillary blood is lower than normal because a smaller proportion of the plasma is filtered in the glomeruli. Also, with upstream vasodilation of efferent arterioles, hydrostatic pressure in the

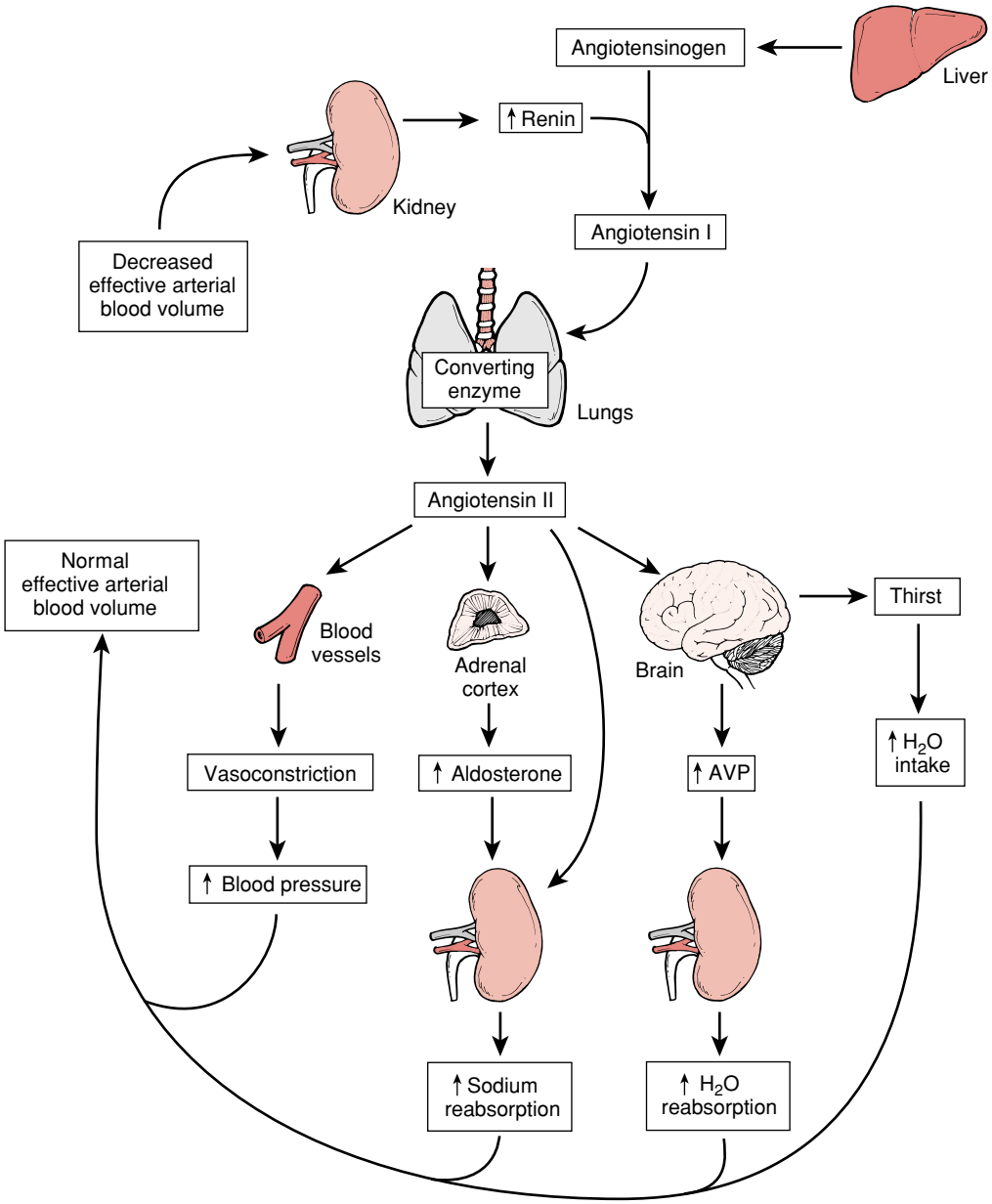

FIGURE 24.9 Components of the renin-angiotensin-aldosterone system. This system is activated by a decrease in the effective arterial blood volume (e.g., following hemorrhage) and results in compensatory changes that help restore arterial blood pressure and blood volume to normal.

peritubular capillaries is increased, leading to a **pressure natriuresis** and **pressure diuresis**. The term *natriuresis* means an increase in Na^+ excretion.

Natriuretic Hormones and Factors. **Atrial natriuretic peptide** (ANP) is a 28 amino acid polypeptide synthesized and stored in myocytes of the cardiac atria (Fig. 24.10). It is released upon stretch of the atria—for example, following volume expansion. This hormone has several actions that increase Na^+ excretion. ANP acts on the kidneys to increase glomerular blood flow and filtration rate and inhibits Na^+ reabsorption by the inner medullary collecting ducts. The second messenger for ANP in the collecting duct is cGMP. ANP directly inhibits aldosterone secretion by the adrenal cortex; it also indirectly inhibits aldosterone secretion by diminishing renal renin release. ANP is a vasodilator and, therefore, lowers blood pressure. Some evidence suggests that ANP inhibits AVP secretion. The actions of ANP are, in many respects, just the opposite of those of the RAAS; ANP promotes salt and water loss by the kidneys and lowers blood pressure.

Several other natriuretic hormones and factors have been described. **Urodilatin** (kidney natriuretic peptide) is a 32-amino acid polypeptide derived from the same prohormone as ANP. It is synthesized primarily by intercalated cells in the cortical collecting duct and secreted into the tubule lu-

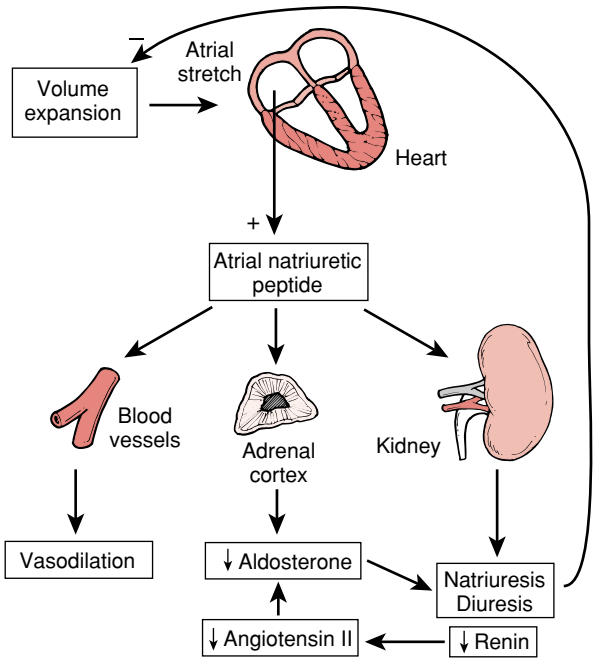

FIGURE 24.10 **Atrial natriuretic peptide and its actions.** ANP release from the cardiac atria is stimulated by blood volume expansion, which stretches the atria. ANP produces effects that bring blood volume back toward normal, such as increased Na^+ excretion.

men, inhibiting Na^+ reabsorption by inner medullary collecting ducts via cGMP. There is also a **brain natriuretic peptide**. **Guanylin** and **uroguanylin** are polypeptide hormones produced by the small intestine in response to salt ingestion. Like ANP and urodilatin, they activate guanylyl cyclase and produce cGMP as a second messenger, as their names suggest. **Adrenomedullin** is a polypeptide produced by the adrenal medulla; its physiological significance is still not certain. **Endoxin** is an endogenous digitalis-like substance produced by the adrenal gland. It inhibits Na^+/K^+-ATPase activity and, therefore, inhibits Na^+ transport by the kidney tubules. **Bradykinin** is produced locally in the kidneys and inhibits Na^+ reabsorption.

Prostaglandins E_2 and **I_2** (prostacyclin) increase Na^+ excretion by the kidneys. These locally produced hormones are formed from arachidonic acid, which is liberated from phospholipids in cell membranes by the enzyme phospholipase A_2. Further processing is mediated by a **cyclooxygenase** (**COX**) enzyme that has two isoforms, COX-1 and COX-2. In most tissues, COX-1 is constitutively expressed, while COX-2 is generally induced by inflammation. In the kidney, COX-1 and COX-2 are both constitutively expressed in cortex and medulla. In the cortex, COX-2 may be involved in macula densa-mediated renin release. COX-1 and COX-2 are present in high amounts in the renal medulla, where the main role of the prostaglandins is to inhibit Na^+ reabsorption. Because the prostaglandins (PGE_2, PGI_2) are vasodilators, the inhibition of Na^+ reabsorption occurs via direct effects on the tubules and collecting ducts and via hemodynamic effects (see Chapter 23). Inhibition of the formation of prostaglandins with common nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, may lead to a fall in renal blood flow and to Na^+ retention.

Renal Sympathetic Nerves. The stimulation of renal sympathetic nerves reduces renal Na^+ excretion in at least three ways:

1) It produces a decline in GFR and renal blood flow, leading to a decreased filtered Na^+ load and peritubular capillary hydrostatic pressure, both of which favor diminished Na^+ excretion.

2) It has a direct stimulatory effect on Na^+ reabsorption by the renal tubules.

3) It causes renin release, which results in increased plasma angiotensin II and aldosterone levels, both of which increase tubular Na^+ reabsorption.

Activation of the sympathetic nervous system occurs in several stressful circumstances (such as hemorrhage) in which the conservation of salt and water by the kidneys is of clear benefit.

Estrogens. Estrogens decrease Na^+ excretion, probably by the direct stimulation of tubular Na^+ reabsorption. Most women tend to retain salt and water during pregnancy, which may be partially related to the high plasma estrogen levels during this time.

Glucocorticoids. Glucocorticoids, such as cortisol (see Chapter 34), increase tubular Na^+ reabsorption and also cause an increase in GFR, which may mask the tubular effect. Usually a decrease in Na^+ excretion is seen.

Osmotic Diuretics. Osmotic diuretics are solutes that are excreted in the urine and increase urinary excretion of Na^+ and K^+ salts and water. Examples are urea, glucose (when the reabsorptive capacity of the tubules for glucose has been exceeded), and mannitol (a six-carbon sugar alcohol used in the clinic to promote Na^+ excretion or cell shrinkage). Osmotic diuretics decrease the reabsorption of Na^+ in the proximal tubule. This response results from the development of a Na^+ concentration gradient (lumen [Na^+] < plasma [Na^+]) across the proximal tubular epithelium in the presence of a high concentration of unreabsorbed solute in the tubule lumen. When this occurs, there is significant back-leak of Na^+ into the tubule lumen, down the concentration gradient. This back-leak results in decreased net Na^+ reabsorption. Because the proximal tubule is where most of the filtered Na^+ is normally reabsorbed, osmotic diuretics, by interfering with this process, can potentially cause the excretion of large amounts of Na^+. Osmotic diuretics may also increase Na^+ excretion by inhibiting distal Na^+ reabsorption (similar to the proximal inhibition) and by increasing medullary blood flow.

Poorly Reabsorbed Anions. Poorly reabsorbed anions result in increased Na^+ excretion. Solutions are electrically neutral; whenever there are more anions in the urine, there must also be more cations. If there is increased excretion of phosphate, ketone body acids (as occurs in uncontrolled diabetes mellitus), HCO_3^-, or SO_4^{2-}, more Na^+ is also excreted. To some extent, the Na^+ in the urine can be replaced by other cations, such as K^+, NH_4^+, and H^+.

Diuretic Drugs. Most of the diuretic drugs used today are specific Na^+ transport inhibitors. For example, the loop diuretic drugs (furosemide, bumetanide) inhibit the Na-K-2Cl cotransporter in the thick ascending limb, the thiazide diuretics inhibit the Na-Cl cotransporter in the distal convoluted tubule, and amiloride blocks the epithelial Na^+ channel in the collecting ducts (see Chapter 23). Spironolactone promotes Na^+ excretion by competitively inhibiting the binding of aldosterone to the mineralocorticoid receptor. The diuretic drugs are really natriuretic drugs; they produce an increased urine output (diuresis) because water reabsorption is diminished whenever Na^+ reabsorption is decreased. Diuretics are commonly prescribed for treating hypertension and edema.

The Kidneys Play a Dominant Role in Regulating Na1 Balance

Figure 24.11 summarizes Na^+ balance throughout the body. Dietary intake of Na^+ varies and, in a typical American diet, amounts to about 100 to 300 mEq/day, mostly in the form of NaCl. Ingested Na^+ is mainly absorbed in the small intestine and is added to the ECF, where it is the major determinant of the osmolality and the amount of water in (or volume of) this fluid compartment. About 50% of the body's Na^+ is in the ECF, about 40% in bone, and about 10% within cells.

Losses of Na^+ occur via the skin, gastrointestinal tract, and kidneys. Skin losses are usually small, but can be considerable with sweating, burns, or hemorrhage. Likewise, gastrointestinal losses are usually small, but they can be large and serious with vomiting, diarrhea, or iatrogenic suction or drainage of gastrointestinal secretions. The kidneys are ordinarily the major routes of Na^+ loss from the body, excreting about 95% of the ingested Na^+ in a healthy person. Thus, the kidneys play a dominant role in the control of Na^+ balance. The kidneys can adjust Na^+ excretion over a wide range, reducing it to low levels when there is a Na^+ deficit and excreting more Na^+ when there is Na^+ excess in the body. Adjustments in Na^+ excretion occur by engaging many of the factors previously discussed.

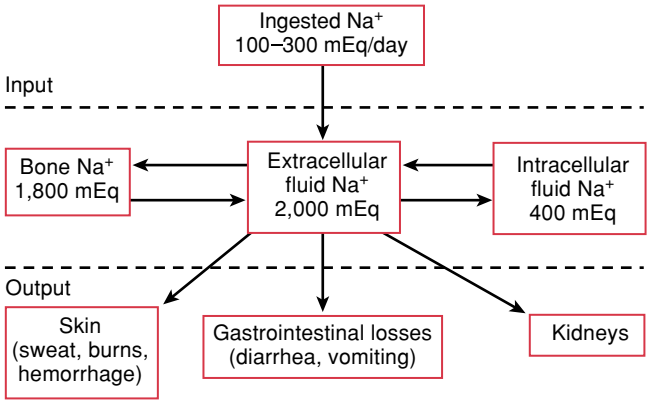

FIGURE 24.11 **Na^+ balance.** Most of the Na^+ consumed in our diets is excreted by the kidneys.

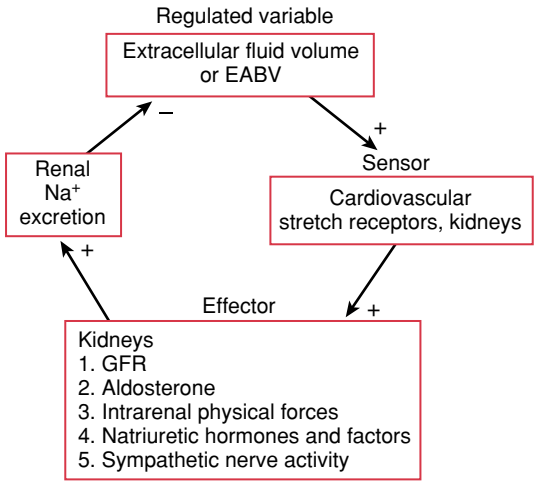

FIGURE 24.12 **The regulation of ECF volume or effective arterial blood volume (EABV) by a negative-feedback control system.** Arterial baroreceptors and the kidneys sense the degree of fullness of the arterial system. The kidneys are the effectors, and they change Na^+ excretion to restore EABV to normal.

In a healthy individual, one can think of the ECF volume as the regulated variable in a negative-feedback control system (Fig. 24.12). The kidneys are the effectors, and they change Na^+ excretion in an appropriate manner. An increase in ECF volume promotes renal Na^+ loss, which restores a normal volume. A decrease in ECF volume leads to decreased renal Na^+ excretion, and this Na^+ retention (with continued dietary Na^+ intake) leads to the restoration of a normal ECF volume. Closer examination of this concept, particularly when considering pathophysiological states, however, suggests that it is of limited usefulness. A more considered view suggests that the effective arterial blood volume (EABV) is actually the regulated variable. In a healthy individual, ECF volume and EABV usually change together in the same direction. In an abnormal condition such as congestive heart failure, however, EABV is low when the ECF volume is abnormally increased. In this condition, there is a potent stimulus for renal Na^+ retention that clearly cannot be the ECF volume.

When EABV is diminished, the degree of fullness of the arterial system is less than normal and tissue blood flow is inadequate. Arterial baroreceptors in the carotid sinuses and aortic arch sense the decreased arterial stretch. This will produce reflex activation of sympathetic nerve fibers to the kidneys, with consequently decreased GFR and renal blood flow and increased renin release. These changes favor renal Na^+ retention. Reduced EABV is also "sensed" in the kidneys in three ways:

1) A low pressure at the level of the afferent arteriole stimulates renin release via the intrarenal baroreceptor mechanism.

2) Decreases in renal perfusion pressure lead to a reduced GFR and, hence, diminished Na^+ excretion.

3) Decreases in renal perfusion pressure will also reduce peritubular capillary hydrostatic pressure, increasing the uptake of reabsorbed fluid and diminishing Na^+ excretion.

When kidney perfusion is threatened, the kidneys retain salt and water, a response that tends to improve their perfusion.

In several important diseases, including heart and liver and some kidney diseases, abnormal renal retention of Na^+ contributes to the development of **generalized edema**, a widespread accumulation of salt and water in the interstitial spaces of the body. The condition is often not clinically evident until a person has accumulated more than 2.5 to 3 L of ECF in the interstitial space. Expansion of the interstitial space has two components: (1) an altered balance of Starling forces exerted across capillaries, and (2) the retention of extra salt and water by the kidneys. Total plasma volume is only about 3.5 L; if edema fluid were derived solely from the plasma, hemoconcentration and circulatory shock would ensue. Conservation of salt and water by the kidneys is clearly an important part of the development of generalized edema.

Patients with congestive heart failure may accumulate many liters of edema fluid, which is easily detected as weight gain (since 1 L of fluid weighs 1 kg). Because of the effect of gravity, the ankles become swollen and pitting edema develops. As a result of heart failure, venous pressure is elevated, causing fluid to leak out of the capillaries because of their elevated hydrostatic pressure. Inadequate pumping of blood by the heart leads to a decrease in EABV, so the kidneys retain salt and water. Alterations in many of the factors discussed above—decreased GFR, increased RAAS activity, changes in intrarenal physical forces, and increased sympathetic nervous system activity—contribute to the renal salt and water retention. To minimize the accumulation of edema fluid, patients are often placed on a reduced Na^+ intake and given diuretic drugs.

Hypertension may often be a result of a disturbance in NaCl (salt) balance. Excessive dietary intake of NaCl or inadequate renal excretion of salt tends to increase intravascular volume; this change translates into an increase in blood pressure. A reduced salt intake, ACE inhibitors, diuretic drugs, or drugs that more directly affect the cardiovascular system (e.g., Ca^{2+} channel blockers or β-adrenergic blockers) are useful therapies in controlling hypertension in many people.

POTASSIUM BALANCE

Potassium (K^+) is the most abundant ion in the ICF compartment. It has many important effects in the body, and its plasma concentration is closely regulated. The kidneys play a dominant role in regulating K^+ balance.

K^+ Influences Cell Volume, Excitability, Acid-Base Balance, and Metabolism

As the major osmotically active solute in cells, the amount of cellular K^+ is the major determinant of the amount of water in (and, therefore, the volume of) the ICF compartment, in the same way that extracellular Na^+ is a major determinant of ECF volume. When cells lose K^+ (and accompanying anions), they also lose water and shrink; the converse is also true.

The distribution of K^+ across plasma membranes—that is, the ratio of intracellular to extracellular K^+ concentrations—is the major determinant of the resting membrane potential of cells and, hence, their excitability (see Chapter 3). Disturbances of K^+ balance often produce altered excitability of nerves and muscles. Low plasma $[K^+]$ leads to membrane hyperpolarization and reduced excitability; muscle weakness is a common symptom. Excessive plasma K^+ levels lead to membrane depolarization and increased excitability. High plasma K^+ levels cause cardiac arrhythmias and, eventually, ventricular fibrillation, usually a lethal event.

K^+ balance is linked to acid-base balance in complex ways (see Chapter 25). K^+ depletion, for example, can lead to metabolic alkalosis, and K^+ excess to metabolic acidosis. A primary disturbance in acid-base balance can also lead to abnormal K^+ balance.

K^+ affects the activity of enzymes involved in carbohydrate metabolism and electron transport. K^+ is needed for tissue growth and repair. Tissue breakdown or increased protein catabolism result in a loss of K^+ from cells.

Most of the Body's K^+ Is in Cells

Total body content of K^+ in a healthy, young adult, 70-kg man is about 3,700 mEq. About 2% of this, about 60 mEq, is in the functional ECF (blood plasma, interstitial fluid, and lymph); this number was calculated by multiplying the plasma $[K^+]$ of 4 mEq/L times the ECF volume (20% of body weight or 14 L). About 8% of the body's K^+ is in bone, dense connective tissue, and cartilage, and another 1% is in transcellular fluids. Ninety percent of the body's K^+ is in the cell compartment.

A normal plasma $[K^+]$ is 3.5 to 5.0 mEq/L. By definition, plasma $[K^+]$ below 3.5 mEq/L is **hypokalemia** and plasma $[K^+]$ above 5.0 mEq/L is **hyperkalemia**. The $[K^+]$ in skeletal muscle cells is about 150 mEq/L cell water. Skeletal muscle cells constitute the largest fraction of the cell mass in the human body and contain about two thirds of the body's K^+. One can easily appreciate that abnormal leakage of K^+ from muscle cells, for example, as a result of trauma, may lead to dangerous hyperkalemia.

A variety of factors influence the distribution of K^+ between cells and ECF (Fig. 24.13):

1) A key factor is the Na^+/K^+-ATPase, which pumps K^+ into cells. If this enzyme is inhibited—as a result of inadequate tissue oxygen supply or digitalis overdose, for example—hyperkalemia may result.

2) A decrease in ECF pH (an increase in ECF $[H^+]$) tends to produce a rise in ECF $[K^+]$. This results from an exchange of extracellular H^+ for intracellular K^+. When a mineral acid such as HCl is added to the ECF, a fall in blood pH of 0.1 unit leads to about a 0.6 mEq/L rise in plasma $[K^+]$. When an organic acid (which can penetrate plasma membranes) is added, the rise in plasma K^+ for a given fall in blood pH is considerably less. The fact that blood pH influences plasma $[K^+]$ is sometimes used in the emergency treatment of hyperkalemia; intravenous infusion of a $NaHCO_3$ solution (which makes the blood more alkaline) will cause H^+ to move out of cells and K^+, in exchange, to move into cells.

3) Insulin promotes the uptake of K^+ by skeletal muscle and liver cells. This effect appears to be a result of stim-

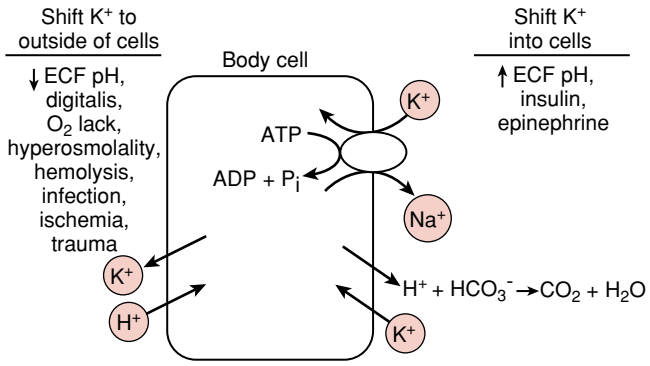

FIGURE 24.13 **Factors influencing the distribution of K^+** between intracellular and extracellular fluids.

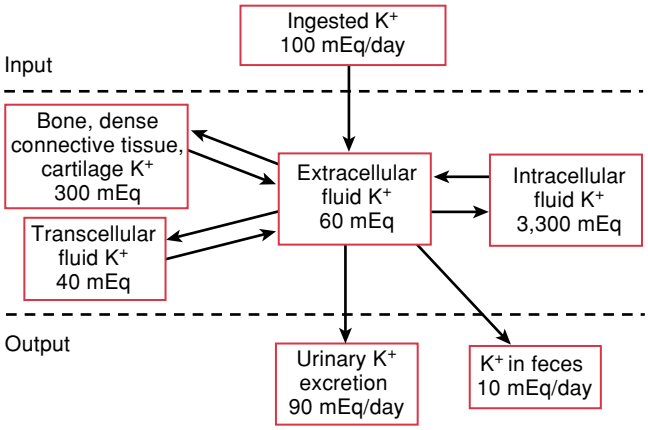

FIGURE 24.14 **K^+** balance for a healthy adult. Most K^+ in the body is in the cell compartment. Renal K^+ excretion is normally adjusted to keep a person in balance.

ulation of plasma membrane Na^+/K^+-ATPase pumps. Insulin (administered with glucose) is also used in the emergency treatment of hyperkalemia.

4) Epinephrine increases K^+ uptake by cells, an effect mediated by β_2-receptors.

5) Hyperosmolality (e.g., a result of hyperglycemia) tends to raise plasma $[K^+]$; hyperosmolality causes cells to shrink and raises intracellular $[K^+]$, which then favors outward diffusion of K^+ into the ECF.

6) Tissue trauma, infection, ischemia, hemolysis, or severe exercise release K^+ from cells and can cause significant hyperkalemia. An artifactual increase in plasma $[K^+]$, **pseudohyperkalemia**, results if blood has been mishandled and red cells have been injured and allowed to leak K^+.

The plasma $[K^+]$ is sometimes taken as an approximate guide to total body K^+ stores. For example, if a condition is known to produce an excessive loss of K^+ (such as taking a diuretic drug), a decrease in plasma $[K^+]$ of 1 mEq/L may correspond to a loss of 200 to 300 mEq K^+. Clearly, however, many factors affect the distribution of K^+ between cells and ECF; in many circumstances, the plasma $[K^+]$ is not a good index of the amount of K^+ in the body.

The Kidneys Normally Maintain K^+ Balance

Figure 24.14 depicts K^+ balance for a healthy adult man. Most of the food we eat contains K^+. K^+ intake (50 to 150 mEq/day) and absorption by the small intestine are unregulated. On the output side, gastrointestinal losses are normally small, but they can be large, especially with diarrhea. Diarrheal fluid may contain as much as 80 mEq K^+/L. K^+ loss in sweat is clinically unimportant. Normally, 90% of the ingested K^+ is excreted by the kidneys. The kidneys are the major sites of control of K^+ balance; they increase K^+ excretion when there is too much K^+ in the body and conserve K^+ when there is too little.

Abnormal Renal K^+ Excretion. The major cause of K^+ imbalances is abnormal renal K^+ excretion. The kidneys may excrete too little K^+; if the dietary intake of K^+ continues, hyperkalemia can result. For example, in Addison's disease, a low plasma aldosterone level leads to deficient K^+ excretion. Inadequate renal K^+ excretion also occurs with acute renal failure; the hyperkalemia caused by inadequate renal excretion is often compounded by tissue trauma, infection, and acidosis, all of which raise plasma $[K^+]$. In chronic renal failure, hyperkalemia usually does not develop until GFR falls below 15 to 20 mL/min because of the remarkable ability of the kidney collecting ducts to adapt and increase K^+ secretion.

Excessive loss of K^+ by the kidneys leads to hypokalemia. The major cause of renal K^+ wasting is iatrogenic, an unwanted side effect of diuretic drug therapy. Hyperaldosteronism causes excessive K^+ excretion. In uncontrolled diabetes mellitus, K^+ loss is increased because of the osmotic diuresis caused by glucosuria and an elevated rate of fluid flow in the cortical collecting ducts. Several rare inherited defects in tubular transport, including Bartter, Gitelman, and Liddle syndromes also lead to excessive renal K^+ excretion and hypokalemia (see Table 23.3).

Changes in Diet and K^+ Excretion. As was discussed in Chapter 23, K^+ is filtered, reabsorbed, and secreted in the kidneys. Most of the filtered K^+ is reabsorbed in the proximal convoluted tubule (70%) and the loop of Henle (25%), and the majority of K^+ excreted in the urine is usually the result of secretion by cortical collecting duct principal cells. The percentage of filtered K^+ excreted in the urine is typically about 15% (Fig. 24.15). With prolonged K^+ depletion, the kidneys may excrete only 1% of the filtered load. However, excessive K^+ intake may result in the excretion of an amount of K^+ that exceeds the amount filtered; in this case, there is greatly increased K^+ secretion by cortical collecting ducts.

When the dietary intake of K^+ is changed, renal excretion changes in the same direction. An important site for this adaptive change is the cortical collecting duct. Figure 24.16 shows the response to an increase in dietary K^+ intake. Two pathways are involved. First, an elevated plasma $[K^+]$ leads to increased K^+ uptake by the basolateral plasma membrane Na^+/K^+-ATPase in collecting duct principal cells, resulting in increased intracellular $[K^+]$, K^+ secretion and K^+ excretion. Second, elevated plasma $[K^+]$ has a direct effect (i.e., not mediated by renin and an-

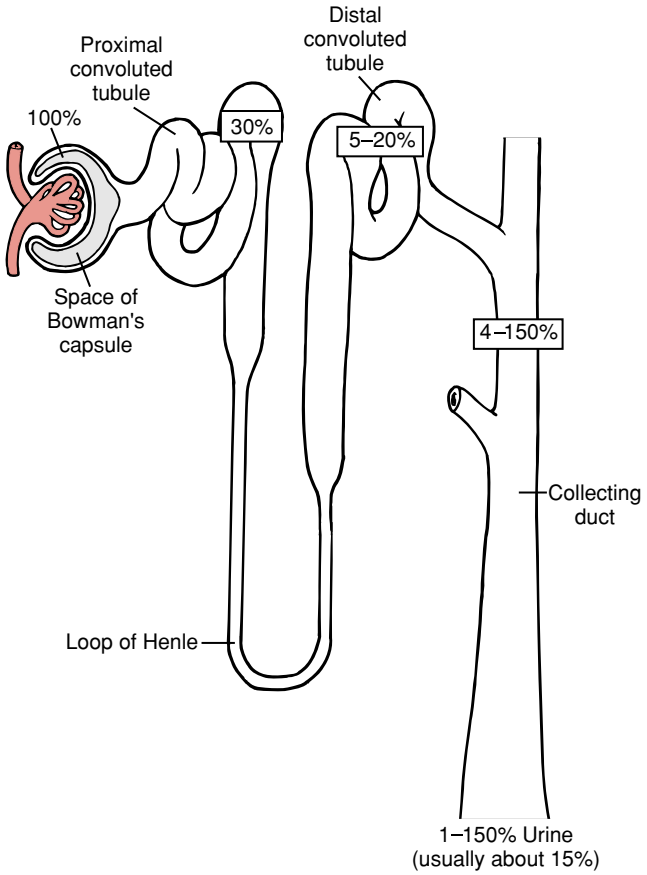

FIGURE 24.15 **The percentage of the filtered load of K^+** remaining in tubular fluid as it flows down the nephron. K^+ is usually secreted in the cortical collecting duct. With K^+ loading, this secretion is so vigorous that the amount of K^+ excreted may actually exceed the filtered load. With K^+ depletion, K^+ is reabsorbed by the collecting ducts.

giotensin) on the adrenal cortex to stimulate the synthesis and release of aldosterone. Aldosterone acts on collecting duct principal cells to (1) increase the Na^+ permeability of the luminal plasma membrane, (2) increase the number and activity of basolateral plasma membrane Na^+/K^+-ATPase pumps, (3) increase the luminal plasma membrane K^+ permeability, and (4) increase cell metabolism. All of these changes result in increased K^+ secretion.

In cases of decreased dietary K^+ intake or K^+ depletion, the activity of the luminal plasma membrane H^+/K^+-ATPase found in α-intercalated cells is increased. This promotes K^+ reabsorption by the collecting ducts. The collecting ducts can greatly diminish K^+ excretion, but it takes a couple of weeks for K^+ loss to reach minimal levels.

Counterbalancing Influences on K^+ Excretion. Considering that aldosterone stimulates both Na^+ reabsorption and K^+ secretion, why is it that Na^+ deprivation, a stimulus that raises plasma aldosterone levels, does not lead to enhanced K^+ excretion? The explanation is related to the fact that Na^+ deprivation tends to lower GFR and increase proximal Na^+ reabsorption (Fig. 24.17). This response leads to a fall in Na^+ delivery and a decreased fluid flow

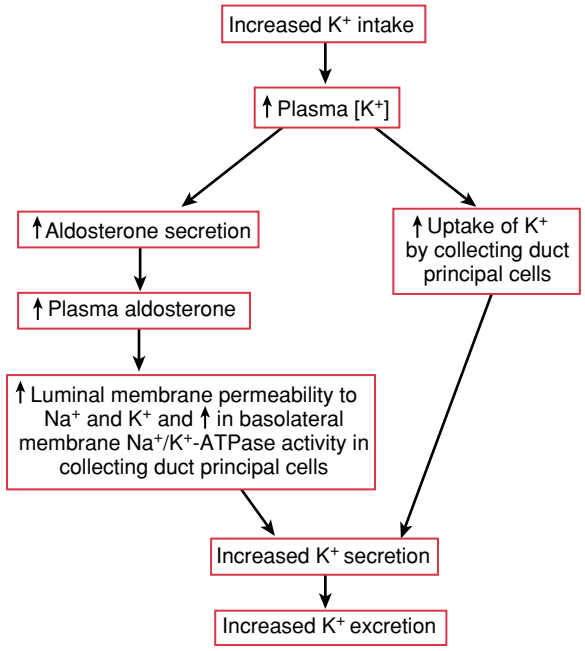

FIGURE 24.16 **Effect of increased dietary K^+** intake on K^+ excretion. K^+ directly stimulates aldosterone secretion and leads to an increase in cell $[K^+]$ in collecting duct principal cells. Both of these lead to enhanced secretion and, hence, excretion, of K^+.

rate in the cortical collecting ducts, which diminishes K^+ secretion and counterbalances the stimulatory effect of aldosterone. Consequently, K^+ excretion is unaltered.

Another puzzling question is: Why is it that K^+ excretion does not increase during water diuresis? In Chapter 23, we mentioned that an increase in fluid flow through the cortical collecting ducts increases K^+ secretion. AVP, in addition to its effects on water permeability, stimulates K^+ secretion by increasing the activity of luminal membrane K^+ channels in cortical collecting duct principal cells. Since plasma AVP levels are low during water diuresis, this will reduce K^+ secretion, oppos-

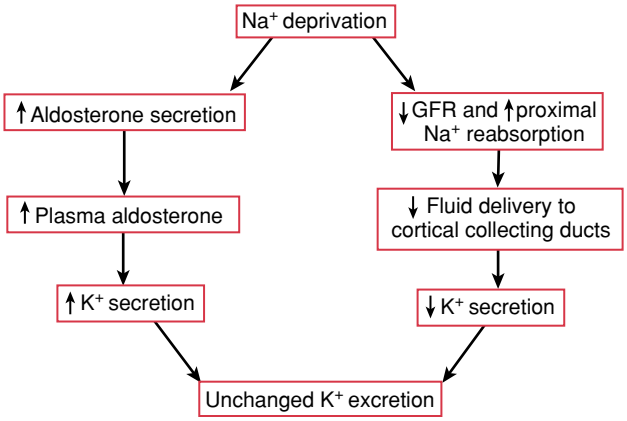

FIGURE 24.17 **Why Na^+** depletion does not lead to enhanced K^+ excretion.

ing the effects of increased flow, with the result that K^+ excretion hardly changes.

CALCIUM BALANCE

The kidneys play an important role in the maintenance of Ca^{2+} balance. Ca^{2+} intake is about 1,000 mg/day and mainly comes from dairy products in the diet. About 300 mg/day are absorbed by the small intestine, a process controlled by 1,25$(OH)_2$ vitamin D_3. About 150 mg Ca^{2+}/day are secreted into the gastrointestinal tract (via saliva, gastric juice, pancreatic juice, bile, and intestinal secretions), so that net absorption is only about 150 mg/day. Fecal Ca^{2+} excretion is about 850 mg/day and urinary excretion about 150 mg/day.

A normal plasma [Ca^{2+}] is about 10 mg/dL, which is equal to 2.5 mmol/L (since the atomic weight of calcium is 40) or 5 mEq/L. About 40% of plasma Ca^{2+} is bound to plasma proteins (mainly serum albumin), 10% is bound to small diffusible anions (such as citrate, bicarbonate, phosphate, and sulfate) and 50% is free or ionized. It is the ionized Ca^{2+} in the blood that is physiologically important and closely regulated (see Chapter 36). Most of the Ca^{2+} in the body is in bone (99%), which constantly turns over. In a healthy adult, the rate of release of Ca^{2+} from old bone exactly matches the rate of deposition of Ca^{2+} in newly formed bone (500 mg/day).

Ca^{2+} that is not bound to plasma proteins (i.e., 60% of the plasma Ca^{2+}) is freely filterable in the glomeruli. About 60% of the filtered Ca^{2+} is reabsorbed in the proximal convoluted tubule (Fig. 24.18). Two thirds is reabsorbed via a paracellular route in response to solvent drag and the small lumen positive potential (+3 mV) found in the late proximal convoluted tubule. One third is reabsorbed via a transcellular route that includes Ca^{2+} channels in the apical plasma membrane and a primary Ca^{2+}-ATPase or 3 Na^+/1 Ca^{2+} exchanger in the basolateral plasma membrane. About 30% of filtered Ca^{2+} is reabsorbed along the loop of Henle. Most of the Ca^{2+} reabsorbed in the thick ascending limb is by passive transport through the tight junctions, propelled by the lumen positive potential.

Reabsorption continues along the distal convoluted tubule. Reabsorption here is increased by thiazide diuretics, which may be prescribed in cases of excessive Ca^{2+} in the urine, **hypercalciuria**, and kidney stone disease (see Clinical Focus Box 24.2). Thiazides inhibit the luminal membrane Na-Cl cotransporter in distal convoluted tubule cells, which leads to a fall in intracellular [Na^+]. This, in turn, promotes Na^+-Ca^{2+} exchange and increased basolateral extrusion of Ca^{2+} and increased Ca^{2+} reabsorption.

The late distal tubule (connecting tubule and initial part of the cortical collecting duct) is an important site of control of Ca^{2+} excretion because this is where parathyroid hormone (PTH) increases Ca^{2+} reabsorption. Ca^{2+} diffuses into the cells, primarily through an epithelial Ca^{2+} channel (ECaC) in the apical membrane, is transported through the cytoplasm by a 1,25$(OH)_2$ vitamin D_3-dependent calcium-binding protein, called calbindin, and is extruded by a Na^+/Ca^{2+} exchange or Ca^{2+}-ATPase in the basolateral plasma membrane. Only about 0.5 to 2% of the filtered Ca^{2+} is usually excreted. (Chapter 34 discusses Ca^{2+} balance and its control by several hormones in more detail.)

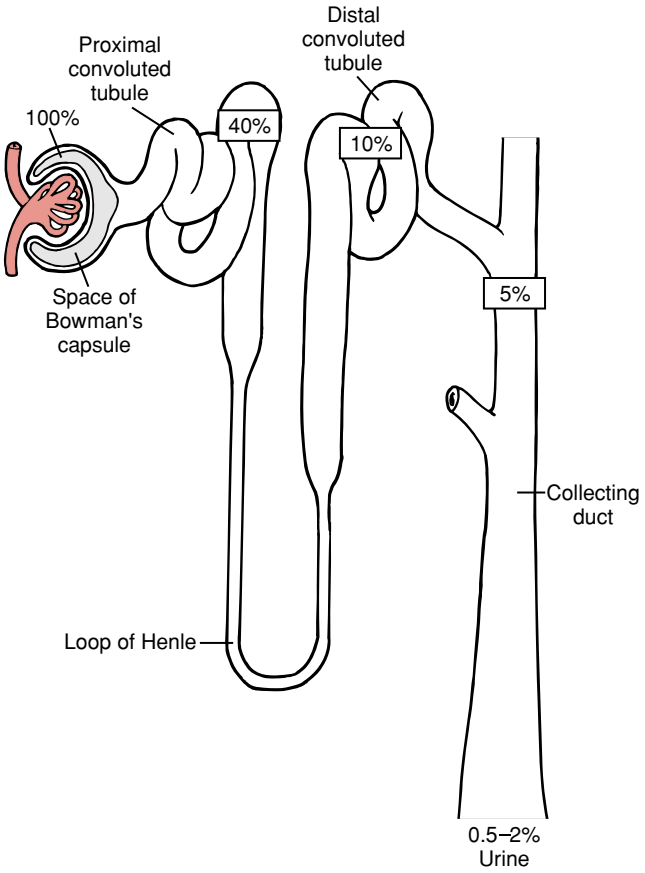

FIGURE 24.18 **The percentage of the filtered load of Ca^{2+}** remaining in tubular fluid as it flows down the nephron. The kidneys filter about 10,800 mg/day (0.6 × 100 mg/L × 180 L/day) and excrete only about 0.5 to 2% of the filtered load, that is, about 50 to 200 mg/day. Thiazides increase Ca^{2+} reabsorption by the distal convoluted tubule, and PTH increases Ca^{2+} reabsorption by the connecting tubule and cortical collecting duct.

MAGNESIUM BALANCE

An adult body contains about 2,000 mEq of Mg^{2+}, of which about 60% is present in bone, about 39% in cells, and about 1% in the ECF. Mg^{2+} is the second most abundant cation in cells, after K^+ (see Table 24.2). The bulk of intracellular Mg^{2+} is not free, but is bound to a variety of organic compounds, such as ATP. Mg^{2+} is present in the plasma at a concentration of about 1 mmol/L (2 mEq/L). About 20% of plasma Mg^{2+} is bound to plasma proteins, 20% is complexed with various anions, and 60% is free or ionized.

About 25% of the Mg^{2+} filtered by the glomeruli is reabsorbed in the proximal convoluted tubule (Fig. 24.19); this is a lower percentage than for Na^+, K^+, Ca^{2+}, or water. The proximal tubule epithelium is rather impermeable to Mg^{2+} under normal conditions, so there is little passive Mg^{2+} reabsorption. The major site of Mg^{2+} reabsorption is the loop of Henle (mainly the thick ascending limb), which

CLINICAL FOCUS BOX 24.2

Kidney Stone Disease (Nephrolithiasis)

A kidney stone is a hard mass that forms in the urinary tract. At least 1% of Americans develop kidney stones at some time during their lives. **Nephrolithiasis** or kidney stone disease occurs more commonly in men than in women and usually strikes men between the ages of 30 and 60. A stone lodged in the ureter will cause bleeding and intense pain. Kidney stone disease causes considerable suffering and loss of time from work, and it may lead to kidney damage. Once a stone forms in a person, stone formation often recurs.

Stones form when poorly soluble substances in the urine precipitate out of solution, causing crystals to form, aggregate, and grow. Most kidney stones (75 to 85%) are made up of insoluble Ca^{2+} salts of oxalate and phosphate. There may be excessive amounts of Ca^{2+} or oxalate in the urine as a result of diet, a genetic defect, or unknown causes. Stones may also form from precipitated ammonium magnesium phosphate (struvite), uric acid, and cystine. Struvite stones (10 to 15% of all stones) are the result of infection with bacteria, usually *Proteus* species. Uric acid stones (5 to 8% of all stones) may form in patients with excessive uric acid production and excretion, as occurs in some patients with gout. Defective tubular reabsorption of cystine (in patients with **cystinuria**) leads to cystine stone (1% of stones). The rather insoluble amino acid cystine was first isolated from a urinary bladder stone by Wollaston in 1810, hence, its name. Because low urine flow rate raises the concentration of all poorly soluble substances in the urine, favoring precipitation, a key to prevention of kidney stones is to drink plenty of water and maintain a high urine output day and night.

Fortunately, most stones are small enough to be passed down the urinary tract and spontaneously eliminated. Microscopic and chemical examination of the eliminated stones is used to determine the nature of the stone and help guide treatment. Sometimes a change in diet is recommended to reduce the amount of potential stone-forming material (e.g., Ca^{2+}, oxalate, or uric acid) in the urine. Thiazide diuretics are useful in reducing Ca^{2+} excretion if excessive urinary Ca^{2+} excretion (hypercalciuria) is the problem. Potassium citrate is useful in treating most stone disease because citrate complexes Ca^{2+} in the urine and inhibits the crystallization of Ca^{2+} salts. It also makes the urine more alkaline (since citrate is oxidized to HCO_3^- in the body). This is helpful in reducing the risk of uric acid stones because urates (favored in an alkaline urine) are more soluble than uric acid (the form favored in an acidic urine). Administering an inhibitor of uric acid synthesis, such as allopurinol, can help reduce the amount of uric acid in the urine.

If the stone is not passed, several options are available. Surgery to remove the stone can be done, but **extracorporeal shock wave lithotripsy** is more common, using a device called a **lithotriptor**. The patient is placed in a tub of water, and the stone is localized by X-ray imaging. Shock waves are generated in the water by high-voltage electric discharges and are focused on the stone through the body wall. The shock waves fragment the stone so that it can be passed down the urinary tract and eliminated. As some renal injury is produced by this procedure, it may not be entirely innocuous. Other procedures include passing a tube with an ultrasound transducer through the skin into the renal pelvis; stone fragments can be removed directly. A ureteroscope with a laser can also be used to break up stones.

reabsorbs about 65% of filtered Mg^{2+}. Reabsorption here is mainly passive and occurs through the tight junctions, driven by the lumen positive potential. Recent studies have identified a tight junction protein that is a channel that facilitates Mg^{2+} movement. Changes in Mg^{2+} excretion result mainly from changes in loop transport. More distal portions of the nephron reabsorb only a small fraction of filtered Mg^{2+} and, under normal circumstances, appear to play a minor role in controlling Mg^{2+} excretion.

An abnormally low plasma [Mg^{2+}] is characterized by neuromuscular and CNS hyperirritability. Abnormally high plasma Mg^{2+} levels have a sedative effect and may cause cardiac arrest. Dietary intake of Mg^{2+} is usually 20 to 50 mEq/day; two thirds is excreted in the feces, and one third is excreted in the urine. The kidneys are mainly responsible for regulating the plasma [Mg^{2+}]. Excess amounts of Mg^{2+} are rapidly excreted by the kidneys. In Mg^{2+}-deficient states, Mg^{2+} virtually disappears from the urine.

PHOSPHATE BALANCE

A normal plasma concentration of inorganic phosphate is about 1 mmol/L. At a normal blood pH of 7.4, 80% of the phosphate is present as HPO_4^{2-} and 20% is present as $H_2PO_4^-$. Phosphate plays a variety of roles in the body: It is an important constituent of bone; it plays a critical role in cell metabolism, structure, and regulation (as organic phosphates); and it is a pH buffer.

Phosphate is mainly unbound in the plasma and freely filtered by the glomeruli. About 60 to 70% of filtered phosphate is actively reabsorbed in the proximal convoluted tubule and another 15% is reabsorbed by the proximal straight tubule via a Na^+-phosphate cotransporter in the luminal plasma membrane (Fig. 24.20). The remaining portions of the nephron and collecting ducts reabsorb little, if any, phosphate. The proximal tubule is the major site of phosphate reabsorption. Only about 5 to 20% of filtered phosphate is usually excreted. Phosphate in the urine is an important pH buffer and contributes to titratable acid excretion (see Chapter 25). Phosphate reabsorption is Tm-limited (see Chapter 23), and the amounts of phosphate filtered usually exceed the maximum reabsorptive capacity of the tubules for phosphate. This is different from the situation for glucose, in which normally less glucose is filtered than can be reabsorbed. If more phosphate is ingested and absorbed by the intestine, plasma [phosphate] rises, more phosphate is filtered, and the filtered load exceeds the Tm more than usual and the extra phosphate is excreted. Thus, the kidneys participate in regulating the plasma phosphate

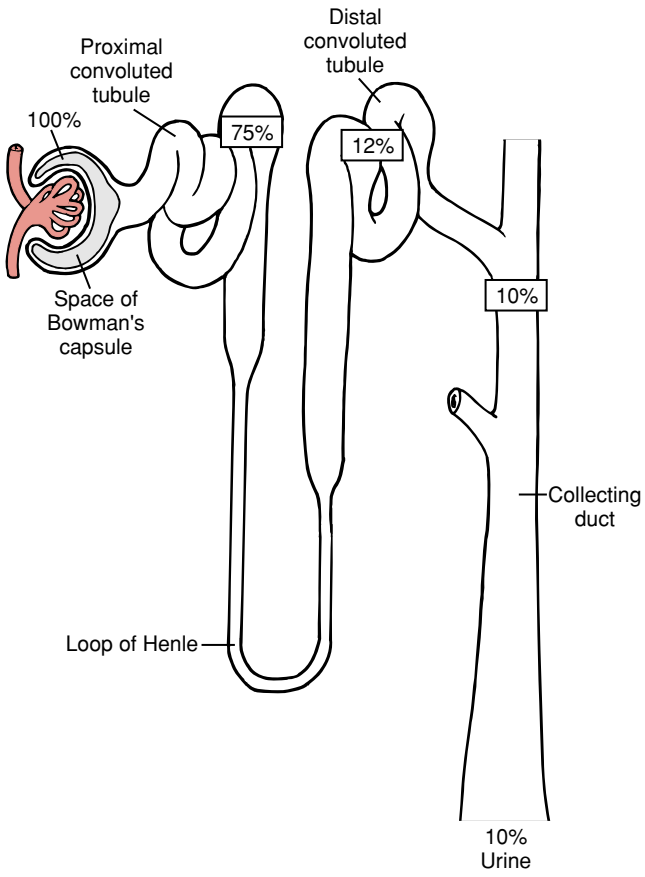

FIGURE 24.19 **The percentage of the filtered load of Mg^{2+} remaining in tubular fluid as it flows down the nephron.** The loop of Henle, specifically the thick ascending limb, is the major site of reabsorption of filtered Mg^{2+}.

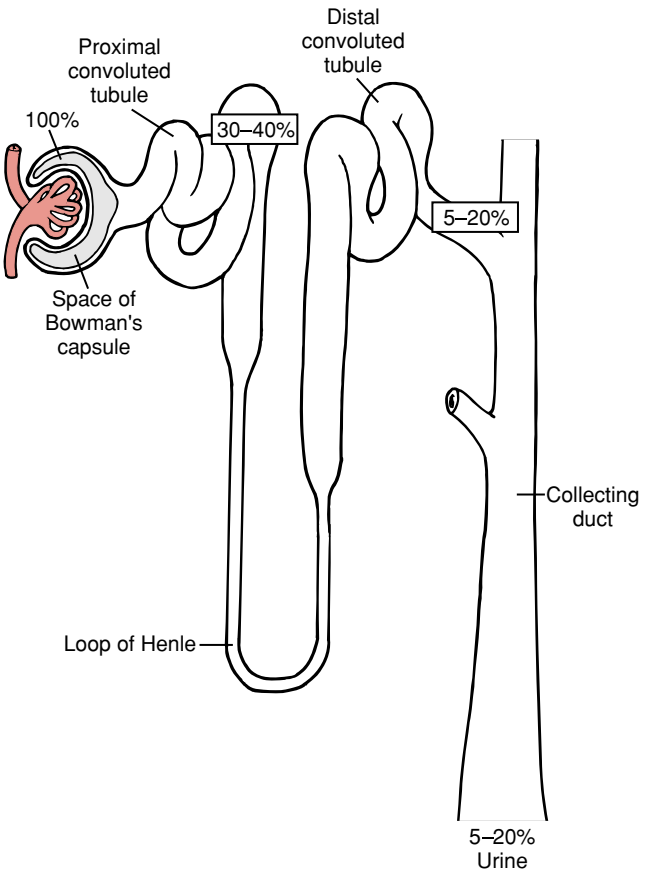

FIGURE 24.20 **The percentage of the filtered load of phosphate remaining in tubular fluid as it flows down the nephron.** The proximal tubule is the major site of phosphate reabsorption, and downstream nephron segments reabsorb little, if any, phosphate.

by an "overflow" type mechanism. When there is an excess of phosphate in the body, they automatically increase phosphate excretion. In cases of phosphate depletion, the kidneys filter less phosphate and the tubules reabsorb a larger percentage of the filtered phosphate.

Phosphate reabsorption in the proximal tubule is controlled by a variety of factors. PTH is of particular importance; it decreases the phosphate Tm, increasing phosphate excretion.

Patients with chronic renal disease often develop an elevated plasma [phosphate] or **hyperphosphatemia**, depending on the severity of the disease. When GFR falls, the filtered phosphate load is diminished, and the tubules reabsorb phosphate more completely. Phosphate excretion is inadequate in the face of continued intake of phosphate in the diet. Hyperphosphatemia is dangerous because of the precipitation of calcium phosphate in soft tissue. For example, when calcium phosphate precipitates in the walls of blood vessels, blood flow will be impaired. Hyperphosphatemia can lead to myocardial failure and pulmonary insufficiency.

When plasma [phosphate] rises, the plasma ionized $[Ca^{2+}]$ tends to fall, for two reasons. First, phosphate forms a complex with Ca^{2+}. Second, hyperphosphatemia decreases production of $1,25(OH)_2$ vitamin D_3 in the kidneys by inhibiting the 1α-hydroxylase enzyme that forms this hormone. With decreased plasma levels of $1,25(OH)_2$ vitamin D_3, there is less Ca^{2+} absorption by the small intestine and a tendency for hypocalcemia.

Low plasma ionized $[Ca^{2+}]$ stimulates hyperplasia of the parathyroid glands and increased secretion of PTH. High plasma [phosphate] also stimulates PTH secretion directly. PTH then inhibits phosphate reabsorption by the proximal tubules, promotes phosphate excretion, and helps return plasma [phosphate] back to normal. Elevated PTH levels, however, also cause mobilization of Ca^{2+} and phosphate from bone. Increased bone reabsorption results, and the bone minerals are replaced with fibrous tissue that renders the bone more susceptible to fracture.

Patients with advanced chronic renal failure are often advised to restrict phosphate intake and consume substances (such as Ca^{2+} salts) that bind phosphate in the intestines, so as to avoid the many problems caused by hyperphosphatemia. Administration of synthetic $1,25(OH)_2$ vitamin D_3 may compensate for deficient renal production of this hormone. This hormone opposes hypocalcemia and inhibits PTH synthesis

and secretion. Parathyroidectomy is sometimes necessary in patients with advanced chronic renal failure.

URINARY TRACT

The kidneys form urine all of the time. The urine is transported by the ureters to the urinary bladder. The bladder is specialized to fill with urine at a low pressure and to empty its contents when appropriate. Contractions of the bladder and its sphincters are controlled by the nervous system.

The Ureters Convey Urine to the Bladder

The **ureters** are muscular tubes that propel the urine from the pelvis of each kidney to the urinary bladder. Peristaltic movements originate in the region of the calyces, which contain specialized smooth muscle cells that generate spontaneous pacemaker potentials. These pacemaker potentials trigger action potentials and contractions in the muscular regions of the renal pelvis that propagate distally to the ureter. Peristaltic waves sweep down the ureters at a frequency of one every 10 seconds to one every 2 to 3 minutes. The ureters enter the base of the bladder obliquely, forming a valvular flap that passively prevents the reflux of urine during contractions of the bladder. The ureters are innervated by sympathetic and parasympathetic nerve fibers. Sensory fibers mediate the intense pain that is felt when a stone distends or blocks a ureter.

The Bladder Stores Urine Until It Can Be Conveniently Emptied

The **urinary bladder** is a distensible hollow vessel containing smooth muscle in its wall (Fig. 24.21). The muscle is called the *detrusor* (from Latin for "that which pushes down"). The neck of the bladder, the involuntary **internal sphincter**, also contains smooth muscle. The bladder body and neck are innervated by parasympathetic **pelvic nerves** and sympathetic **hypogastric nerves**. The external sphincter, the **compressor urethrae**, is composed of skeletal muscle and innervated by somatic nerve fibers that travel in the **pudendal nerves**. Pelvic, hypogastric, and pudendal nerves contain both motor and sensory fibers.

The bladder has two functions: to serve as a distensible reservoir for urine and to empty its contents at appropriate intervals. When the bladder fills, it adjusts its tone to its capacity, so that minimal increases in bladder pressure occur. The external sphincter is kept closed by discharges along the pudendal nerves. The first sensation of bladder filling is experienced at a volume of 100 to 150 mL in an adult, and the first desire to void is elicited when the bladder contains about 150 to 250 mL of urine. A person becomes uncomfortably aware of a full bladder when the volume is 350 to 400 mL; at this volume, hydrostatic pressure in the bladder is about 10 cm H_2O. With further volume increases, bladder pressure rises steeply, partly as a result of reflex contractions of the detrusor. An increase in volume to 700 mL creates pain and often loss of control. The sensations of bladder filling, of conscious desire to void, and painful distension are mediated by afferents in the pelvic nerves.

Micturition Involves Autonomic and Somatic Nerves

Micturition (urination), the periodic emptying of the bladder, is a complex act involving both autonomic and somatic nerve pathways and several reflexes that can be either inhibited or facilitated by higher centers in the brain. The basic reflexes occur at the level of the sacral spinal cord and are modified by centers in the midbrain and cerebral cortex. Distension of the bladder is sensed by stretch receptors in the bladder wall; these induce reflex contraction of the detrusor and relaxation of the internal and external sphincters. This reflex is released by removing inhibitory influences from the cerebral cortex. Fluid flow through the urethra reflexively causes further contraction of the detrusor and relaxation of the external sphincter. Increased parasympathetic nerve activity stimulates contraction of the detrusor and relaxation of the internal sphincter. Sympathetic innervation is not essential for micturition. During micturition, the perineal and levator ani muscles relax, shortening the urethra and decreasing urethral resistance. Descent of the diaphragm and contraction of abdominal muscles raises intra-abdominal pressure, and aids in the expulsion of urine from the bladder.

Micturition is fortunately under voluntary control in healthy adults. In the young child, however, it is purely re-

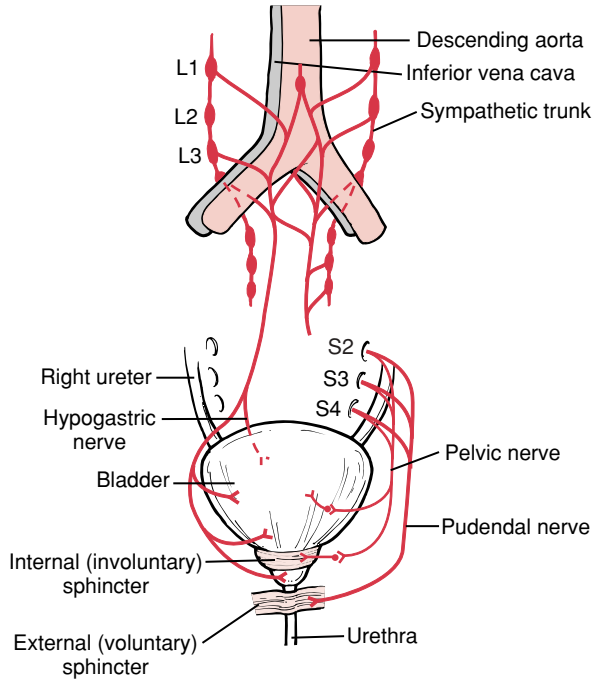

FIGURE 24.21 **The innervation of the urinary bladder.** The parasympathetic pelvic nerves arise from spinal cord segments S2 to S4 and supply motor fibers to the bladder musculature and internal (involuntary) sphincter. Sympathetic motor fibers supply the bladder via the hypogastric nerves, which arise from lumbar segments of the spinal cord. The pudendal nerves supply somatic motor innervation to the external (voluntary) sphincter. Sensory afferents (dashed lines) from the bladder travel mainly in the pelvic nerves but also to some extent in the hypogastric nerves. (Modified from Anderson JE. Grant's Atlas of Anatomy. 8th Ed. Baltimore: Williams & Wilkins, 1983.)

flex and occurs whenever the bladder is sufficiently distended. At about 2½ years of age, it begins to come under cortical control and, in most children, complete control is achieved by age 3. Damage to the nerves that supply the bladder and its sphincters can produce abnormalities of micturition and incontinence. An increased resistance of the upper urethra commonly occurs in older men and is a result of enlargement of the surrounding prostate gland. This condition is called **benign prostatic hyperplasia**, and it results in decreased urine stream, overdistension of the bladder as a result of incomplete emptying, and increased urgency and frequency of urination.

REVIEW QUESTIONS

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

1. Which of the following body fluid volumes cannot be directly determined with a single indicator?
   (A) Extracellular fluid volume
   (B) Intracellular fluid volume
   (C) Plasma volume
   (D) Total body water
2. Which of the following results in thirst?
   (A) Cardiac failure
   (B) Decreased plasma levels of angiotensin II
   (C) Distension of the cardiac atria
   (D) Distension of the stomach
   (E) Hypotonic volume expansion
3. Arginine vasopressin (AVP) is synthesized in the
   (A) Adrenal cortex
   (B) Anterior hypothalamus
   (C) Anterior pituitary
   (D) Collecting ducts of the kidneys
   (E) Posterior pituitary
4. A 60-kg woman is given 10 microcuries (μCI) (370 kilobecquerels) of radioiodinated serum albumin (RISA) intravenously. Ten minutes later, a venous blood sample is collected, and the plasma RISA activity is 4 μCI/L. Her hematocrit ratio is 0.40. What is her blood volume?
   (A) 417 mL
   (B) 625 mL
   (C) 2.5 L
   (D) 4.17 L
   (E) 6.25 L
5. Which of the following leads to decreased Na^+ reabsorption by the kidneys?
   (A) An increase in central blood volume
   (B) An increase in colloid osmotic pressure in the peritubular capillaries
   (C) An increase in GFR
   (D) An increase in plasma aldosterone level
   (E) An increase in renal sympathetic nerve activity
6. The nephron segment that reabsorbs the largest percentage of filtered Mg^{2+} is the
   (A) Proximal convoluted tubule
   (B) Thick ascending limb
   (C) Distal convoluted tubule
   (D) Cortical collecting duct
   (E) Medullary collecting duct
7. Which of the following causes decreased renin release by the kidneys?
   (A) Decreased fluid and solute delivery to the macula densa
   (B) Hemorrhage
   (C) Intravenous infusion of isotonic saline
   (D) Narrowing (stenosis) of the renal artery
   (E) Stimulation of renal sympathetic nerves
8. Which of the following may cause hyperkalemia?
   (A) Epinephrine injection
   (B) Hyperaldosteronism
   (C) Insulin administration
   (D) Intravenous infusion of a $NaHCO_3$ solution
   (E) Skeletal muscle injury
9. Parathyroid hormone (PTH)
   (A) Decreases tubular reabsorption of Ca^{2+}
   (B) Decreases tubular reabsorption of phosphate
   (C) Inhibits bone resorption.
   (D) Secretion is decreased in patients with chronic renal failure
   (E) Secretion is stimulated by a rise in plasma ionized Ca^{2+}
10. Aldosterone acts on cortical collecting ducts to
    (A) Decrease K^+ secretion
    (B) Decrease Na^+ reabsorption
    (C) Decrease water permeability
    (D) Increase K^+ secretion
    (E) Increase water permeability
11. In response to an increase in GFR, the proximal tubule and the loop of Henle demonstrate an increase in the rate of Na^+ reabsorption. This phenomenon is called
    (A) Autoregulation
    (B) Glomerulotubular balance
    (C) Mineralocorticoid escape
    (D) Saturation of tubular transport
    (E) Tubuloglomerular feedback
12. A 60-year-old woman is always thirsty and wakes up several times during the night to empty her bladder. Plasma osmolality is 295 mOsm/kg H_2O (normal range, 281 to 297 mOsm/kg H_2O), urine osmolality is 100 mOsm/kg H_2O, and plasma AVP levels are higher than normal. The urine is negative for glucose. The most likely diagnosis is
    (A) Diabetes mellitus
    (B) Diuretic drug abuse
    (C) Nephrogenic diabetes insipidus
    (D) Neurogenic diabetes insipidus
    (E) Primary polydipsia
13. The volume of the extracellular fluid is most closely related to the amount of which solute in this compartment?
    (A) HCO_3^-
    (B) Glucose
    (C) K^+
    (D) Serum albumin
    (E) Na^+
14. A homeless man was found comatose, lying in the doorway of a downtown department store at night. His plasma osmolality was 370 mOsm/kg H_2O (normal, 281 to 297 mOsm/kg H_2O), plasma [Na^+] was 140 mEq/L (normal, 136 to 145 mEq/L), plasma [glucose] 100 mg/dL (normal fasting level, 70 to 110 mg/dL), and BUN 15 mg/dL (normal, 7 to 18 mg/dL). His most likely problem is
    (A) Alcohol intoxication
    (B) Dehydration
    (C) Diabetes insipidus
    (D) Diabetes mellitus
    (E) Renal failure
15. A hypertensive patient is given an angiotensin-converting enzyme (ACE) inhibitor. Which of the following changes would be expected?
    (A) Plasma aldosterone level will rise
    (B) Plasma angiotensin I level will rise
    (C) Plasma angiotensin II level will rise
    (D) Plasma bradykinin level will fall
    (E) Plasma renin level will fall
16. If a person consumes a high-K^+ diet, the majority of K^+ excreted in the urine is derived from
    (A) Glomerular filtrate
    (B) K^+ that is not reabsorbed in the proximal tubule

(continued)

(C) K^+ secreted in the loop of Henle
(D) K^+ secreted by the cortical collecting duct
(E) K^+ secreted by the inner medullary-collecting duct

17. Which of the following set of values would lead you to suspect that a person has syndrome of inappropriate secretion of ADH (SIADH)?

	Plasma Osmolality (mOsm/kg H_2O)	Plasma [Na^+] (mEq/L)	Urine Osmolality (mOsm/kg H_2O)
(A)	300	145	100
(B)	270	130	50
(C)	285	140	600
(D)	270	130	450
(E)	285	140	1,200

18. A dehydrated hospitalized patient with uncontrolled diabetes mellitus has a plasma [K^+] of 4.5 mEq/L (normal, 3.5 to 5.0 mEq/L), a plasma [glucose] of 500 mg/dL, and an arterial blood pH of 7.00 (normal, 7.35 to 7.45). These data suggest that the patient has
(A) A decreased total body store of K^+
(B) A normal total body store of K^+
(C) An increased total body store of K^+
(D) Hypokalemia
(E) Hyperkalemia

19. Intravenous infusion of 2.0 L of isotonic saline (0.9% NaCl) results in increased
(A) Intracellular fluid volume
(B) Plasma aldosterone level
(C) Plasma arginine vasopressin (AVP) concentration
(D) Plasma atrial natriuretic peptide (ANP) concentration
(E) Plasma volume, but no change in other body fluid compartments

20. The kidneys of a person with congestive heart failure avidly retain Na^+. The best explanation for this is that the
(A) Effective arterial blood volume is decreased
(B) Extracellular fluid volume is decreased
(C) Extracellular fluid volume is increased
(D) Total blood volume is decreased
(E) Total blood volume is increased

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