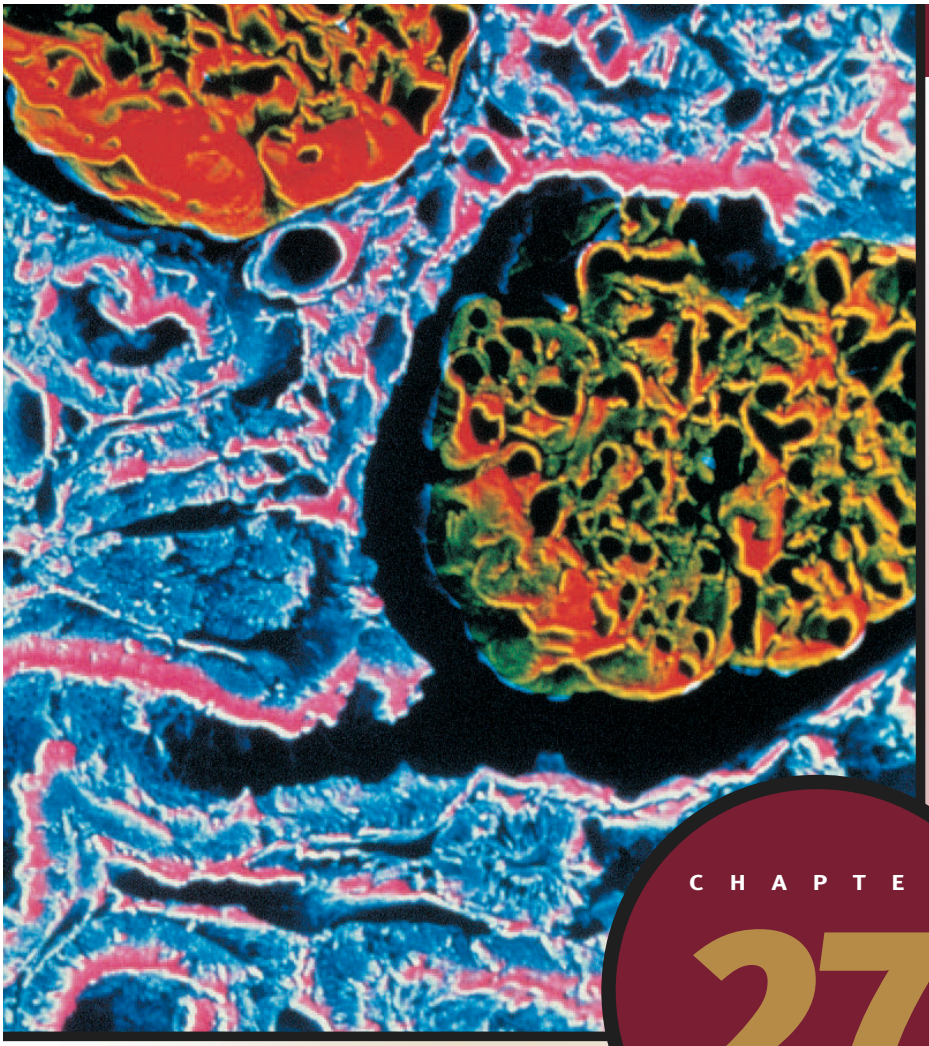


*Color enhanced SEM of a cross-section of renal corpuscles in the renal cortex.*

# Water, Electrolytes, and Acid–Base Balance

CHAPTER 27

Life depends on many complex and highly regulated chemical reactions, all of which occur in water. Many of these reactions are catalyzed by enzymes that can function only within a narrow range of conditions. Changes in the total amount of water, the pH, or the concentration of specific electrolytes can alter chemical reactions on which life depends. Homeostasis requires the maintenance of these parameters within a narrow range of values, and failure to maintain homeostasis can result in illness or death.

The kidneys, along with the respiratory, integumentary, and gastrointestinal systems, regulate water volume, electrolyte concentrations, and pH. The nervous and endocrine systems coordinate the activities of these systems.

This chapter covers *body fluids* (986), the *regulation of body fluid concentration and volume* (987), the *regulation of intracellular fluid composition* (992), the *regulation of specific electrolytes in the extracellular fluid* (993), and the *regulation of acid–base balance* (1003).

# Body Fluids

***Objectives***

- *List the major body fluid compartments and the approximate percent of body weight contributed by the fluid within each compartment, and describe how age and body fat influence the compartments.*
- *Compare the composition of intracellular and extracellular fluids.*

The proportion of body weight composed of water decreases from birth to old age, with the greatest decrease occurring during the first 10 years of life (table 27.1). Because the water content of adipose tissue is relatively low, the fraction of the body's weight composed of water decreases as the amount of adipose tissue increases. The relatively lower water content of adult females when compared to adult males reflects the greater development of subcutaneous adipose tissue characteristic of women.

For people of all ages and body compositions, the two major fluid compartments are the intracellular and extracellular fluid compartments. The **intracellular** (in-tră-sel′ū-lăr) **fluid compartment** includes all the fluid in the several trillion cells of the body. The intracellular fluid from all cells has a similar composition, and it accounts for approximately 40% of total body weight.

The **extracellular** (eks-tră-sel′ū-lăr) **fluid compartment** includes all of the fluid outside the cells and constitutes nearly 20% of total body weight. The extracellular fluid compartment can be divided into several subcompartments. The major ones are interstitial fluid and plasma; others include lymph, cerebrospinal fluid, and synovial fluid. **Interstitial** (in-ter-stish′ăl) **fluid** occupies the extracellular spaces outside the blood vessels, and **plasma** (plaz′mă) occupies the extracellular space within blood vessels. All the other subcompartments of the extracellular compartment constitute relatively small volumes.

Although the fluid contained in each subcompartment differs somewhat in composition from that in the others, continuous and extensive exchange occurs between the subcompartments. Water diffuses from one subcompartment to another, and small molecules and ions are either transported or diffuse freely between them. Large molecules like proteins are much more restricted in their movement because of the permeability characteristics of the membranes that separate the fluid subcompartments (table 27.2).

The osmotic pressure of most fluid compartments is approximately equal. For example, the osmotic pressure of the hyaluronic acid in synovial joints is roughly equal to the osmotic pressure of the proteins in intraocular fluid.

**Table 27.1 Approximate Volumes of Body Fluid Compartments***

| Age of Person | Total Body Water | Intracellular Fluid | Extracellular Fluid | | |
|---|---|---|---|---|---|
| | | | Plasma | Interstitial | Total |
| Infants | 75 | 45 | 4 | 26 | 30 |
| Adult males | 60 | 40 | 5 | 15 | 20 |
| Adult females | 50 | 35 | 5 | 10 | 15 |

*Expressed as percentage of body weight.

**Table 27.2 Approximate Concentration of Major Solutes in Body Fluid Compartments***

| Solute | Plasma | Interstitial Fluid | Intracellular Fluid† |
|---|---|---|---|
| **Cations** | | | |
| Sodium ($Na^+$) | 153.2 | 145.1 | 12.0 |
| Potassium ($K^+$) | 4.3 | 4.1 | 150.0 |
| Calcium ($Ca^{2+}$) | 3.8 | 3.4 | 4.0 |
| Magnesium ($Mg^{2+}$) | 1.4 | 1.3 | 34.0 |
| TOTAL | 162.7 | 153.9 | 200.0 |
| **Anions** | | | |
| Chloride ($Cl^-$) | 111.5 | 118.0 | 4.0 |
| Bicarbonate ($HCO_3^-$) | 25.7 | 27.0 | 12.0 |
| Phosphate ($HPO_4^{2-}$ plus $HPO_4^-$) | 2.2 | 2.3 | 40.0 |
| Protein | 17.0 | 0.0 | 54.0 |
| Other | 6.3 | 6.6 | 90.0 |
| TOTAL | 162.7 | 153.9 | 200.0 |

*Expressed as milliequivalents per liter (mEq/L).
†Data are from skeletal muscle.

1. *Define the terms intracellular fluid, extracellular fluid, interstitial fluid, and plasma.*
2. *How do age and percent body fat affect the proportion of body weight composed of water?*
3. *Compare the osmotic concentration among most fluid compartments.*

# Regulation of Body Fluid Concentration and Volume

***Objectives***

- *Describe the mechanisms by which water content of the body is regulated.*
- *Describe the mechanisms by which the osmolality of the extracellular fluid is regulated.*
- *Describe the mechanisms by which the volume of the extracellular fluid is regulated.*

## Regulation of Water Content

The body's water content is regulated so that the total volume of water in the body remains constant. Thus the volume of water taken into the body is equal to the volume lost each day. Changes in the water volume in body fluids alter the osmolality of body fluids, blood pressure, and interstitial fluid pressure. The total volume of water entering the body each day is 1500–3000 mL. Most of that volume (90%) comes from ingested fluids, some comes from food, and a smaller amount, approximately 10%, is derived from the water produced during cellular metabolism (table 27.3 and see figure 24.32).

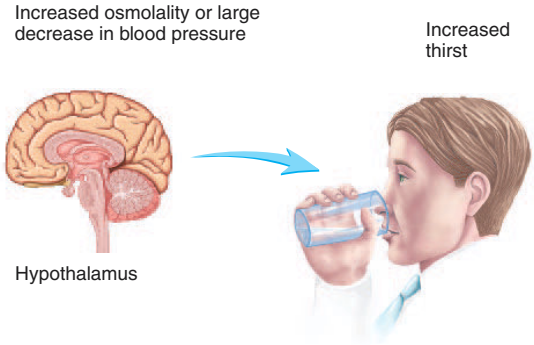
The movement of water across the wall of the gastrointestinal tract depends on osmosis, and the volume of water entering the body depends, to a large degree, on the volume of water consumed. If a large volume of dilute liquid is consumed, the rate at which water enters the body fluids increases. If a small volume of concentrated liquid is consumed, the rate decreases.

Although fluid consumption is heavily influenced by habit and by social settings, water ingestion does depend, at least in part, on regulatory mechanisms. The sensation of thirst results from an increase in the osmolality of the extracellular fluids and from a reduction in plasma volume. Cells of the supraoptic nucleus within the hypothalamus can detect an increased extracellular fluid osmolality and initiate activity in neural circuits that results in a conscious sensation of thirst (figure 27.1*a*).

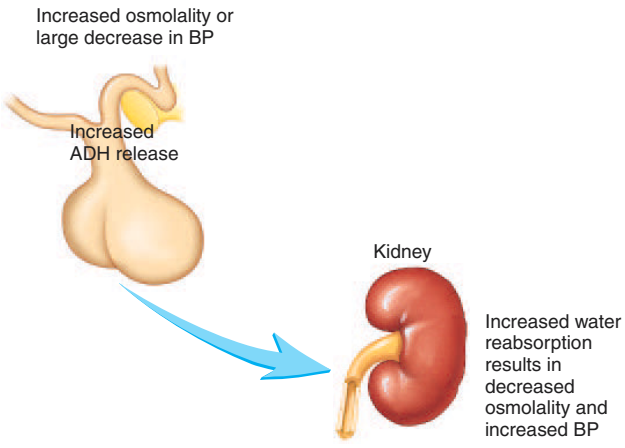
Baroreceptors can also influence the sensation of thirst. When they detect a decrease in blood pressure, action potentials are conducted to the brain along sensory neurons to influence the sensation of thirst. Low blood pressure associated with hemorrhagic shock, for example, is correlated with an intense sensation of thirst.

**Table 27.3 Summary of Water Intake and Loss**

| Sources of Water | Routes by Which Water Is Lost |
|---|---|
| Ingestion (90%) | Urine (61%) |
| Cellular Metabolism (10%) | Evaporation (35%)<br>Perspiration<br>Insensible<br>Sensible<br>Respiratory passages |
| | Feces (4%) |




(a) Increased blood osmolality affects hypothalamic neurons, and large decreases in blood pressure affect baroreceptors in the aortic arch, carotid sinuses, and atrium. As a result of these stimuli, an increase in thirst results, which increases water intake. Increased water intake reduces blood osmolality.




(b) Increased blood osmolality affects hypothalamic neurons, and decreased blood pressure affects baroreceptors in the aortic arch, carotid sinuses, and atrium. As a result of these stimuli, an increased rate of antidiuretic hormone (ADH) secretion from the posterior pituitary results, which increases water reabsorption by the kidney.

**Figure 27.1** Regulation of Extracellular Fluid Concentration

When renin is released from the juxtaglomerular apparatuses of the kidneys, it increases the formation of angiotensin II in the circulatory system (see chapters 21 and 26). Angiotensin II opposes a decrease in blood pressure by acting on the brain to stimulate the sensation of thirst, by acting on the adrenal cortex to increase aldosterone secretion, and by acting on blood vessel smooth muscle cells to increase vasoconstriction.

When people who are dehydrated are allowed to drink water, they eventually consume a quantity sufficient to reduce the osmolality of the extracellular fluid to its normal value. They don't normally consume the water all at once. Instead, they drink intermittently until the proper osmolality of the extracellular fluid is established. The thirst sensation is temporarily reduced after the ingestion of small amounts of liquid. At least two factors are responsible for this temporary interruption of the thirst sensation. First, when the oral mucosa becomes wet after it has been dry, sensory neurons conduct action potentials to the thirst center of the hypothalamus and temporarily decrease the sensation of thirst. Second, consumed fluid increases the gastrointestinal tract volume, and stretch of the gastrointestinal wall initiates sensory action potentials in stretch receptors. The sensory neurons conduct action potentials to the thirst center of the hypothalamus, where they temporarily suppress the sensation of thirst. Because absorption of water from the gastrointestinal tract requires time, mechanisms that temporarily suppress the sensation of thirst prevent the consumption of extreme volumes of fluid that would exceed the amount required to reduce blood osmolality. A longer-term suppression of the thirst sensation results when the extracellular fluid osmolality and blood pressure are within their normal ranges.

Learned behavior can be very important in avoiding periodic dehydration through the consumption of fluids either with or without food, even though blood osmolality is not reduced. The volume of fluid ingested by a healthy person usually exceeds the minimum volume required to maintain homeostasis, and the kidneys eliminate the excess water in urine.

Water loss from the body occurs through three major routes (see table 27.3). The greatest amount of water, approximately 61%, is lost through the urine. Approximately 35% of water loss occurs through evaporation from respiratory passages, of water that diffuses through the skin, and by perspiration. Approximately 4% is lost in the feces.

The volume of water lost through the respiratory system depends on the temperature and humidity of the air, the body temperature, and the volume of air expired. Water lost through simple evaporation from the skin is called **insensible perspiration** (see chapter 25) and it plays a role in heat loss. For each degree that the body temperature rises above normal, an increased volume of 100–150 mL of water is lost each day in the form of insensible perspiration.

**Sweat,** or **sensible perspiration,** is secreted by the sweat glands (see chapters 5 and 25), and, in contrast to insensible perspiration, it contains solutes. Sweat resembles extracellular fluid in its composition, with sodium chloride as the major component, but it also contains some potassium, ammonia, and urea (table 27.4). The volume of fluid lost as sweat is negligible for a person at rest in a cool environment. The volume of sweat produced is determined primarily by neural mechanisms that regulate body temperature, although some sweat is produced as a result of sympathetic stimulation in response to stress. Under conditions of exercise, elevated environmental temperature, or fever, the volume increases substantially and it plays an important role in heat loss. Sweat losses of 8–10 L/day have been measured in outdoor workers in the summertime.

**Table 27.4 Composition of Sweat**

| Solute | Concentration (mM) |
|---|---|
| Sodium | 9.8–77.2 |
| Potassium | 3.9–9.2 |
| Chloride | 5.5–65.1 |
| Ammonia | 1.7–5.6 |
| Urea | 6.5–12.1 |

Adequate fluid replacement during conditions of extensive sweating is important. Sweat is usually hyposmotic to plasma. The loss of a large volume of hyposmotic sweat causes a decrease in body fluid volume and an increase in body fluid concentration. Fluid volume is lost primarily from the extracellular space, which leads to an increase in extracellular fluid osmolality, a reduction in plasma volume, and an increase in hematocrit. During conditions of severe dehydration, the change can be great enough to cause blood viscosity to increase substantially. The increased workload created for the heart by that increase in viscosity can result in heart failure.

Relatively little water is lost by way of the digestive tract. Although the total volume of fluid secreted into the gastrointestinal tract is large, nearly all the fluid is reabsorbed under normal conditions (see chapter 24). Severe vomiting or diarrhea, however, are exceptions and can result in a large volume of fluid loss.

The kidneys are the primary organs that regulate the composition and volume of body fluids by controlling the volume and concentration of water excreted in the form of urine (see chapter 26). Urine production varies greatly and can range from a small volume of concentrated urine to a large volume of dilute urine in response to mechanisms that regulate the body's water content. The mechanisms that respond to changes in extracellular fluid osmolality and extracellular fluid volume keep the total body water levels within a narrow range of values.

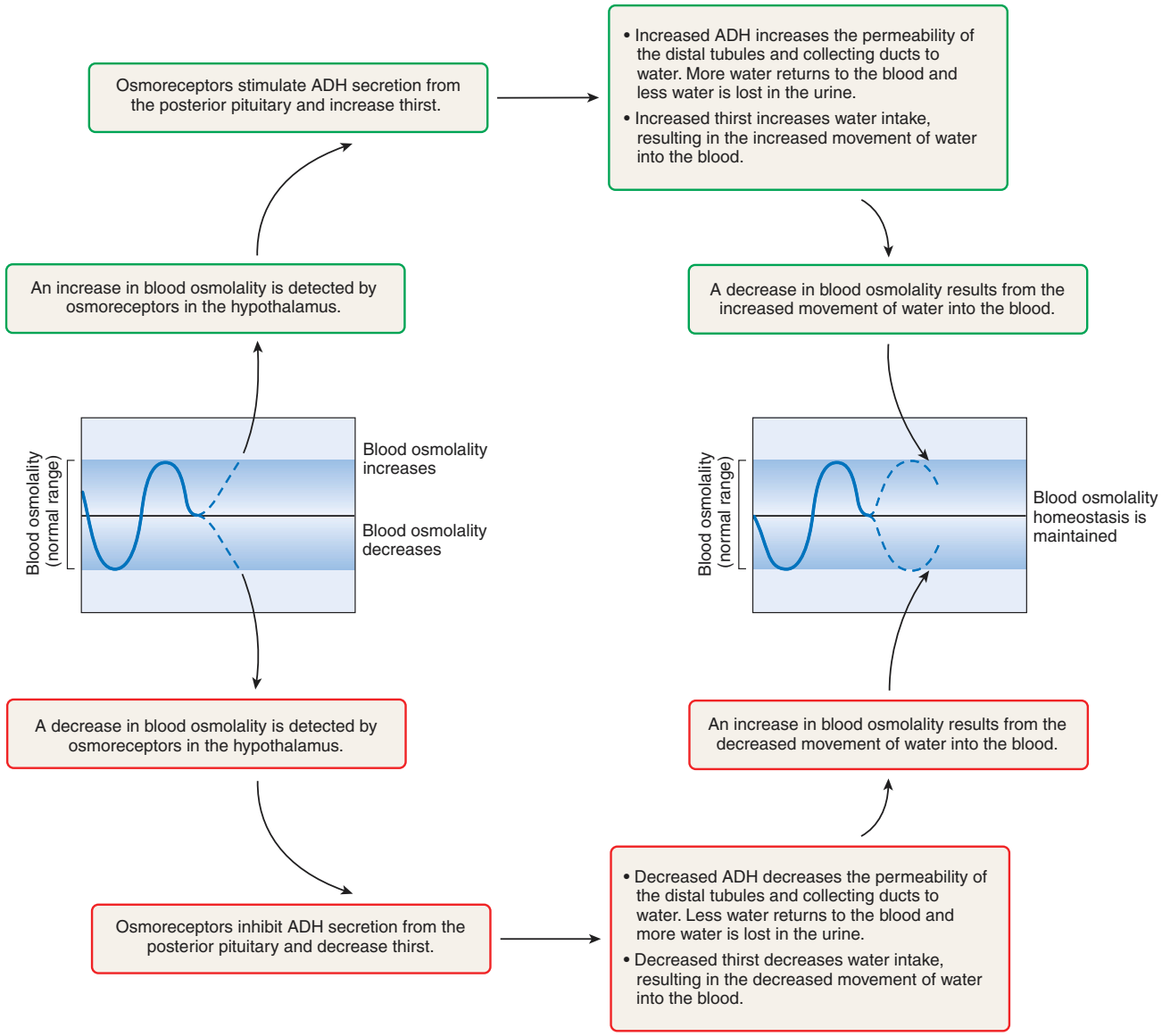
4. *List three factors that increase thirst. Name two things that inhibit the sense of thirst.*
5. *Describe three routes for the loss of water from the body. Contrast insensible and sensible perspiration.*
6. *What are the primary organs that regulate the composition and volume of body fluids?*

## Regulation of Extracellular Fluid Osmolality

Adding water to a solution, or removing water from it, changes the osmolality, or concentration, of the solution. Consider a solution contained in a pan on a stove. Adding water to the solution decreases its osmolality, or dilutes it. Boiling the solution in the pan removes water by evaporation. The removal of water from the solution increases its osmolality and makes it more concentrated. Adding or removing water from the body fluids maintains their osmolality between 285 and 300 mOsm/kg.

An increase in the osmolality of the extracellular fluid triggers thirst and antidiuretic hormone (ADH) secretion. Water that is consumed is absorbed from the intestine and enters the extracellular fluid. ADH acts on the distal tubules and collecting ducts of the kidneys to increase reabsorption of water from the filtrate. The increase in the amount of water entering the extracellular fluid causes a decrease in osmolality (figures 27.1*b* and 27.2). The ADH and thirst mechanisms are sensitive to even small changes in extracellular fluid osmolality and the response is fast (from minutes to a few hours). Larger increases in extracellular fluid osmolality such as during dehydration results in an even greater increase in thirst and in ADH secretion.

A decrease in extracellular fluid osmolality inhibits thirst and ADH secretion. Less water is consumed, and less water is reabsorbed from the filtrate in the kidneys. Consequently, more water is lost as a large volume of dilute urine. The result is an increase in the osmolality of the extracellular fluid (see figure 27.2). For example, consumption of a large volume of water in a beverage results in reduced extracellular fluid osmolality. This results in reduced ADH secretion, less reabsorption of water from the filtrate in the kidneys, and the production of a large volume of dilute urine. This response occurs quickly enough so that the osmolality of the extracellular fluid is maintained within a normal range of values.




**Homeostasis Figure 27.2** Hormonal Regulation of Blood Osmolality

7. *What two mechanisms are triggered by an increase in the osmolality of the extracellular fluid?*
8. *Describe how the osmolality of the extracellular fluid is affected when these mechanisms are activated.*

## Regulation of Extracellular Fluid Volume

The volume of extracellular fluid can increase, or decrease, even if the osmolality of the extracellular fluid is maintained within a narrow range of values. Sensory receptors that detect changes in blood pressure are important in the regulation of extracellular fluid volume. Carotid sinus and aortic arch baroreceptors monitor blood pressure in large arteries, receptors in the juxtaglomerular apparatuses monitor pressure changes in the afferent arterioles of the kidneys, and receptors in the walls of the atria of the heart and large veins are sensitive to the smaller changes in blood pressure that occur within them. These receptors activate neural mechanisms and three major hormonal mechanisms that regulate extracellular fluid volume (figure 27.3).

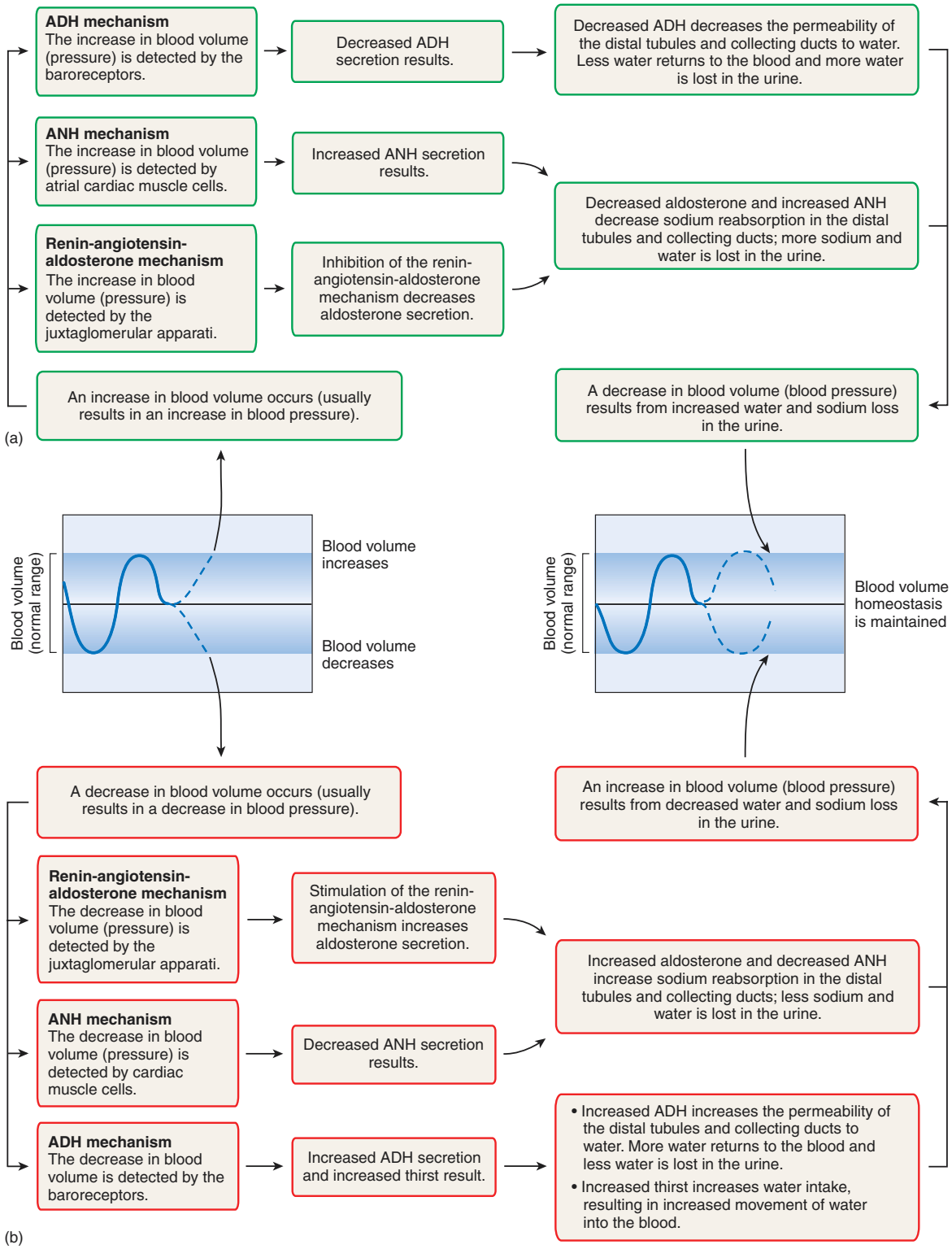
1. *Neural mechanisms.* Neural mechanisms change the frequency of action potentials carried by sympathetic neurons to the afferent arterioles of the kidney in response to changes in blood pressure. When baroreceptors detect an increase in arterial and venous blood pressure, the frequency of action potentials carried by sympathetic neurons to the afferent arterioles decreases. Consequently, the afferent arterioles dilate. This increases glomerular capillary pressure, resulting in an increase in the glomerular filtration rate (GFR), an increase in filtrate volume, and an increase in urine volume.

   When baroreceptors detect a decrease in arterial and venous blood pressure, there's an increase in the frequency of action potentials carried by sympathetic neurons to the afferent arterioles. Consequently, the afferent arterioles constrict. This decreases GFR, filtrate volume, and urine volume.
2. *Renin-angiotensin-aldosterone mechanism.* The renin-angiotensin-aldosterone mechanism responds to small changes in blood volume. Increased blood pressure results from increased blood volume. Juxtaglomerular cells detect increases in blood pressure in the afferent arterioles and decrease the rate of renin secretion. The decrease in renin secretion results in a decreased conversion of angiotensinogen to angiotensin II. Reduced angiotensin II causes a decrease in the rate of aldosterone secretion from the adrenal cortex. Decreased aldosterone levels reduce the rate of $Na^+$ reabsorption, primarily from the distal tubules and collecting ducts. Consequently, more $Na^+$ remains in the filtrate and fewer $Na^+$ are reabsorbed. The effect is to increase the osmolality of the filtrate, which reduces the ability of the kidney to reabsorb water. The water remains, with the excess $Na^+$, in the filtrate. Thus, the volume of urine produced by the kidney increases and the extracellular fluid volume decreases (see figure 27.3).

   A decrease in blood volume causes a decrease in blood pressure in the afferent arterioles, which results in an increased rate of renin secretion by the juxtaglomerular cells. The increase in renin secretion results in an increased conversion of angiotensinogen to angiotensin II. The increased angiotensin II causes an increase in the rate of aldosterone secretion from the adrenal cortex. Increased aldosterone increases the rate of $Na^+$ reabsorption, primarily from the distal tubules and collecting ducts. Consequently, less $Na^+$ remains in the filtrate and more $Na^+$ is reabsorbed. The effect is to decrease the osmolality of the filtrate. This increases the ability of the kidney to reabsorb water and to increase extracellular fluid volume. Thus the volume of urine produced by the kidney decreases and the extracellular fluid volume and blood pressure increase (figure 27.3 and figure 27.4*a*).
3. *Atrial natriuretic hormone (ANH) mechanism.* The ANH mechanism is most important in responding to increases in extracellular fluid volume. An increase in pressure in the atria of the heart, which usually results from an increase in blood volume, stimulates the secretion of ANH, which decreases $Na^+$ reabsorption in the distal tubules and collecting ducts. This increases the rate of $Na^+$ and water loss in the urine. Thus, increased ANH secretion decreases extracellular fluid volume (see figure 27.3 and figure 27.4*b*).

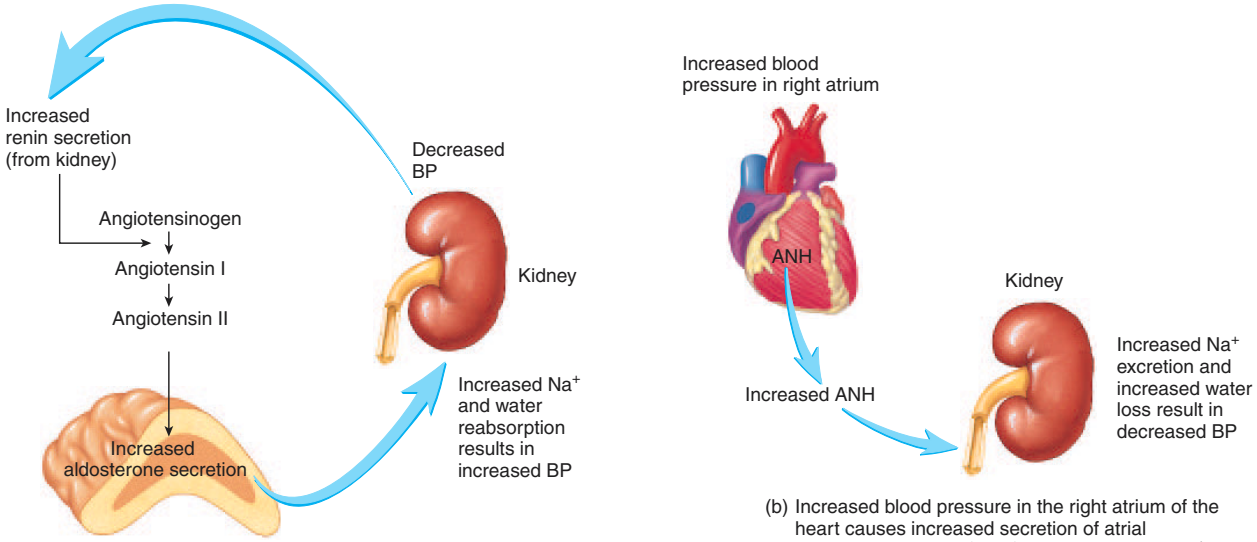
   ANH doesn't appear to respond strongly to decreases in blood volume. However, a decrease in pressure in the atria of the heart inhibits the secretion of ANH. The decreased ANH decreases the inhibition of $Na^+$ reabsorption in the distal tubules and collecting ducts. Therefore, the rate of $Na^+$ reabsorption increases and water reabsorption also increases. Thus, decreased ANH secretion is consistent with a decreased urine volume and an increase in extracellular fluid volume (see figure 27.3).
4. *Antidiuretic hormone (ADH) mechanism.* The ADH mechanism plays an important role in regulating extracellular fluid volume in response to large changes in blood pressure (of 5%–10%). An increase in blood pressure results in a decrease in ADH secretion. As a result, the reabsorption of water from the lumen of the distal tubules and collecting ducts decreases, resulting in a larger volume of dilute urine. This response helps decrease extracellular fluid volume and blood pressure (see figures 27.1*b* and 27.3).

   A decrease in blood pressure results in an increase in ADH secretion. Consequently, the reabsorption of water from the lumen of the distal tubules and collecting ducts increases, resulting in a smaller volume of concentrated urine. This response helps increase extracellular fluid volume and blood pressure (see figures 27.1*b* and 27.3).




## Homeostasis Figure 27.3 Hormonal Regulation of Blood Volume

(*a*) Regulation of blood volume (responses to increased blood volume) (*b*) Regulation of blood volume (responses to decreased blood volume).




(a) Low blood pressure (BP) stimulates renin secretion from the kidney. Renin stimulates the production of angiotensin I, which is converted to angiotensin II, which in turn stimulates aldosterone secretion from the adrenal cortex. Aldosterone increases $Na^+$ and water reabsorption in the kidney.

(b) Increased blood pressure in the right atrium of the heart causes increased secretion of atrial natriuretic hormone (ANH), which increases $Na^+$ excretion and water loss in the form of urine.

**Figure 27.4** Regulation of Extracellular Fluid Volume

The mechanisms that maintain extracellular fluid concentration and volume function together. However, when mechanisms that maintain fluid volume don't function normally, it's possible to have an increased extracellular fluid volume even though the extracellular concentration of fluids is maintained within a normal range of values. For example, increased aldosterone secretion from an enlarged adrenal cortex increases $Na^+$ reabsorption by the kidney and the total volume of extracellular fluid increases. Mechanisms, such as the regulation of ADH secretion, keep the concentration of the body fluids constant. The blood pressure can be elevated and edema can result, but the osmolality of the extracellular fluid is maintained between 285 and 300 mOsm/kg. Similarly, in people suffering from heart failure, the resulting reduced blood pressure activates mechanisms that increase blood pressure to its normal range of values. Those mechanisms include the release of renin from the kidneys. Consequently, the renin-angiotensin-aldosterone mechanism is activated as in the case of elevated aldosterone secretion, the result is an increase in the extracellular fluid volume and edema in the periphery, including edema in the lungs (congestive heart failure).

9. *What sensory receptors are responsible for activating neural and hormonal mechanisms that regulate extracellular fluid volume?*
10. *What is the effect on sympathetic stimulation, afferent arterioles, GFR, filtrate volume, urine volume, and extracellular fluid volume when baroreceptors detect an increase in arterial and venous blood pressure?*
11. *Describe the response of the renin-angiotensin-aldosterone mechanism to a decrease in blood pressure. How is extracellular fluid volume and urine volume affected?*
12. *What effect does ANH have on extracellular fluid volume?*
13. *How does an increase in blood pressure affect the secretion of ADH? How does ADH affect extracellular fluid volume?*

## Regulation of Intracellular Fluid Composition

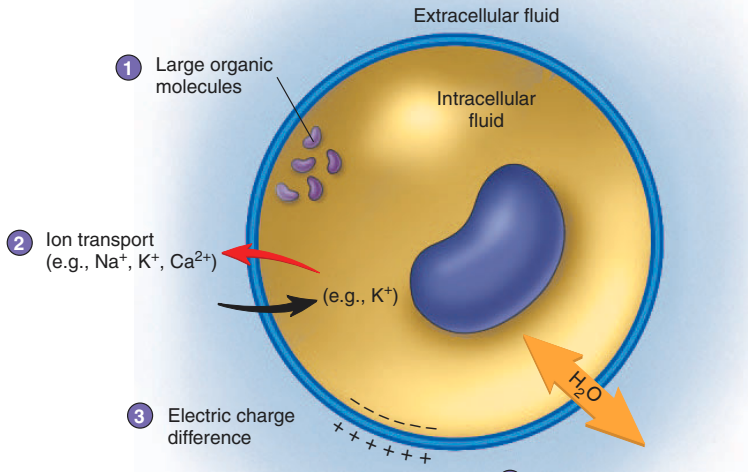
***Objective***

- ***Describe the factors that influence intracellular fluid composition.***

The composition of intracellular fluid is substantially different from that of extracellular fluid. Plasma membranes, which separate the two compartments, are selectively permeable—they are relatively impermeable to proteins and other large molecules and have limited permeability to smaller molecules and ions. Consequently, most large molecules synthesized within cells, such as proteins, remain within the intracellular fluid. Some substances, such as electrolytes, are actively transported across the plasma membrane, and their concentrations in the intracellular fluid are determined by the transport processes and by the electric charge difference across the plasma membrane (figure 27.5).

Water movement across the plasma membrane is controlled by osmosis. Thus, the net movement of water is affected by changes in the concentration of solutes in the extracellular and intracellular

1. Large organic molecules such as proteins, which cannot cross the plasma membrane, are synthesized inside cells and influence the concentration of solutes inside the cells.
2. The transport of ions across the plasma membrane, such as $Na^+$, $K^+$, and $Ca^{2+}$, influences the concentration of ions inside and outside the cell.
3. An electric charge difference across the plasma membrane influences the distribution of ions inside and outside the cell.
4. The distribution of water inside and outside the cell is determined by osmosis.




**Process Figure 27.5** Regulation of Intracellular and Extracellular Distribution of Water and Solutes

fluids. For example, as dehydration develops, the concentration of solutes in the extracellular fluid increases, resulting in the movement of water by osmosis from the intracellular fluid into the extracellular fluid. If dehydration is severe, enough water moves from the intracellular fluid to cause the cells to function abnormally. If water intake increases after a period of dehydration, the concentration of solutes in the extracellular fluids decreases, which results in the movement of water back into the cells.

14. *What factors determine the composition of intracellular fluid? What characteristic of plasma membranes is responsible for maintaining the differences between intracellular and extracellular fluid?*

# Regulation of Specific Electrolytes in the Extracellular Fluid

***Objectives***

- *Diagram the mechanisms by which sodium, chloride, potassium, calcium, magnesium, and phosphate ions are regulated in the extracellular fluid.*
- *Describe how the regulatory mechanisms respond to an increase or a decrease in extracellular sodium, chloride, potassium, calcium, magnesium, and phosphate ion concentration.*

**Electrolytes** (ē-lek′trō-līts) are molecules or ions with an electric charge. Ingestion of water and electrolytes adds them to the body, whereas organs like the kidneys and, to a lesser degree, the liver, skin, and lungs remove them from the body. The concentrations of electrolytes in the extracellular fluid are regulated so that they don't change unless the individual is growing, gaining weight, or losing weight. Regulation of electrolytes involves the coordinated participation of several organ systems.

## Regulation of Sodium Ions

**Sodium ions ($Na^+$)** are the dominant extracellular cations. Because of their abundance in the extracellular fluids, they exert substantial osmotic pressure. Approximately 90%–95% of the osmotic pressure of the extracellular fluid is caused by $Na^+$ and the negative ions associated with them.

### Diet and $Na^+$ Homeostasis

In the United States, the quantity of $Na^+$ ingested each day is 20–30 times the amount needed. Less than 0.5 g is required to maintain homeostasis, but the average individual ingests approximately 10–15 g of sodium chloride daily. Regulation of the $Na^+$ content in the body, therefore, depends primarily on the excretion of excess quantities of $Na^+$. The mechanisms for conserving $Na^+$ in the body are effective, however, when the $Na^+$ intake is very low.

The kidneys are the major route by which $Na^+$ is excreted. $Na^+$ readily passes from the glomerulus into the lumen of Bowman's capsule and is present in the same concentration in the filtrate as in the plasma. The concentration of $Na^+$ excreted in the urine is determined by the amount of $Na^+$ and water reabsorbed from filtrate in the nephron. If $Na^+$ reabsorption from the nephron decreases, large quantities are lost in the urine. If $Na^+$ reabsorption from the nephron increases, only small quantities are lost in the urine.

The rate of $Na^+$ transport in the proximal tubule is relatively constant, but the $Na^+$ transport mechanisms of the distal tubule and the collecting duct are under hormonal control. When **aldosterone** is present, the reabsorption of $Na^+$ from the distal tubule and the collecting duct is very efficient. As little as 0.1 g of sodium is excreted in the urine each day in the presence of high blood levels of aldosterone. When aldosterone is absent, $Na^+$ reabsorption in the nephron is greatly reduced, and as much as 30–40 g of sodium can be lost in the urine daily.

$Na^+$ are also excreted from the body in **sweat.** Normally only a small quantity of $Na^+$ is lost each day in the form of sweat, but the amount increases during conditions of heavy exercise in a warm environment. The mechanisms that regulate sweating control the quantity of $Na^+$ excreted through the skin. As the body temperature increases, thermoreceptor neurons within the hypothalamus respond by increasing the rate of sweat production. As the rate of sweat production increases, the quantity of $Na^+$ lost in the urine decreases to keep the extracellular concentration of $Na^+$ constant. The loss of $Na^+$ in sweat is rarely physiologically significant.

The primary mechanisms that regulate $Na^+$ concentrations in the extracellular fluid don't directly monitor $Na^+$ levels but are sensitive to changes in extracellular fluid osmolality or changes in blood pressure (see figure 27.3 and table 27.5). The quantity of $Na^+$ in the body has a dramatic effect on extracellular osmotic pressure and extracellular fluid volume. For example, if the quantity of $Na^+$ increases, the osmolality of the extracellular fluid increases. An increase in the osmolality of the extracellular fluids stimulates ADH secretion, which increases the reabsorption of water by the kidney and causes a small volume of concentrated urine to be produced. It also increases the sensation of thirst.

**Table 27.5 Homeostasis: Mechanisms Regulating Blood Sodium**

| Mechanism | Stimulus | Response to Stimulus | Effect of Response | Result |
|---|---|---|---|---|
| **Response to Changes in Blood Osmolatility** | | | | |
| Antidiuretic hormone (ADH); the most important regulator of blood osmolality | Increased blood osmolality (e.g., increased $Na^+$ concentration) | Increased ADH secretion from the posterior pituitary; mediated through cells in the hypothalamus | Increased water reabsorption in the kidney; production of a small volume of concentrated urine | Decreases blood osmolality as reabsorbed water dilutes the blood |
| | Decreased blood osmolality (e.g., decreased $Na^+$ concentration) | Decreased ADH secretion from the posterior pituitary; mediated through cells in the hypothalamus | Decreased water reabsorption in the kidney; production of a large volume of dilute urine | Increased blood osmolality as water is lost from the blood into the urine |
| **Response to Changes in Blood Pressure** | | | | |
| Renin-angiotension-aldosterone | Decreased blood pressure in the kidney's afferent arterioles | Increased renin release from the juxtaglomerular apparatuses; renin initiates the conversion of angiotensinogen to angiotensin; angiotensin I is converted to angiotensin II, which increases aldosterone secretion from the adrenal cortex | Increased $Na^+$ reabsorption in the kidney (because of increased aldosterone); increased water reabsorption as water follows the $Na^+$; decreased urine volume | Increased blood pressure as blood volume increases because of increased water reabsorption; blood osmolality is maintained because both $Na^+$ and water are reabsorbed* |
| | Increased blood pressure in the kidney's afferent arterioles | Decreased renin release from the juxtaglomerular apparatuses, resulting in reduced formation of angiotensin I; reduced angiotensin I leads to reduced angiotensin II, which causes a decrease in aldosterone secretion from the adrenal cortex | Decreased $Na^+$ reabsorption in the kidney (because of decreased aldosterone); decreased water reabsorption as fewer $Na^+$ are reabsorbed; increased urine volume | Decrease blood pressure as blood volume decreases because water is lost in the urine; blood osmolality is maintained because both $Na^+$ and water are lost in the urine* |

*continued*

**Table 27.5** *continued*

| Mechanism | Stimulus | Response to Stimulus | Effect of Response | Result |
|---|---|---|---|---|
| **Response to Changes in Blood Pressure—cont'd** | | | | |
| Atrial natriuretic hormone (ANH) | Decreased blood pressure in the atria of the heart | Decreased ANH released from the atria | Increased $Na^+$ reabsorption in the kidney; increased water reabsorption as water follows the $Na^+$; decreased urinary volume | Increased blood pressure as blood volume increases because of increased water reabsorption; blood osmolality is maintained because both $Na^+$ and water are reabsorbed* |
| | Increased blood pressure in the atria of the heart | Increased ANH released from the atria | Decreased $Na^+$ reabsorption in the kidney; decreased water reabsorption as water is lost with $Na^+$ in the urine; increased urinary volume | Decreased blood osmolality as blood volume decreases because water is lost in the urine; blood osmolality is maintained because both $Na^+$ and water are lost in the urine* |
| ADH—activated by significant decreases in blood pressure; normally regulates blood osmolality (see above) | Decreased arterial blood pressure | Increased ADH secretion from the posterior pituitary; mediated through baroreceptors | Increased water reabsorption in the kidney; production of a small volume of concentrated urine | Increased blood pressure resulting from increased blood volume; decreased blood osmolality |
| | Increased arterial blood pressure | Decreased ADH secretion from the posterior pituitary; mediated through baroreceptors | Decreased water reabsorption in the kidney; production of a large volume of dilute urine | Decreased blood pressure resulting from decreased blood volume; increased blood osmolality |

*Abbreviations:* ADH 5 antidiuretic hormone.
*Assumes normal levels of ADH.

Consequently there is an increase in extracellular fluid volume. A decrease in the quantity of $Na^+$ in the body decreases the osmolality of the extracellular fluid. This inhibits ADH secretion, which stimulates a large volume of dilute urine to be produced, and it decreases the sensation of thirst. Thus, extracellular osmolality increases. By regulating extracellular fluid osmolality and extracellular fluid volume, the concentration of $Na^+$ in the body fluids is maintained within a narrow range of values.

Elevated blood pressure under resting conditions increases $Na^+$ and water excretion (see figure 27.3 and table 27.5). If blood pressure is low, the total $Na^+$ content of the body is usually also low. In response to low blood pressure, mechanisms such as the renin-angiotensin-aldosterone mechanism are activated that increase $Na^+$ concentration and water volume in the extracellular fluid (see figure 27.3 and table 27.5).

**P R E D I C T** 1

**In response to hemorrhagic shock, the kidneys produce a small volume of very concentrated urine. Explain how the rate of filtrate formation changes and how $Na^+$ transport changes in the distal part of the nephron in response to hemorrhagic shock.**

Cells in the walls of the atria synthesize ANH, which is secreted in response to an elevation in blood pressure within the right atrium. ANH acts on the kidneys to increase urine production by inhibiting the reabsorption of $Na^+$ (see figure 27.4*b* and table 27.5). It also inhibits the effect of ADH on the distal tubules and collecting ducts, and inhibits ADH secretion (see chapter 26, 971).

Deviations from the normal concentration range for $Na^+$ in body fluids result in significant symptoms. Some major causes of **hypernatremia** (hī′per-nă-trē′mē-ă), or an elevated plasma $Na^+$ concentration, and **hyponatremia** (hī′pō-nă-trē′mē-ă), or a reduced plasma $Na^+$ concentration, and the major symptoms of each, are listed in table 27.6.

15. *Name the substance responsible for most of the osmotic pressure of the extracellular fluid.*
16. *How does aldosterone affect the amount of sodium in the urine?*
17. *What role does sweating play in $Na^+$ balance?*
18. *How does increased blood pressure result in a loss of water and salt? What happens when blood pressure decreases?*
19. *What effect does ANH have on $Na^+$ and water loss in urine?*

**P R E D I C T** 2

**If a person consumes an excess amount of $Na^+$ and water, predict the effect on (a) blood pressure, (b) urine volume, and (c) urine concentration.**

**Table 27.6 Consequences of Abnormal Plasma Levels of Sodium Ions**

| Major Causes | Symptoms |
|---|---|
| **Hypernatremia** | |
| High dietary sodium rarely causes symptoms | Thirst, fever, dry mucous membranes, restlessness; most serious symptoms—convulsions and pulmonary edema |
| Administration of hypertonic saline solutions (e.g., sodium bicarbonate treatment for acidosis) | |
| Oversecretion of aldosterone (i.e., aldosteronism) | When occurring with an increased water volume—weight gain, edema, elevated blood pressure, and bounding pulse |
| Water loss (e.g., because of fever, respiratory infections, diabetes insipidus, diabetes mellitus, diarrhea) | |
| **Hyponatremia** | |
| Inadequate dietary intake of sodium rarely causes symptoms—can occur in those on low-sodium diets and those taking diuretics | Lethargy, confusion, apprehension, seizures, and coma |
| Extrarenal losses—vomiting, prolonged diarrhea, gastrointestinal suctioning, burns | When accompanied by reduced blood volume—reduced blood pressure, tachycardia, and decreased urine output |
| Dilution—intake of large water volume after excessive sweating | When accompanied by increased blood volume—weight gain, edema, and distension of veins |
| Hyperglycemia, which attracts water into the circulatory system but reduces the concentration of $Na^+$ | |

## Regulation of Chloride Ions

The predominant anions in the extracellular fluid are **chloride ions ($Cl^-$).** The electrical attraction of anions and cations makes it difficult to separate these charged particles. Consequently, the regulatory mechanisms that influence the concentration of cations in the extracellular fluid also influence the concentration of anions. The mechanisms that regulate $Na^+$, $K^+$, and $Ca^{2+}$ levels in the body are important in influencing $Cl^-$ levels.

*20. What mechanisms regulate $Cl^-$ concentrations?*

## Regulation of Potassium Ions

The extracellular concentration of **potassium ions ($K^+$)** must be maintained within a narrow range. The concentration gradient of $K^+$ across the plasma membrane has a major influence on the resting membrane potential, and cells that are electrically excitable are highly sensitive to slight changes in that concentration gradient. An increase in extracellular $K^+$ concentration leads to depolarization, and a decrease in extracellular $K^+$ concentration leads to hyperpolarization of the resting membrane potential. **Hyperkalemia** (hī′per-kă-lē′mē-ă) is an abnormally high level of $K^+$ in the extracellular fluid, and **hypokalemia** (hī′pō-ka-lē′mē-ă) is an abnormally low level of $K^+$ in the extracellular fluid. Major causes of hyperkalemia and hypokalemia and their symptoms are listed in table 27.7.

$K^+$ pass freely through the filtration membrane of the renal corpuscle. They are actively reabsorbed in the proximal tubules and actively secreted in the distal tubules and collecting ducts. $K^+$ secretion into the distal tubule and collecting duct is highly regulated and primarily responsible for controlling the extracellular concentration of $K^+$.

Aldosterone plays a major role in regulating the concentration of $K^+$ in the extracellular fluid by increasing the rate of $K^+$ secretion in the distal tubule and collecting duct. Aldosterone secretion from the adrenal cortex is stimulated by elevated $K^+$ blood levels (figure 27.6; see chapter 26). Aldosterone secretion is stimulated in response to increased angiotensin II. The elevated aldosterone concentrations in the circulatory system increase $K^+$ secretion into the nephron, thereby lowering blood levels of $K^+$.

Circulatory system shock can result from plasma loss, dehydration, and tissue damage, such as occurs in burn patients. This shock causes the extracellular $K^+$ to be more concentrated than normal, which stimulates aldosterone secretion from the adrenal cortex. Aldosterone secretion also occurs in response to decreased blood pressure, which stimulates the renin-angiotensin-aldosterone mechanism. Homeostasis is reestablished as $K^+$ excretion increases. Also, increased $Na^+$ and water reabsorption stimulated by aldosterone results in an increase in extracellular fluid volume that dilutes the $K^+$ in the body fluids. Blood pressure increases toward normal as water reabsorption increases and when vasoconstriction is stimulated by angiotensin II.

*21. What effect does an increase or decrease in extracellular $K^+$ concentration have on resting membrane potential?*

*22. Where are $K^+$ secreted in the nephron? How is its secretion regulated?*

## Regulation of Calcium Ions

The extracellular concentration of **calcium ions ($Ca^{2+}$),** like that of $K^+$, is regulated within a narrow range. The normal concentration of $Ca^{2+}$ in plasma is 9.4mg/100mL. **Hypocalcemia** (hī′pō-kal-sē′mē-ă) is a below-normal level of $Ca^{2+}$ in the extracellular fluid, and **hypercalcemia** (hī′per-kal-sē′mē-ă) is an above-normal level of $Ca^{2+}$ in the extracellular fluid. Major symptoms develop when the extracellular concentration of $Ca^{2+}$ declines below 6 mg/100 mL or increases above 12 mg/100 mL. Decreases and increases in the extracellular concentration of $Ca^{2+}$ markedly affect the electrical properties of excitable tissues. Hypocalcemia increases the permeability of plasma membranes to $Na^+$. As a result, nerve and muscle tissues undergo spontaneous action potential

**Table 27.7 Consequences of Abnormal Concentrations of Potassium Ions**

| Major Causes | Symptoms |
|---|---|
| **Hyperkalemia** | |
| Movement of $K^+$ from intracellular to extracellular fluid resulting from cell trauma (e.g., burns or crushing injuries) and alterations in plasma membrane permeability (e.g., acidosis, insulin deficiency, and cell hypoxia) | Mild hyperkalemia (caused mainly by partial depolarization of plasma membranes): |
| | Increased neuromuscular irritability, restlessness |
| | Intestinal cramping and diarrhea |
| Decreased renal excretion of $K^+$ (e.g., from decreased secretion of aldosterone in persons with Addison's disease) | Electrocardiogram—alterations, including rapid repolarization with narrower and taller T waves and shortened QT intervals |
| | Severe hyperkalemia (caused mainly by partial depolarization of plasma membranes severe enough to hamper action potential conduction): |
| | Muscle weakness, loss of muscle tone, and paralysis |
| | Electrocardiogram—alterations, including changes caused by reduced rate of action potential conduction (e.g., depressed ST segment, prolonged PR interval, wide QRS complex, arrhythmias, and cardiac arrest) |
| **Hypokalemia** | |
| Alkalosis ($K^+$ shift into cell in exchange for $H^+$) | Symptoms are mainly due to hyperpolarization of membranes |
| Insulin administration (promotes cellular uptake of $K^+$) | Decreased neuromuscular excitability—skeletal muscle weakness |
| Reduced $K^+$ intake (especially with anorexia nervosa and alcoholism) | Decreased tone in smooth muscle |
| Increased renal loss (excessive aldosterone secretion, improper use of diuretics, kidney diseases that result in reduced ability to reabsorb $Na^+$) | Cardiac muscle—delayed ventricular repolarization, bradycardia, and atrioventricular block |

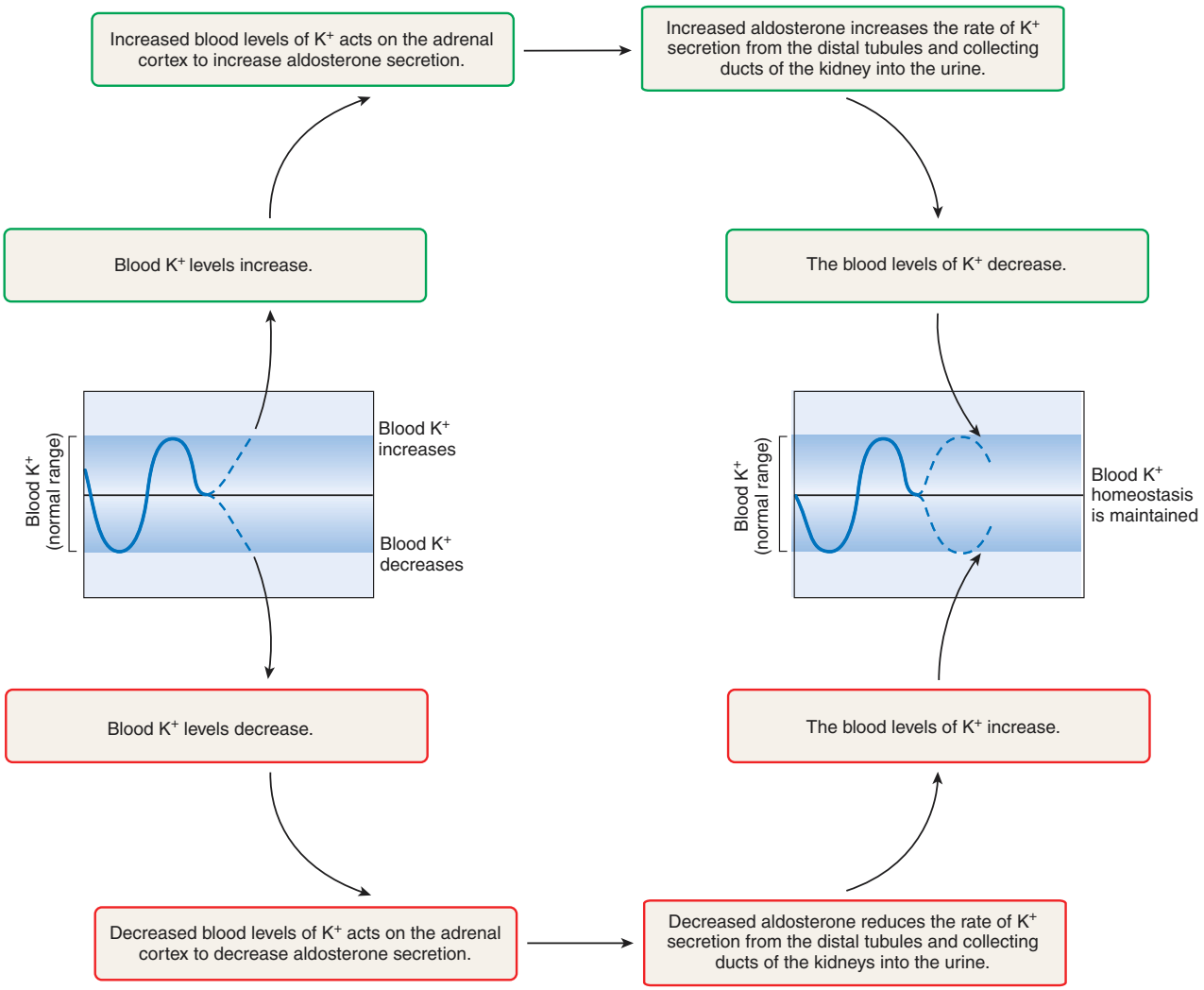
generation. Hypercalcemia decreases the permeability of the plasma membrane to $Na^+$, thus preventing normal depolarization of nerve and muscle cells. High extracellular $Ca^{2+}$ levels cause the deposition of calcium carbonate salts in soft tissues, resulting in irritation and inflammation of those tissues. Table 27.8 lists the major causes and symptoms of hypocalcemia and hypercalcemia.

The kidneys, intestinal tract, and bones are important in maintaining extracellular $Ca^{2+}$ levels (figure 27.7). Almost 99% of total body calcium is contained in bone. Part of the extracellular $Ca^{2+}$ regulation involves the regulation of $Ca^{2+}$ deposition into and resorption from bone (see chapter 6). Long-term regulation of $Ca^{2+}$ levels, however, depends on maintaining a balance between $Ca^{2+}$ absorption across the wall of the intestinal tract and $Ca^{2+}$ excretion by the kidneys.

**Parathyroid** (par-ă-thī′royd) **hormone,** secreted by the parathyroid glands, increases extracellular $Ca^{2+}$ levels and reduces extracellular phosphate levels (see figure 27.7). The rate of parathyroid hormone secretion is regulated by extracellular $Ca^{2+}$ levels.

**Table 27.8 Consequences of Abnormal Concentrations of Calcium**

| Major Causes | Symptoms |
|---|---|
| **Hypocalcemia** | |
| Nutritional deficiencies | Symptoms are mainly due to increased permeability of plasma membranes to $Na^+$ |
| Vitamin D deficiency | Increase in neuromuscular excitability—confusion, muscle spasms, hyperreflexia, and intestinal cramping |
| Decreased parathyroid hormone secretion | |
| Malabsorption of fats (reduced vitamin D absorption) | Severe neuromuscular excitability—convulsions, tetany, inadequate respiratory movements |
| Bone tumors that increase $Ca^{2+}$ deposition | Electrocardiogram—prolonged QT interval (prolonged ventricular depolarization) |
| | Reduced absoption of phosphate from the intestine |
| **Hypercalcemia** | |
| Excessive parathyroid hormone secretion | Symptoms are mainly due to decreased permeability of plasma membranes to $Na^+$ |
| Excess vitamin D | Loss of membrane excitability—fatigue, weakness, lethargy, anorexia, nausea, and constipation |
| | Electrocardiogram—shortened QT segment and depressed T waves |
| | Kidney stones |




**Homeostasis Figure 27.6** Regulation of Potassium Ions in the Extracellular Fluid

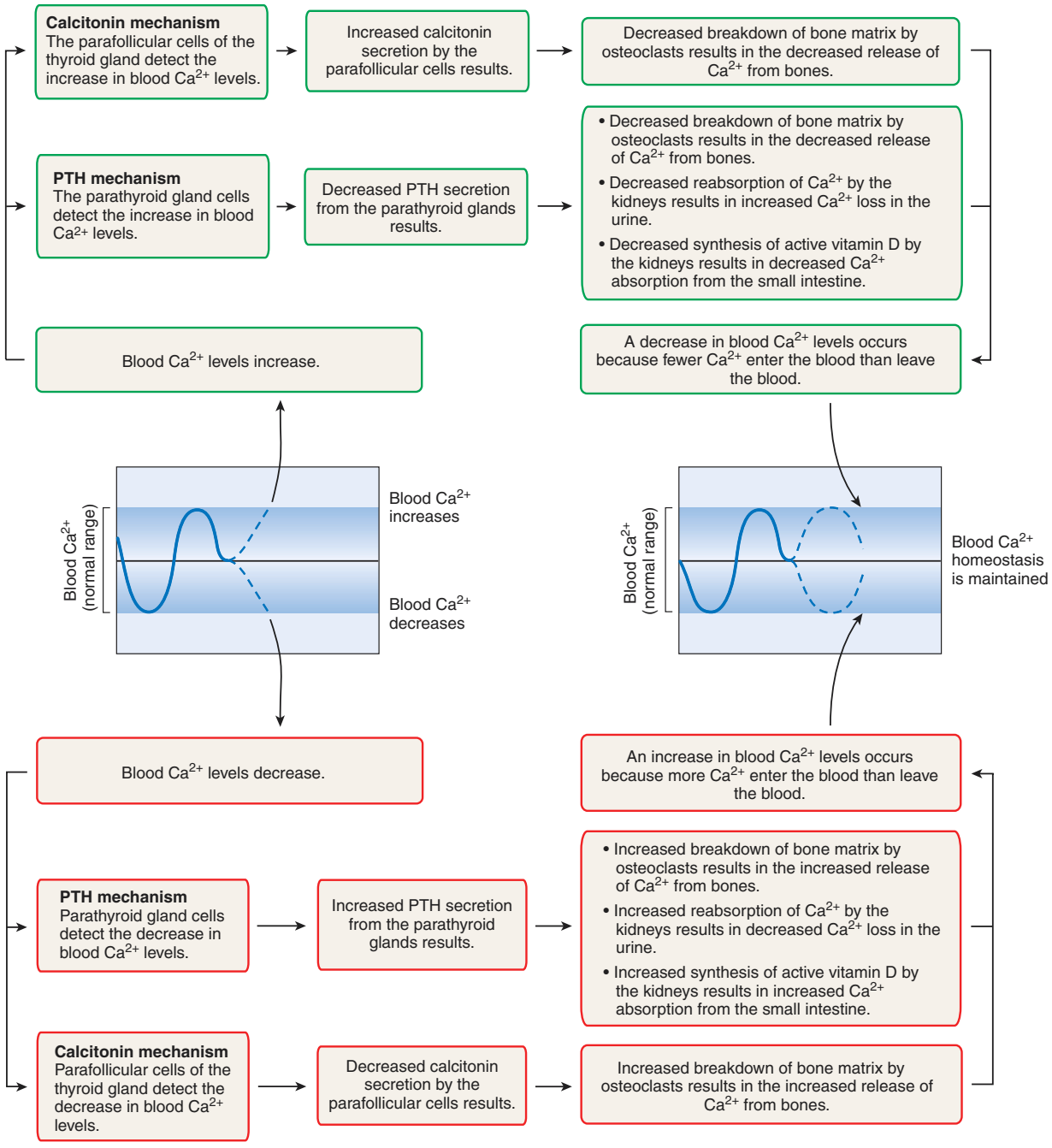
Aldosterone acts on the kidney to regulate the extracellular concentration of $K^+$.

Elevated $Ca^{2+}$ levels inhibit and reduced levels stimulate its secretion. Parathyroid hormone causes increased osteoclast activity, which results in the degradation of bone and the release of $Ca^{2+}$ and phosphate ions into body fluids. Parathyroid hormone increases the rate of $Ca^{2+}$ reabsorption from nephrons in the kidneys and increases the concentration of phosphate ions in the urine. It also increases the rate at which vitamin D is converted to 1,25-dihydroxycholecalciferol, or **active vitamin D.** Active vitamin D acts on the intestinal tract to increase $Ca^{2+}$ absorption across the intestinal mucosa.

A lack of parathyroid hormone secretion results in a rapid decline in extracellular $Ca^{2+}$ concentration. A reduction in the rate of absorption of $Ca^{2+}$ from the intestinal tract, increased $Ca^{2+}$ excretion by the kidneys, and reduced bone resorption cause this decline. A lack of parathyroid hormone secretion can result in death because of tetany of the respiratory muscles caused by hypocalcemia.

Vitamin D can be obtained from food or from vitamin D biosynthesis. Normally, vitamin D biosynthesis is adequate, but prolonged lack of exposure to sunlight reduces the biosynthesis because ultraviolet light is required for one step in the process (see chapter 5). The consumption of dietary vitamin D can involve the ingestion of active vitamin D or one of its precursors.

Without vitamin D, the transport of $Ca^{2+}$ across the wall of the intestinal tract is negligible. This leads to inadequate $Ca^{2+}$ absorption, even though large amounts of these ions may be present in the diet. Thus, $Ca^{2+}$ absorption depends on both the consumption of an adequate amount of calcium in food and the presence of an adequate amount of vitamin D.




## Homeostasis Figure 27.7 Regulation of Calcium Ions in the Extracellular Fluid

Parathyroid hormone and calcitonin play major roles in regulating the extracellular concentration of $Ca^{2+}$.

**Calcitonin** (kal-si-tō′nin), which is secreted by the parafollicular cells of the thyroid gland, reduces extracellular $Ca^{2+}$ levels. It's most effective when $Ca^{2+}$ levels are elevated, although greater-than-normal calcitonin levels in the blood are not consistently effective in causing blood levels of $Ca^{2+}$ to decline below normal values. The major effect of calcitonin is on bone. It inhibits osteoclast activity and prolongs the activity of osteoblasts. Thus, it decreases bone demineralization and increases bone mineralization (see chapter 6).

Elevated $Ca^{2+}$ levels stimulate calcitonin secretion, whereas reduced $Ca^{2+}$ levels inhibit it. Increased calcitonin secretion reduces blood levels of $Ca^{2+}$, but large doses of calcitonin don't

consistently reduce blood levels of $Ca^{2+}$ below normal levels. Although calcitonin reduces the blood levels of $Ca^{2+}$ when they are elevated, it's not as important as parathyroid hormone in the regulation of blood $Ca^{2+}$ levels (see figure 27.7).

23. *What effects on extracellular $Ca^{2+}$ concentrations does an increase or a decrease in parathyroid hormone have? What causes these effects?*
24. *What effect does calcitonin have on extracellular $Ca^{2+}$ levels?*

## Regulation of Magnesium Ions

Most of the magnesium in the body is stored in bones or in the intracellular fluid. Less than 1% of the total are ions found in the extracellular fluid. Approximately one-half of those ions are bound to plasma proteins and one-half are free. The free magnesium ion ($Mg^{2+}$) concentration is 1.8–2.4 mEq/L. $Mg^{2+}$ are cofactors for intracellular enzymes, such as the $Na^+$–$K^+$ ATPase involved in actively transporting $Na^+$ out and $K^+$ into cells. Low and high levels of plasma magnesium produce symptoms (table 27.9) that are associated with the effect of magnesium on $Na^+$–$K^+$ active transport.

Free $Mg^{2+}$ passes through the filtration membranes of the kidney into the filtrate. About 85%–90% of those ions are reabsorbed from the filtrate, and only about 10%–15% enter the urine. Of the $Mg^{2+}$ reabsorbed, most is reabsorbed by the loop of Henle. The remainder are reabsorbed by the proximal tubule, distal tubule, and collecting duct.

The capacity of the kidney to reabsorb $Mg^{2+}$ is limited. If the level of free $Mg^{2+}$ increases in the extracellular fluid, there's an increase in the rate of $Mg^{2+}$ loss in the urine. If the level of free $Mg^{2+}$ decreases in the extracellular fluid, there's a decrease in the rate of $Mg^{2+}$ loss in the urine. Control of $Mg^{2+}$ reabsorption isn't clear, but decreased extracellular concentration of the ions causes a greater rate of reabsorption in the nephron (figure 27.8).

25. *In what part of the nephron are most $Mg^{2+}$ reabsorbed? What effect does a decreased extracellular concentration of $Mg^{2+}$ have on reabsorption in the nephron?*

## Regulation of Phosphate Ions

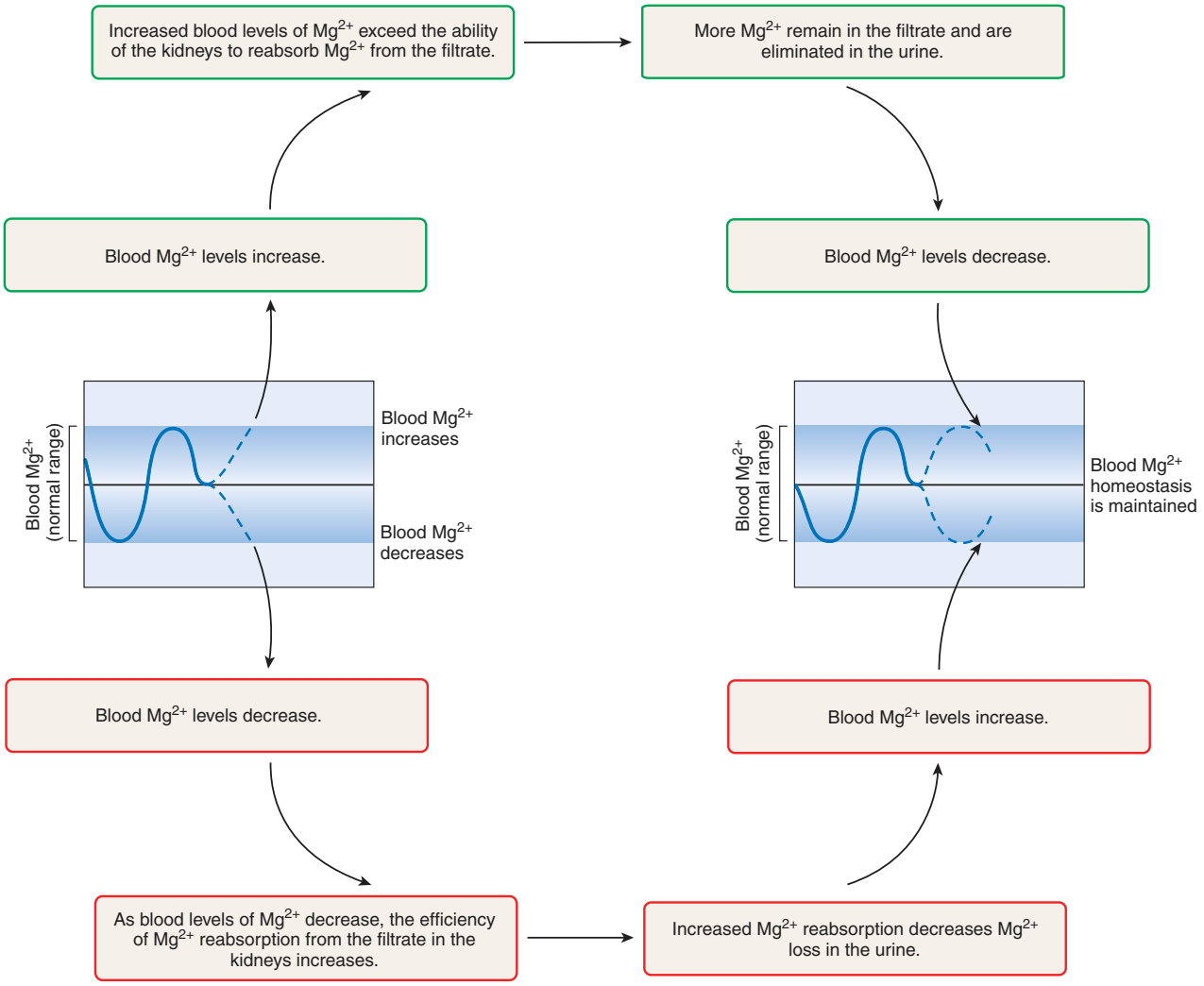
About 85% of phosphate is in the form of calcium phosphate salts found in bone (hydroxyapatite) and teeth. Most of the remaining phosphate is found inside cells. Many of the phosphate ions are covalently bound to other organic molecules. Phosphate ions are bound to lipids (to form phospholipids), proteins, and carbohydrates, and they are important components of DNA, RNA, and ATP. Phosphates also play important roles in the regulation of enzyme activity, and phosphate ions dissolved in the intracellular fluid act as buffers (see phosphate buffers under "Regulation of Acid–Base Balance," p. 1003). The extracellular concentration of phosphate ions is between 1.7 and 2.6 mEq/L. Phosphate ions are in the form of $H_2PO_4^-$, $HPO_4^{2-}$, and $PO_4^{3-}$. The most common phosphate ion is $HPO_4^{2-}$.

The capacity of the kidneys to reabsorb phosphate ions is limited. If the level of phosphate ions increases in the extracellular fluid, the excess phosphate remains in the filtrate, and there is an increase in the rate of phosphate loss in the urine. If the level of phosphate ions decreases in the extracellular fluid, nearly all of the phosphate ions are reabsorbed, and there is a decrease in the rate of phosphate ion loss in the urine (figure 27.9).

A diet low in phosphate can, over time, increase the rate of phosphate reabsorption. Consequently, most of the phosphate that enters the filtrate is reabsorbed to maintain the extracellular phosphate concentration. Parathyroid hormone (PTH) can play a significant role in regulating extracellular phosphate levels. PTH promotes bone resorption. Thus, large amounts of both $Ca^{2+}$ and phosphate ions are released into the extracellular space. PTH decreases the reabsorption of phosphate ions from renal tubules so that a greater proportion of the tubular phosphate is lost in the urine. Thus, whenever plasma PTH is increased, tubular phosphate

**Table 27.9 Consequences of Abnormal Plasma Levels of Magnesium Ions**

| Major Causes | Symptoms |
|---|---|
| **Hypomagnesemia (rare)** | |
| Malnutrition<br>Alcoholism<br>Reduced absorption of magnesium in the intestine<br>Renal tubular dysfunction<br>Some diuretics | Symptoms result from increased neuromuscular excitability, and include irritability, increased reflexes, muscle weakness, tetany, and convulsions |
| **Hypermagnesemia (rare)** | |
| Renal failure<br>Magnesium-containing antacids | Symptoms result from depressed skeletal muscle contractions and nerve functions, and include nausea, vomiting, muscle weakness, hypotension, bradycardia, and reduced respiration |




**Homeostasis Figure 27.8** Regulation of Blood Magnesium Concentration in the Extracellular Fluid

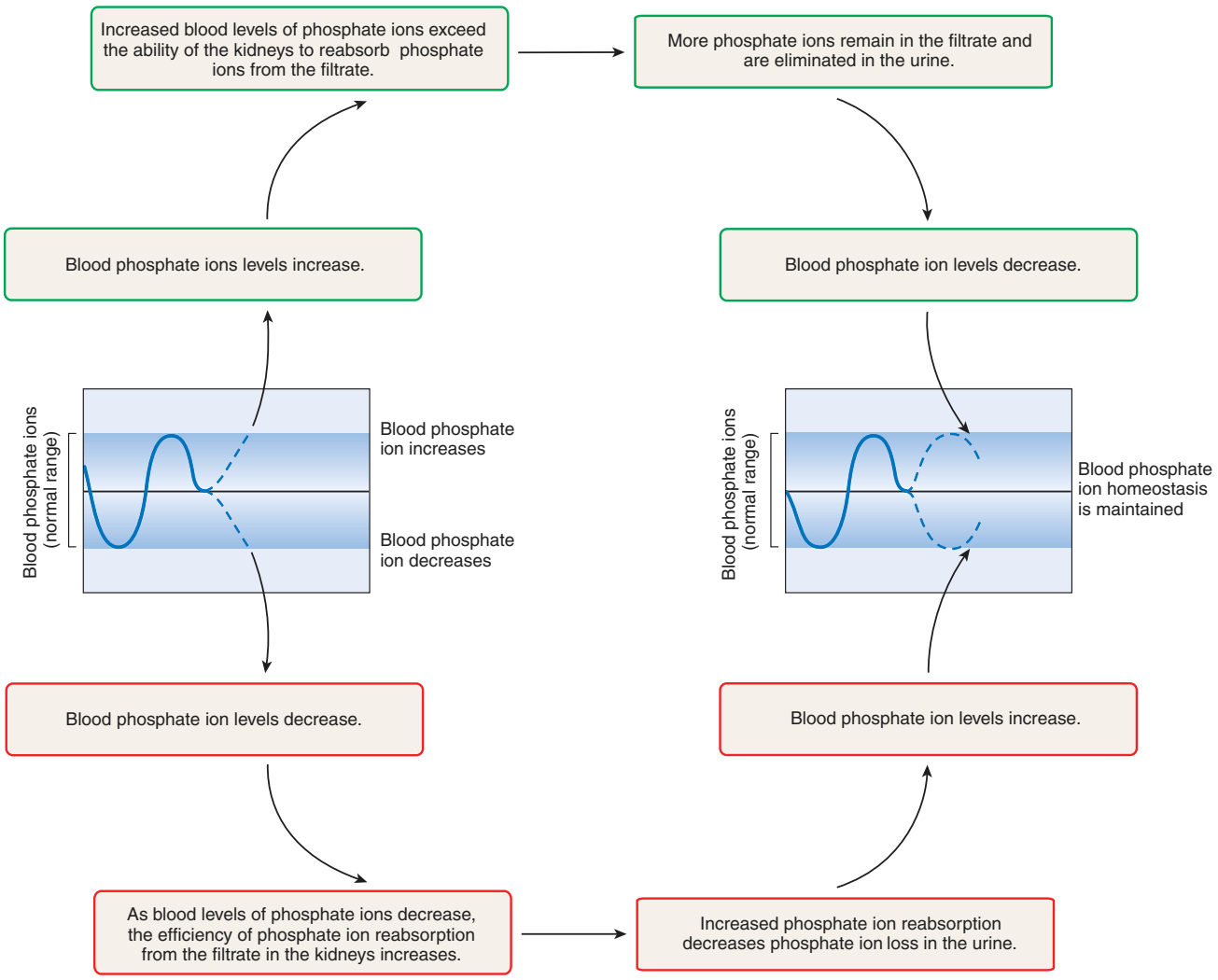
reabsorption is decreased, and more phosphate enters the urine. If phosphate levels in the extracellular fluid increase above normal levels, $Ca^{2+}$ and phosphate ions precipitate as calcium phosphate salts in soft tissues.

Elevated blood levels of phosphate may occur with acute or chronic renal failure as a result of a very reduced rate of filtrate formation by the kidney. The rate of phosphate excretion is consequently reduced. Also, the chronic use of laxatives containing phosphates may result in elevated blood levels of phosphate. Symptoms of elevated phosphate levels are related to reduced blood $Ca^{2+}$ levels because phosphate ions and $Ca^{2+}$ precipitate out of solution and are deposited in soft tissues of the body. Prolonged elevation of blood levels of phosphate can result in calcium phosphate deposits in the lungs, kidneys, joints, and other soft tissues. The consequences of increased or reduced plasma levels of phosphates are presented in table 27.10.

26. *Explain how the kidneys control plasma levels of phosphate ions. How does an increased level of PTH affect tubular phosphate reabsorption? What are the consequences of prolonged elevation of blood levels of phosphate ions?*

**PREDICT** 3

**Mary Thon runs several miles each day. List the mechanisms through which water loss changes during her run.**




**Homeostasis Figure 27.9** Regulation of Blood Phosphate Concentration in the Extracellular Fluid

**Table 27.10 Consequences of Abnormal Plasma Levels of Phosphate Ions**

| Major Causes | Symptoms |
|---|---|
| **Hypophosphatemia** | |
| Reduced absorption from the intestine associated with vitamin D deficiency and alcohol abuse | Reduced rate of metabolism, reduced transport of oxygen, reduced white blood cell functions, and blood clotting |
| Increased renal excretion with hyperparathyroidism | |
| **Hyperphosphatemia** | |
| Renal failure | Symptoms are related to reduced plasma $Ca^{2+}$ concentrations due to calcium phosphate deposited in tissues such as the lungs, kidneys, and joints. |
| Tissue destruction with chemotherapy used to treat metastatic tumors | |
| Hyperparathyroidism initially leading to elevated plasma $Ca^{2+}$ combined with reduced excretion of phosphate by the kidney | |

# Regulation of Acid–Base Balance

***Objectives***

- ***Define the terms acid and base.***
- ***Explain how buffers regulate body fluid pH, and list the major buffers that exist in the body fluids.***
- ***Diagram the mechanisms that regulate body fluid pH, and describe how they respond to either acidosis or alkalosis.***

$H^+$ affect the activity of enzymes and interact with many electrically charged molecules. Consequently, most chemical reactions within the body are highly sensitive to the $H^+$ concentration of the fluid in which they occur. The maintenance of the $H^+$ concentration within a narrow range of values is essential for normal metabolic reactions. The major mechanisms that regulate the $H^+$ concentration are the buffer systems, the respiratory system, and the kidneys.

## Acids and Bases

**Acids,** for most purposes, can be defined as substances that release $H^+$ into a solution, and **bases** bind to $H^+$ and remove them from solution. Many bases release hydroxide ions ($OH^-$), which react with $H^+$ to form water ($H_2O$). Acids and bases are grouped as either strong or weak. Strong acids and strong bases completely dissociate to form ions in solution. Hydrochloric acid is a strong acid, which dissociates to form $H^+$ and $Cl^-$ (figure 27.10), and sodium hydroxide is a strong base, which dissociates to form $Na^+$and $OH^-$. In contrast to strong acids, weak acids dissociate, but most molecules remain intact. Many of the weak acid molecules do not dissociate to release $H^+$ into the solution. For each type of weak acid an equilibrium is established (see figure 27.10). The proportion of weak acid molecules that release $H^+$ into solution is very predictable, and is influenced by the pH of the solution into which the weak acid is placed. Weak acids are common in living systems and they play important roles in preventing large changes in pH in body fluid pH.

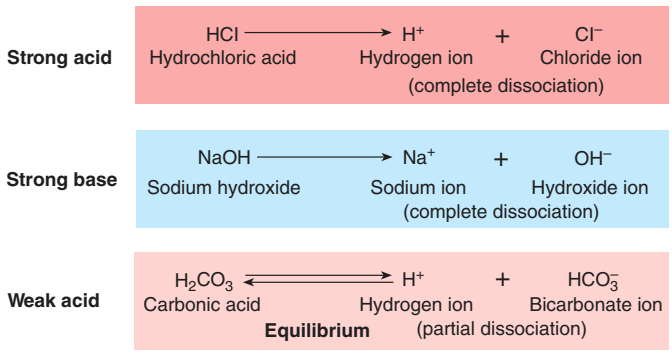



**Figure 27.10 Comparison of Strong and Weak Acids**

Strong acids and bases completely dissociate when dissolved in water. Weak acids do not completely dissociate. Weak acids partially dissociate so that an equilibrium is established between the acid and the ions that are formed when the dissociation occurs.

***27. Define the terms acid and base. Describe weak acids. Why are weak acids important in living systems?***

## Buffer Systems

**Buffers** (bŭf′erz) (see chapter 2) resist changes in the pH of a solution. Buffers within body fluids stabilize the pH by chemically binding to excess $H^+$ when they are added to a solution or by releasing $H^+$ when their concentration in a solution begins to fall.

Several important buffer systems function together to resist changes in the pH of body fluids (table 27.11). The carbonic acid/bicarbonate buffer system, protein molecules like hemoglobin and plasma proteins, and phosphate compounds all act as buffers.

### *Carbonic Acid/Bicarbonate Buffer System*

Carbonic acid ($H_2CO_3$) is a weak acid. When it is dissolved in water, the following equilibrium is established:

$$H_2CO_3 \rightleftarrows HCO_3^- + H^+$$

The carbonic acid/bicarbonate buffer system depends on the equilibrium that is quickly established between $H_2CO_3$ and the $H^+$ and bicarbonate ($HCO_3^-$). When an amount of $H^+$ is added to this solution, by adding a small amount of a strong acid, a large proportion of the $H^+$ binds to $HCO_3^-$ to form $H_2CO_3$, and only a small percentage remain as free $H^+$. Thus, a large decrease in pH is resisted by the carbonic acid/bicarbonate buffer system when acidic substances are added to a solution containing $H_2CO_3$.

**Table 27.11 Buffer Systems**

| | |
|---|---|
| Protein Buffer System | Intracellular proteins and plasma proteins form a large pool of protein molecules that can act as buffer molecules. Because of their high concentration, they provide approximately three-fourths of the buffer capacity of the body. Hemoglobin in red blood cells is an important intracellular protein. Other intracellular molecules like histone proteins and nucleic acids also act as buffers. |
| Bicarbonate Buffer System | Components of the bicarbonate buffer system are not present in high enough concentrations in the extracellular fluid to constitute a powerful buffer system. Because the concentrations of the components of the buffer system are regulated, however, it plays an exceptionally important role in controlling the pH of extracellular fluid. |
| Phosphate Buffer System | Concentration of the phosphate buffer components is low in the extracellular fluids compared to the other buffer systems, but it's an important intracellular buffer system. |

When an amount of $H^+$ is removed from a solution containing $H_2CO_3$, by addding a small amount of a strong base, many of the $H_2CO_3$ form $HCO_3^-$ and $H^+$. Thus, a large increase in pH is resisted when basic substances are added to a solution containing $H_2CO_3$.

The carbonic acid/bicarbonate buffer system plays an important role in regulating the extracellular pH. It quickly responds to the addition of substances, such as $CO_2$ or lactic acid produced by increased metabolism during exercise (see chapter 23) and increased fatty acid and ketone body production during periods of elevated fat metabolism (see chapter 25). It also responds to the addition of basic substances, such as the consumption of large amounts of $NaHCO_3$ as an antacid. The carbonic acid/bicarbonate buffer system has a limited capacity to resist changes in pH, but it remains very important because it plays an essential role in the control of pH by both the respiratory system and the kidneys (see Mechanisms of Acid-Base Balance Regulation below).

### *Protein Buffer System*

Intracellular proteins and plasma proteins form a large pool of protein molecules, which act as buffer molecules. They provide approximately three fourths of the buffer capacity of the body because of their high concentration. Hemoglobin in red blood cells is one of the most important intracellular proteins. Other intracellular molecules like histone proteins associated with nucleic acids also act as buffers. The capacity of proteins to function as buffers is due to the functional groups of amino acids, such as carboxy1 ($-COOH$) or amino ($-NH_2$) groups. These functional groups can act like weak acids and bases. Consequently, as the $H^+$ concentration increases, more $H^+$ bind to the functional groups, and when the $H^+$ concentration decreases, $H^+$ are released from the functional groups (see table 27.11).

### *Phosphate Buffer System*

The concentration of phosphate and phosphate-containing molecules is low in the extracellular fluid compared with the other buffer systems, but it is an important intracellular buffer system. Phosphate-containing molecules such as DNA, RNA, ATP, as well as phosphate ions, such as $HPO_4^{2-}$, in solution act as buffers. Phosphate ions act as weak acids and, therefore, can bind to $H^+$, to form $H_2PO_4^-$, when the pH decreases and ions, such as $H_2PO_4^-$, release $H^+$ into the solution when the pH begins to increase (see table 27.11).

28. *Define the term buffer. Describe how a buffer works when $H^+$ ions are added to a solution or when they are removed from a solution.*
29. *Name the three buffer systems of the body. Which of these systems provides the largest proportion of buffer capacity in the body?*

## Mechanisms of Acid–Base Balance Regulation

Buffers and the mechanisms of acid-base balance regulation work together and play essential roles in the regulation of acid–base balance (figure 27.11). Buffers almost instantaneously resist changes in the pH of body fluids. The mechanisms of acid–base regulation depend on the regulation of respiration and kidney function. The respiratory system responds within a few minutes to changes in pH to bring the pH of body fluids back toward its normal range. Its capacity to regulate pH, however, is not as great as that of the kidneys, nor does the respiratory system have the same ability to return the pH to its precise range of normal values. In contrast, the kidneys respond more slowly, within hours to days, to alterations of body fluid pH, and their capacity to respond is substantial.

## Respiratory Regulation of Acid-Base Balance

The respiratory system regulates acid–base balance by influencing the carbonic acid/bicarbonate buffer system. Carbon dioxide ($CO_2$) reacts with water ($H_2O$) to form carbonic acid ($H_2CO_3$), which dissociates to form $H^+$ and $HCO_3^-$ as follows:

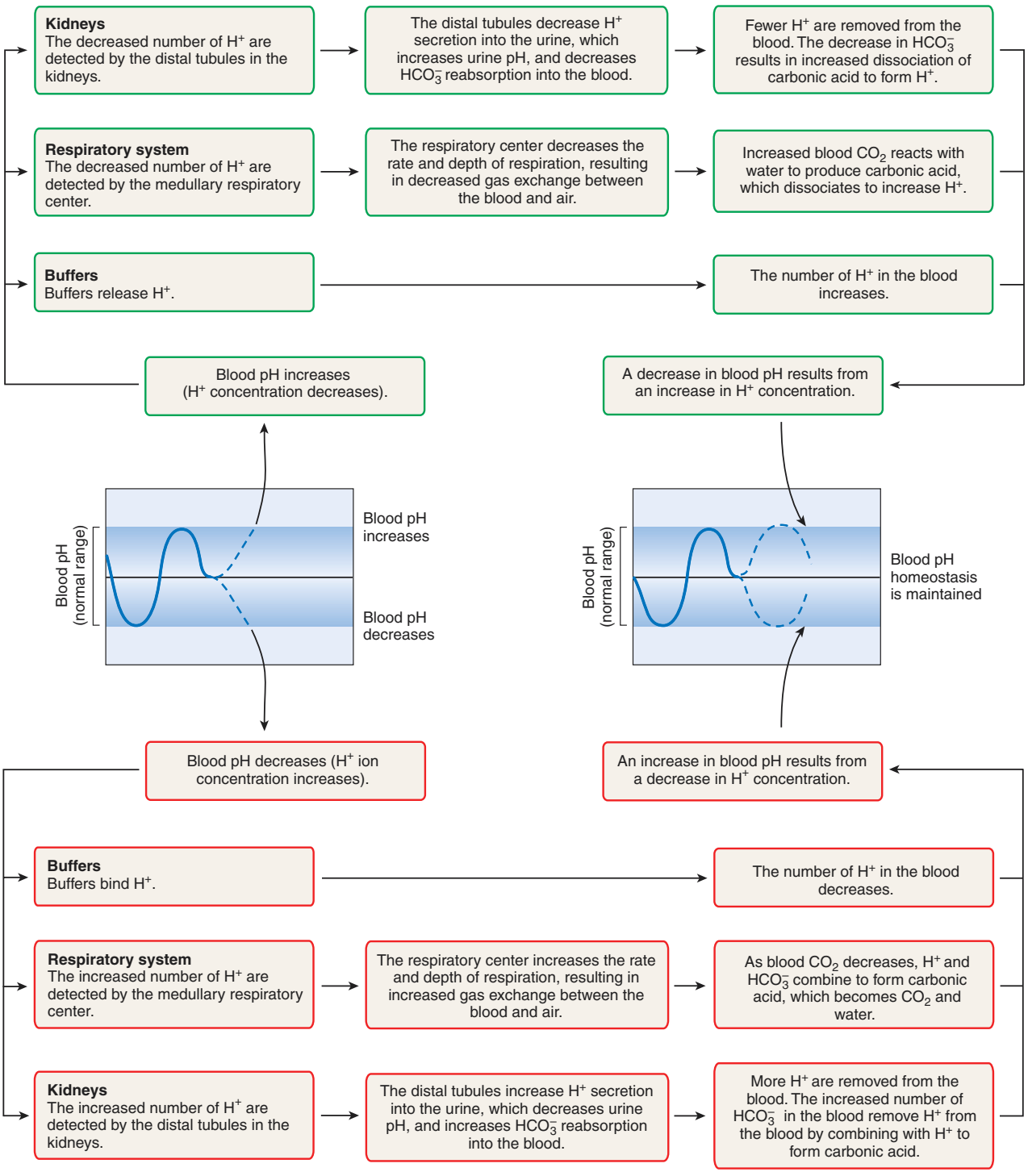
$$H_2O + CO_2 \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$

This reaction is in equilibrium. As $CO_2$ increases, $CO_2$ combines with $H_2O$. The higher the concentration of $CO_2$, the greater the amount of $H_2CO_3$ formed. $H_2CO_3$ then dissociates to form $H^+$ and $HCO_3^-$. If $CO_2$ levels decline, however, the equilibrium shifts in the opposite direction so that $H^+$ and $HCO_3^-$ combine to form $H_2CO_3$, which then forms $CO_2$ and $H_2O$. Thus, $H^+$ and $HCO_3^-$ decrease in the solution.

The reaction between $CO_2$ and $H_2O$ is catalyzed by an enzyme, **carbonic anhydrase,** which is found in a relatively high concentration in red blood cells and on the surface of capillary epithelial cells (figure 27.12). This enzyme does not influence equilibrium but accelerates the rate at which the reaction proceeds in either direction so that equilibrium is achieved quickly.

Decreases in body fluid pH, regardless of the cause, stimulate neurons in the respiratory center in the brainstem and cause the rate and depth of ventilation to increase. The increased rate and depth of ventilation cause $CO_2$ to be eliminated from the body through the lungs at a greater rate, and the concentration of $CO_2$ in the body fluids decreases. As $CO_2$ levels decline, the carbonic/bicarbonate buffer system reacts. $H^+$ combine with $HCO_3^-$ to form $H_2CO_3$ which then form $CO_2$ and $H_2O$. Consequently, the concentration of $H^+$ decreases toward its normal range as $CO_2$ exits through the respiratory system (see figure 27.12).

Increases in body fluid pH, regardless of the cause, inhibit neurons in the respiratory center in the brainstem and cause the rate and depth of ventilation to decrease. The decreased rate and depth of ventilation, causes less $CO_2$ to be eliminated from the body through the lungs. The concentration of $CO_2$ in the body fluids increases because $CO_2$ is continually produced as a byproduct of metabolism in all tissues. Thus, the body fluid concentration of $H_2CO_3$ increases also. As $H_2CO_3$ increases, it results in an increase in the $H^+$ concentration, and the pH decreases toward its normal range.



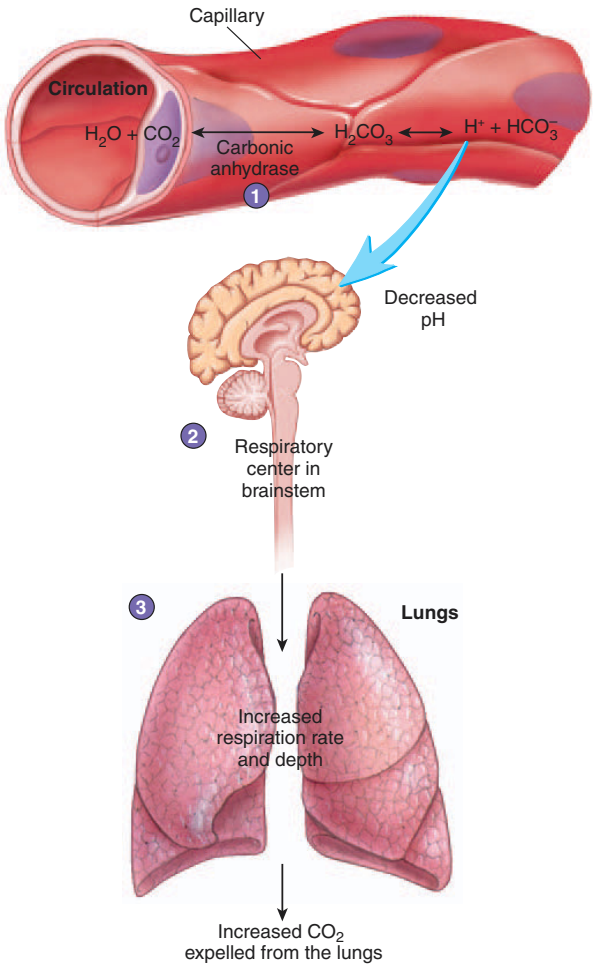

## Homeostasis Figure 27.11 Regulation of Acid–Base Balance

Important mechanism through which the pH of the body fluids is regulated by the lungs and the kidneys.

1. $CO_2$ reacts with $H_2O$ to form $H_2CO_3$. An enzyme, carbonic anhydrase, found in red blood cells and on the surface of blood vessel epithelium, catalyzed the reaction. $H_2CO_3$ dissociates to form $H^+$ and $HCO_3^-$. An equilibrium is quickly established.

2. A decreased pH of the extracellular fluid stimulates the respiratory center and causes an increased rate and depth of respiration.

3. An increased rate and depth of respiration causes $CO_2$ to be expelled from the lungs, thus reducing the extracellular $CO_2$ levels. As $CO_2$ levels decrease, the extracellular concentration of $H^+$ decreases, and the extracellular fluid pH increases.




**Process Figure 27.12** Respiratory Regulation of Body Fluid Acid–Base Balance

## Renal Regulation of Acid-Base Balance

Cells of the kidney tubules directly regulate acid–base balance by increasing or decreasing the rate of $H^+$ secretion into the filtrate (figure 27.13) and the rate of $HCO_3^-$ reabsorption. Carbonic anhydrase is present within nephron cells and catalyzes the formation of $H_2CO_3$ from $CO_2$ and $H_2O$. The carbonic acid molecules dissociate to form $H^+$ and $HCO_3^-$. A countertransport system then exchanges $H^+$ for $Na^+$ across the apical membrane of the cells. Thus, cells of the kidney tubules secrete $H^+$ into the filtrate and reabsorbs $Na^+$. The $Na^+$ and $HCO_3^-$ are cotransported across the basal membrane. After the $Na^+$ and $HCO_3^-$ are cotransported from the kidney tubule cells, they diffuse into the peritubular capillaries. As a result, $H^+$ are secreted into the lumen of the kidney tubules, and $HCO_3^-$ pass into the extracellular fluid.

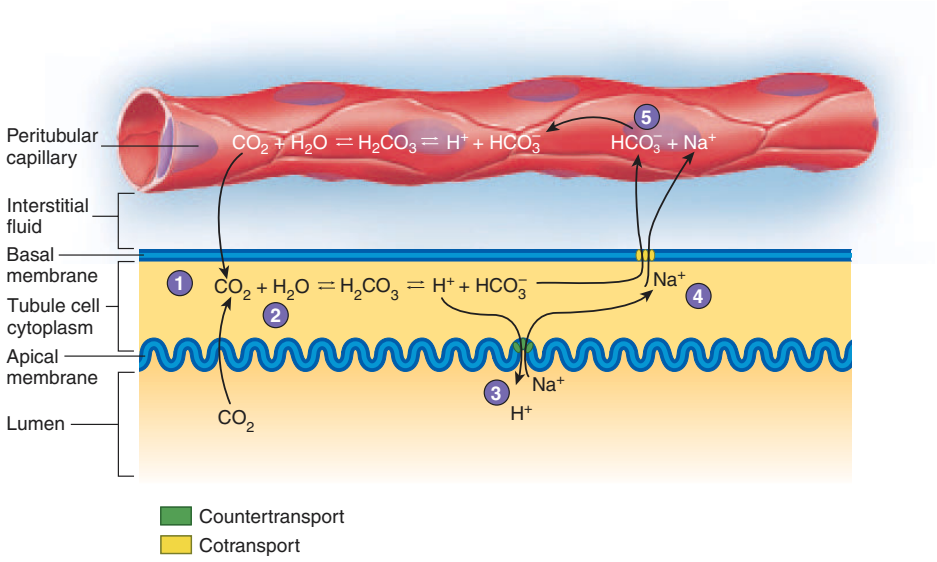
The reabsorbed $HCO_3^-$ combine with excess $H^+$ in the extracellular fluid to form $H_2CO_3$. This combination removes $H^+$ from the extracellular fluid and increases extracellular pH. The rate of $H^+$ secretion and $HCO_3^-$ reabsorption increases when the pH of the body fluids decreases, and this process slows when the pH of the body fluids increases (see figure 27.13).

Some of the $H^+$ secreted by cells of the kidney tubules into the filtrate combine with $HCO_3^-$, which enters the filtrate through the filtration membrane, in the form of sodium bicarbonate ($NaHCO_3$). Within the kidney tubules $H^+$ combines with $HCO_3^-$ to form $H_2CO_3$, which then dissociate to form $CO_2$ and $H_2O$. The $CO_2$ diffuses from the filtrate into the cells of the kidney tubules, where it can react with $H_2O$ to form $H_2CO_3$, which subsequently dissociates to form $H^+$ ions and $HCO_3^-$ (see figure 27.13). Once again, $H^+$ are transported into the lumen of the kidney tubules in exchange for $Na^+$, whereas $HCO_3^-$ enter the extracellular fluid. As a result, many of the $HCO_3^-$ entering the filtrate reenter the extracellular fluid.

$H^+$ secreted into the nephron normally exceed the amount of $HCO_3^-$ that enter the kidney tubules through the filtration membrane. Because the $H^+$ combine with $HCO_3^-$, almost all the $HCO_3^-$ are reabsorbed from the kidney tubules (see figure 27.13). Few $HCO_3^-$ are lost in the urine unless the pH of the body fluids becomes elevated.

The rate of $H^+$ secretion into the filtrate and the rate of $HCO_3^-$ reabsorption into the extracellular fluid decrease if the pH of the body fluids increases. As a result, the amount of bicarbonate

1. When the filtrate or blood pH decreases, $H^+$ combine with $HCO_3^-$ to form carbonic acid that is converted into $CO_2$ and $H_2O$. The $CO_2$ diffuses into tubule cells.
2. In the tubule cells, $CO_2$ combines with $H_2O$ to form $H_2CO_3$ that dissociates to form $H^+$ and $HCO_3^-$.
3. A countertransport mechanism secretes $H^+$ into the filtrate in exchange for $Na^+$ from the filtrate. As a result, filtrate pH decreases.
4. $HCO_3^-$ is cotransported with $Na^+$ into the interstitial fluid. They then diffuse into capillaries.
5. In capillaries, $HCO_3^-$ combine with $H^+$, which increases blood pH.




## Process Figure 27.13 Kidney Regulation of Body Fluid Acid–Base Balance

As the extracellular pH decreases, the rate of $H^+$ secretion by tubule cells of the kidney and $HCO_3^-$ reabsorption increase.

filtered into the kidney tubules exceeds the amount of secreted $H^+$, and the excess of $HCO_3^-$ pass into the urine. Excretion of excess $HCO_3^-$ in the urine diminishes the amount of $HCO_3^-$ in the extracellular fluid. This allows extracellular $H^+$ to increase and, as a consequence, the pH of the body fluids decreases toward its normal range.

### Cushing's Syndrome and Alkalosis

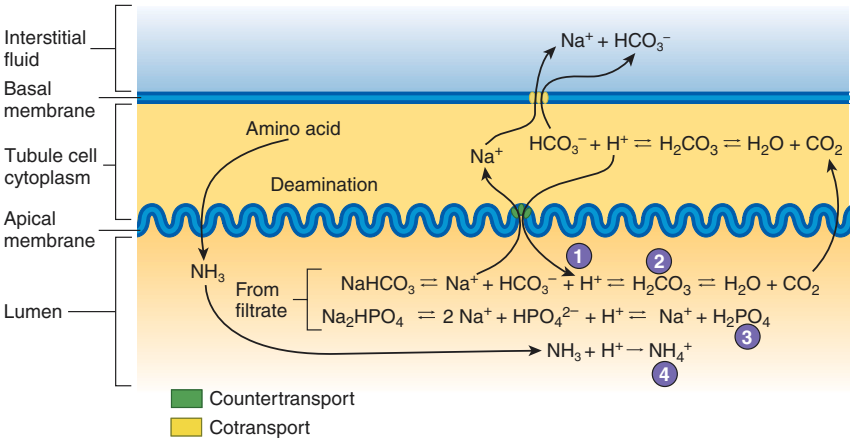
Aldosterone increases the rate of $Na^+$ reabsorption and $K^+$ secretion by the kidneys, but in high concentrations aldosterone also stimulates $H^+$ secretion. Elevated aldosterone levels, such as occur in patients with Cushing's syndrome, can, therefore, elevate body fluid pH above normal (alkalosis). The major factor that influences the rate of $H^+$ secretion, however, is the pH of the body fluids.

**PREDICT** 4

**Predict the effect of aldosterone hyposecretion on body fluid pH.**

The secretion of $H^+$ into the urine can decrease the filtrate pH to approximately 4.5. A filtrate pH below 4.5 inhibits the secretion of additional $H^+$. The $H^+$ that pass into the filtrate are greater than the quantity required to decrease the pH of an unbuffered solution below 4.5. Buffers in the filtrate combine with many of the secreted $H^+$. $HCO_3^-$, phosphate ions ($HPO_4^{2-}$), and **ammonia** ($NH_3$) in the filtrate act as buffers. Both $HCO_3^-$ and $HPO_4^-$ enter the kidney tubules through the filtration membrane along with the rest of the filtrate, and $NH_3$ diffuses across the wall of nephron cells to enter the filtrate. These ions combine with $H^+$ secreted by the nephron (figure 27.14).

1. $H^+$ secreted into the filtrate are buffered.
2. $H^+$ can react with $HCO_3^-$ that enters the filtrate to form $H_2CO_3$ which is in equilibrium with $H_2O$ and $CO_2$.
3. $H^+$ can react with $HPO_4^{2-}$ that enters the filtrate to form $H_2PO_4^-$.
4. $H^+$ can react with $NH_3$ formed by amino acid deamination and secreted into the nephron to form $NH_4^+$.




## Process Figure 27.14 Hydrogen Ion Buffering in the Filtrate

The secretion of $H^+$ into the filtrate decreases filtrate pH. As the concentration of $H^+$ increases in the filtrate, the ability of tubule cells to secrete additional $H^+$ becomes limited. Buffering the $H^+$ in the filtrate decreases their concentration and enables tubule cells to secrete additional $H^+$.

## Clinical Focus Acidosis and Alkalosis

The normal pH value of the body fluids is between 7.35 and 7.45. When the pH value of body fluids is below 7.35, the condition is called **acidosis** (as-i-dō′sis), and when the pH is above 7.45, it is called **alkalosis** (al′kă-lō′sis).

Metabolism produces acidic products that lower the pH of the body fluids. For example, $CO_2$ is a by-product of metabolism, and $CO_2$ combines with water to form $H_2CO_3$. Also, lactic acid is a product of anaerobic metabolism, protein metabolism produces phosphoric and sulfuric acids, and lipid metabolism produces fatty acids. These acidic substances must continuously be eliminated from the body to maintain pH homeostasis. The failure to eliminate acidic products of metabolism results in acidosis. Excess elimination of acidic products of metabolism results in alkalosis.

The major effect of acidosis is depression of the central nervous system. When the pH of the blood falls below 7.35, the central nervous system malfunctions, and the individual becomes disoriented and possibly comatose as the condition worsens.

A major effect of alkalosis is hyperexcitability of the nervous system. Peripheral nerves are affected first, resulting in spontaneous nervous stimulation of muscles. Spasms and tetanic contractions and possibly extreme nervousness or convulsions result. Severe alkalosis can cause death as a result of tetany of the respiratory muscles.

Although buffers help resist changes in the pH of body fluids, the respiratory system and the kidneys regulate the pH of the body fluids. Malfunctions in either the respiratory system or the kidneys can result in acidosis or alkalosis.

Acidosis and alkalosis are categorized by the cause of the condition. **Respiratory acidosis** or **respiratory alkalosis** results from abnormalities in the respiratory system. **Metabolic acidosis** or **metabolic alkalosis** results from all causes other than abnormal respiratory functions.

Inadequate ventilation of the lungs causes respiratory acidosis (table A). The rate at which $CO_2$ is eliminated from the body fluids through the lungs falls. This increases the concentration of $CO_2$ in the body fluids. As $CO_2$ levels increase, $CO_2$ reacts with water to form $H_2CO_3$. $H_2CO_3$ forms $H^+$ and $HCO_3^-$. The increase in $H^+$ concentration causes the pH of the body fluids to decrease. If the pH of the body fluids falls below 7.35, symptoms of respiratory acidosis become apparent.

Buffers help resist a decrease in pH, and the kidneys help compensate for failure of the lungs to prevent respiratory acidosis by increasing the rate at which they secrete $H^+$ into the filtrate and reabsorb $HCO_3^-$. The capacity of buffers to resist changes in pH can be exceeded, however, and a period of 1–2 days is required for the kidney to become maximally functional. Thus, the kidneys are not effective if respiratory acidosis develops quickly. The kidneys are very effective if respiratory acidosis develops slowly or if it lasts long enough for the kidneys to respond. For example, the kidneys cannot compensate for respiratory acidosis occurring in response to a severe asthma attack that begins quickly and subsides within hours. If, however, respiratory acidosis results from emphysema, which develops over a long time, the kidneys play a significant role in helping to compensate.

Respiratory alkalosis results from hyperventilation of the lungs (see table A). This increases the rate at which $CO_2$ is eliminated from the body fluids and results in a decrease in the concentration of $CO_2$ in the body fluids. As $CO_2$ levels decrease, $H^+$ react with $HCO_3^-$ to form $H_2CO_3$. The $H_2CO_3$ forms $H_2O$ and $CO_2$. The resulting decrease in the concentration of $H^+$ causes the pH of the body fluids to increase. If the pH of body fluids increases above 7.45, symptoms of respiratory alkalosis become apparent.

The kidneys help to compensate for respiratory alkalosis by decreasing the rate of $H^+$ ion secretion into the filtrate and the rate of $HCO_3^-$ reabsorption. If an increase in pH occurs, the kidneys need 1–2 days to compensate. Thus, the kidneys are not effective if respiratory alkalosis develops quickly. They are very effective, however, if respiratory alkalosis develops slowly. For example, the kidneys are not effective in compensating for respiratory alkalosis that occurs in response to hyperventilation triggered by emotions, which usually begins quickly and subsides within minutes or hours. If alkalosis results, however, from staying at a high altitude over a 2- or 3-day period, the kidneys play a significant role in helping to compensate.

Metabolic acidosis results from all conditions that decrease the pH of the body fluids below 7.35, with the exception of conditions resulting from altered function of the respiratory system (see table A). As $H^+$

$NH_3$ is produced in the cells of the nephron when amino acids like glycine are deaminated. Subsequently, $NH_3$ diffuses from the nephron cells into the filtrate and combines with $H^+$ in the filtrate to form **ammonium ions** ($NH_4^+$) (see figure 27.14). The rate of $NH_3$ production increases when the pH of the body fluids has been depressed for 2–3 days, such as during prolonged respiratory or metabolic acidosis. The elevated ammonia production increases the buffering capacity of the filtrate, allowing secretion of additional $H^+$ into the urine.

$HCO_3^-$, $HPO_4^-$, and $NH_3$ constitute major buffers within the filtrate, but other weak acids, such as lactic acid in the filtrate, also combine with $H^+$ and increase the amount of $H^+$ that can be secreted into the filtrate.

30. *Name the three mechanisms that play essential roles in the regulation of acid-base balance.*
31. *What happens to blood pH when blood $CO_2$ levels go up or down? What causes this change?*

## Table A Acidosis and Alkalosis

| |
|---|
| **Acidosis** |
| ***Respiratory Acidosis*** |
| Reduced elimination of $CO_2$ from the body fluids |
| Asphyxia |
| Hypoventilation (e.g., impaired respiratory center function due to trauma, tumor, shock, or renal failure) |
| Advanced asthma |
| Severe emphysema |
| ***Metabolic Acidosis*** |
| Elimination of large amounts of $HCO_3^-$ resulting from mucous secretion (e.g., severe diarrhea and vomiting of lower intestinal contents) |
| Direct reduction of the body fluid pH as acid is absorbed (e.g., ingestion of acidic drugs like aspirin) |
| Production of large amounts of fatty acids and other acidic metabolites, such as ketone bodies (e.g., untreated diabetes mellitus) |
| Inadequate oxygen delivery to tissue resulting in anaerobic respiration and lactic acid buildup (e.g., exercise, heart failure, or shock) |
| **Alkalosis** |
| ***Respiratory Alkalosis*** |
| Reduced $CO_2$ levels in the extracellular fluid (e.g., hyperventilation due to emotions) |
| Decreased atmospheric pressure reduces oxygen levels, which stimulates the chemoreceptor reflex, causing hyperventilation (e.g., high altitudes) |
| ***Metabolic Alkalosis*** |
| Elimination of $H^+$ and reabsorption of $HCO_3^-$ in the stomach or kidney (e.g., severe vomiting or formation of acidic urine in response to excess aldosterone) |
| Ingestion of alkaline substances (e.g., large amounts of sodium bicarbonate) |

accumulate in the body fluids, buffers first resist a decline in pH. If the buffers cannot compensate for the increase in $H^+$, the respiratory center helps regulate body fluid pH. The reduced pH stimulates the respiratory center, which causes hyperventilation. During hyperventilation, $CO_2$ is eliminated at a greater rate. The elimination of $CO_2$ also eliminates excess $H^+$ and helps maintain the pH of the body fluids within a normal range.

If metabolic acidosis persists for many hours and if the kidneys are functional, the kidneys can also help compensate for metabolic acidosis by secreting $H^+$ ions at a greater rate and increasing the rate of $HCO_3^-$ reabsorption. Symptoms of metabolic acidosis appear if the respiratory and renal systems are not able to maintain the pH of the body fluids within its normal range.

Metabolic alkalosis results from all conditions that increase the pH of the body fluids above 7.45, with the exception of conditions resulting from altered function of the respiratory system. As $H^+$ decrease in the body fluids, buffers first resist an increase in pH. If the buffers cannot compensate for the decrease in $H^+$, the respiratory center helps regulate body fluid pH. The increased pH inhibits respiration. Reduced respiration allows $CO_2$ to accumulate in the body fluids. $CO_2$ reacts with water to produce $H_2CO_3$. If metabolic alkalosis persists for several hours, and if the kidneys are functional, the kidneys reduce the rate of $H^+$ secretion to help reverse alkalosis (see table A).

32. *What effect do increased $CO_2$ levels or decreased pH have on respiration? How does this change in respiration affect blood pH?*
33. *Describe the process by which nephron cells move $H^+$ ions into the kidney tubule lumen and $HCO_3^-$ into the extracellular fluid.*
34. *Describe the process by which $HCO_3^-$ are reabsorbed from the kidney tubule lumen.*
35. *Name the factors that cause an increase and a decrease in $H^+$ ion secretion.*
36. *What is the purpose of buffers in the urine? Describe how the ammonia buffer system operates.*

## S U M M A R Y

Water, acid, base, and electrolyte levels are maintained within a narrow range of concentrations. The urinary, respiratory, gastrointestinal, integumentary, nervous, and endocrine systems play a role in maintaining fluid, electrolyte, and pH balance.

### Body Fluids (p. 986)

1. Intracellular fluid is inside cells.
2. Extracellular fluid is outside cells and includes interstitial fluid and plasma.

### Regulation of Body Fluid Concentration and Volume (p. 987)

#### Regulation of Water Content

1. Water crosses the gastrointestinal tract through osmosis.
2. An increase in extracellular osmolality or a decrease in blood pressure stimulates the sense of thirst.
3. Wetting the oral mucosa or stretch of the gastrointestinal tract inhibits thirst.
4. Learned behavior plays a role in the amount of fluid ingested.
5. Routes of water loss
   - Water is lost through evaporation from the respiratory system and the skin (insensible perspiration and sweat).
   - Water loss into the gastrointestinal tract normally is small. Vomiting or diarrhea can significantly increase this loss.
   - The kidneys are the primary regulator of water excretion. Urine output can vary from a small amount of concentrated urine to a large amount of dilute urine.

#### Regulation of Extracellular Fluid Osmolality

1. Increased water consumption and ADH secretion occur in response to increases in extracellular fluid osmolality. Decreased water consumption and ADH secretion occur in response to decreases in extracellular fluid osmolality.
2. Increased water consumption and ADH decrease extracellular fluid osmolality by increasing water absorption from the intestine and water reabsorption from the nephrons. Decreased water consumption and ADH increase extracellular fluid osmolality by decreasing absorption from the intestine and water reabsorption from the nephrons.

#### Regulation of Extracellular Fluid Volume

1. Increased extracellular fluid volume results in decreased aldosterone secretion, increased ANH secretion, decreased ADH secretion, and decreased sympathetic stimulation of afferent arterioles. The effect of these changes is to decrease $Na^+$ reabsorption and to increase urine volume to decrease extracellular fluid volume.
2. Decreased extracellular fluid volume results in increased aldosterone secretion, decreased ANH secretion, increased ADH secretion, and increased sympathetic stimulation of the afferent arterioles. The effect of these changes is to increase $Na^+$ reabsorption and to decrease urine volume so as to increase extracellular fluid volume.

### Regulation of Intracellular Fluid Composition (p. 992)

1. Substances used or produced inside the cell and substances exchanged with the extracellular fluid determine the composition of intracellular fluid.
2. Intracellular fluid is different from extracellular fluid because the plasma membrane regulates the movement of materials.
3. The difference between intracellular and extracellular fluid concentrations determines water movement.

### Regulation of Specific Electrolytes in the Extracellular Fluid (p. 993)

The intake and elimination of substances from the body and the exchange of substances between the extracellular and intracellular fluids determine extracellular fluid composition.

#### Regulation of Sodium Ions

1. Sodium is responsible for 90%–95% of extracellular osmotic pressure.
2. The amount of $Na^+$ excreted in the kidneys is the difference between the amount of $Na^+$ that enters the nephron and the amount that is reabsorbed from the nephron.
   - Glomerular filtration rate determines the amount of $Na^+$ entering the nephron.
   - Aldosterone determines the amount of $Na^+$ reabsorbed.
3. Small quantities of $Na^+$ are lost in sweat.
4. Increased blood osmolality leads to the production of a small volume of concentrated urine and to thirst. Decreased blood osmolality leads to the production of a large volume of dilute urine and to decreased thirst.
5. Increased blood pressure increases water and salt loss.
   - Baroreceptor reflexes reduce ADH secretion.
   - Renin secretion is inhibited, leading to reduced aldosterone production.

#### Regulation of Chloride Ions

Chloride ions are the dominant negatively charged ions in extracellular fluid.

#### Regulation of Potassium Ions

1. The extracellular concentration of $K^+$ affects resting membrane potentials.
2. The amount of $K^+$ excreted depends on the amount that enters with the glomerular filtrate, the amount actively reabsorbed by the nephron, and the amount secreted into the distal convoluted tubule.
3. Aldosterone increases the amount of $K^+$ secreted.

#### Regulation of Calcium Ions

1. Elevated extracellular calcium levels prevent membrane depolarization. Decreased levels lead to spontaneous action potential generation.
2. Parathyroid hormone increases extracellular $Ca^{2+}$ levels and decreases extracellular phosphate levels. It stimulates osteoclast activity, increases calcium reabsorption from the kidneys, and stimulates active vitamin D production.
3. Vitamin D stimulates $Ca^{2+}$ uptake in the intestines.
4. Calcitonin decreases extracellular $Ca^{2+}$ levels.

#### Regulation of Magnesium Ions

The capacity of the kidney to reabsorb magnesium is limited so that excess magnesium is lost in the urine and decreased extracellular magnesium results in a greater degree of magnesium reabsorption.

#### Regulation of Phosphate Ions

1. Under normal conditions, reabsorption of phosphate occurs at a maximum rate in the nephron.
2. An increase in plasma phosphate increases the amount of phosphate in the nephron beyond that which can be reabsorbed, and the excess is lost in the urine.

## Regulation of Acid–Base Balance (p. 1003)

### Acids and Bases

Acids release $H^+$ into solution, and bases remove them.

### Buffer Systems

1. A buffer resists changes in pH.
   - When $H^+$ are added to a solution, the buffer removes them.
   - When $H^+$ are removed from a solution, the buffer replaces them.
2. Carbonic acid/bicarbonate, proteins, and phosphate compounds are important buffers.

### Mechanisms of Acid–Base Balance Regulation

Buffers, the respiratory system, and the kidneys regulate acid–base balance.

### Respiratory Regulation of Acid–Base Balance

1. Respiratory regulation of pH is achieved through the carbonic acid/bicarbonate buffer system.
   - As carbon dioxide levels increase, pH decreases.
   - As carbon dioxide levels decrease, pH increases.
   - Carbon dioxide levels and pH affect the respiratory centers. Hypoventilation increases blood carbon dioxide levels, and hyperventilation decreases blood carbon dioxide levels.

### Renal Regulation of Acid–Base Balance

1. The secretion of $H^+$ into the filtrate and the reabsorption of $HCO_3^-$ into extracellular fluid cause extracellular pH to increase.
   - Carbonic acid dissociates to form $H^+$ and $HCO_3^-$ in nephron cells.
   - Active transport pumps $H^+$ into the nephron lumen and $Na^+$ into the nephron cell.
   - $Na^+$ and $HCO_3^-$ diffuse into the extracellular fluid.
2. $HCO_3^-$ in the filtrate are reabsorbed.
   - $HCO_3^-$ combine with $H^+$ to form carbonic acid, which dissociates to form carbon dioxide and water.
   - Carbon dioxide diffuses into nephron cells and forms carbonic acid, which dissociates to form $HCO_3^-$ and $H^+$.
   - $HCO_3^-$ diffuse into the extracellular fluid, and $H^+$ are secreted into the filtrate.
3. The rate of $H^+$ secretion increases as body fluid pH decreases or as aldosterone levels increase.
4. Secretion of $H^+$ is inhibited when urine pH falls below 4.5.
   - Carbonic acid/bicarbonate, ammonia, and phosphate buffers in the urine resist a drop in pH.
   - As the buffers absorb $H^+$, more $H^+$ are pumped into the urine.

## REVIEW AND COMPREHENSION

1. Extracellular fluid
   a. is much like intracellular fluid in composition.
   b. includes interstitial fluid.
   c. osmotic concentration tends to vary greatly in the different fluid compartments of the body.
   d. all of the above.
2. The sensation of thirst increases when
   a. the levels of angiotensin II increase.
   b. the osmolality of the blood decreases.
   c. blood pressure increases.
   d. renin secretion decreases.
3. Insensible perspiration
   a. is lost through sweat glands.
   b. results in heat loss from the body.
   c. increases when ADH secretion increases.
   d. results in the loss of solutes such as $Na^+$ and $Cl^-$.
4. The composition and volume of body fluid are regulated primarily by the
   a. skin.
   b. lungs.
   c. kidneys.
   d. heart.
   e. spleen.
5. Which of these conditions *decreases* extracellular fluid volume?
   a. constriction of afferent arterioles
   b. increased ADH secretion
   c. decreased ANH secretion
   d. decreased aldosterone secretion
   e. stimulation of sympathetic nerves to the kidneys
6. A decrease in blood pressure
   a. results in increased aldosterone secretion.
   b. causes decreased ADH secretion.
   c. inhibits sympathetic stimulation.
   d. results in vasodilation.
   e. all of the above.
7. Which of these results in an increased blood $Na^+$ concentration?
   a. decrease in ADH secretion
   b. decrease in aldosterone secretion
   c. increase in ANH
   d. decrease in renin secretion
8. Which of these mechanisms is the most important for regulating blood osmolality?
   a. ADH
   b. renin-angiotensin-aldosterone
   c. ANH
   d. parathyroid hormone
9. A decrease in extracellular $K^+$
   a. produces depolarization of the plasma membrane.
   b. results when aldosterone levels increase.
   c. occurs when tissues are damaged (e.g., in burn patients).
   d. increases ANH secretion.
   e. increases PTH secretion.
10. $Ca^{2+}$ concentration in the blood decreases when
    a. vitamin D levels are lower than normal.
    b. calcitonin secretion decreases.
    c. parathyroid hormone secretion increases.
    d. all of the above.
11. An acid
    a. solution has a pH greater than 7.
    b. is a substance that releases $H^+$ into a solution.
    c. is considered weak if it completely dissociates in water.
    d. all of the above.
12. Buffers
    a. release $H^+$ when pH increases.
    b. resist changes in the pH of a solution.
    c. include the proteins of the blood.
    d. all of the above.
13. Which of these is *not* a buffer system in the body?
    a. sodium chloride buffer system
    b. carbonic acid/bicarbonate buffer system
    c. phosphate buffer system
    d. protein buffer system

14. Which of these systems regulating blood pH is the fastest acting?
    a. respiratory
    b. kidney
15. An increase in blood carbon dioxide levels is followed by a(n) _____ in $H^+$ and a(n) _____ in blood pH.
    a. increase, increase
    b. increase, decrease
    c. decrease, increase
    d. decrease, decrease
16. High levels of bicarbonate ions in the urine indicate
    a. a low level of $H^+$ secretion into the urine.
    b. that the kidneys are causing blood pH to increase.
    c. that urine pH is decreasing.
    d. all of the above.
17. High levels of ammonium ions in the urine indicate
    a. a high level of $H^+$ secretion into the urine.
    b. that the kidneys are causing blood pH to decrease.
    c. that urine pH is too alkaline.
    d. all of the above.
18. Blood plasma pH is normally
    a. slightly acidic.
    b. strongly acidic.
    c. slightly alkaline.
    d. strongly alkaline.
    e. neutral.
19. Acidosis
    a. increases neuron excitability.
    b. can produce tetany by affecting the peripheral nervous system.
    c. may lead to coma.
    d. may produce convulsions through the central nervous system.
20. Respiratory alkalosis is caused by _____ and can be compensated for by the production of a more _____ urine.
    a. hypoventilation, alkaline
    b. hypoventilation, acidic
    c. hyperventilation, acidic
    d. hyperventilation, alkaline

*Answers in Appendix F*

## CRITICAL THINKING

1. In patients with diabetes mellitus, not enough insulin is produced; as a consequence, blood glucose levels increase. If blood glucose levels rise high enough, the kidneys are unable to absorb the glucose from the glomerular filtrate, and glucose "spills over" into the urine. What effect does this glucose have on urine concentration and volume? How does the body adjust to the excess glucose in the urine?
2. A patient suffering from a tumor in the hypothalamus produces excessive amounts of ADH, a condition called syndrome of inappropriate ADH (SIADH) production. For this patient, the excessive ADH production is chronic and has persisted for many months. A student nurse keeps a fluid intake–output record on the patient. She is surprised to find that fluid intake and urinary output are normal. What effect was she expecting? Can you explain why urinary output is normal?
3. A patient exhibits the following symptoms: elevated urine ammonia and increased rate of respiration. Does the patient have metabolic acidosis or metabolic alkalosis?
4. Swifty Trotts has an enteropathogenic *Escherichia coli* infection that produces severe diarrhea. What does this diarrhea do to his blood pH, urine pH, and respiratory rate?
5. Acetazolamide is a diuretic that blocks the activity of the enzyme carbonic anhydrase inside kidney tubule cells. This blockage prevents the formation of carbonic acid from carbon dioxide and water. Normally, carbonic acid dissociates to form $H^+$ and $HCO_3^-$, and the $H^+$ are exchanged for $Na^+$ from the urine. Blocking the formation of $H^+$ in the cells of the nephron tubule blocks sodium reabsorption, thus inhibiting water reabsorption and producing the diuretic effect. With this information in mind, what effect does acetazolamide have on blood pH, urine pH, and respiratory rate?
6. As part of a physiology experiment, Hardy Breath, an anatomy and physiology student, is asked to breathe through a 3-foot long glass tube. What effect does this action have on his blood pH, urine pH, and respiratory rate?
7. A young girl is suspected of having epilepsy and, therefore, is prone to having convulsions. On the basis of your knowledge of acid–base balance and respiration, propose a hypothetical experiment that might suggest that the girl is susceptible to convulsions.
8. Hardy Explorer climbed to the top of a very high mountain. To celebrate, he drank a glass of whiskey. Alcohol stimulates hydrochloric acid secretion in the stomach. What do you expect to happen to Hardy's respiratory rate and the pH of his urine?

*Answers in Appendix G*

## ANSWERS TO PREDICT QUESTIONS

1. During hemorrhagic shock, blood pressure decreases, and visceral blood vessels constrict (see chapter 21). As a consequence, blood flow to the kidneys and the blood pressure in the glomeruli decrease dramatically. The total filtration pressure decreases, and the amount of filtrate formed each minute decreases. The rate at which $Na^+$ enter the nephron, therefore, decreases. In addition, renin is secreted from the kidneys in large amounts. Renin causes the formation of angiotensin I from angiotensinogen. Angiotensin I converts to angiotensin II, which stimulates aldosterone secretion. Aldosterone increases the rate at which $Na^+$ are reabsorbed from the filtrate in the distal tubule and collecting ducts.
2. a. If the amount of $Na^+$ and water ingested in food exceeds that needed to maintain a constant extracellular fluid composition, it increases total blood volume and also increases blood pressure.
   b. Excessive $Na^+$ and water intake causes an increase in total blood volume and blood pressure. The elevated blood pressure causes a reflex response that results in decreased ADH secretion. The elevated pressure also causes reduced renin secretion from the kidneys, resulting in a reduction in the rate at which angiotensin II is formed. The reduction in angiotensin II reduces the rate of aldosterone secretion. Together these changes cause increased loss of $Na^+$ in the urine and an increase in the volume of urine produced. Increased $Na^+$ and increased blood pressure also cause the secretion of ANH, which inhibits ADH secretion and $Na^+$ reabsorption in the nephron.

c. If the amount of water ingested is large, urine concentration is reduced, urine volume is increased, and the concentration of $Na^+$ in the urine is low. If the amount of salt ingested is great, the concentration of salt in the urine can be high, and the urine volume is larger and contains a substantial concentration of salt.

3. During conditions of exercise, the amount of water lost is increased because of increased evaporation from the respiratory system, increased insensible perspiration, and increased sweat. The amount of water lost in the form of sweat can increase substantially. The amount of urine formed decreases during conditions of exercise.

4. Aldosterone hyposecretion results in acidosis. Aldosterone increases the rate at which $Na^+$ are reabsorbed from nephrons, but it also increases the rate at which $K^+$ and $H^+$ are secreted. Hyposecretion of aldosterone decreases the rate at which $H^+$ are secreted by the nephrons and, therefore, can result in acidosis.