

CHAPTER

6

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Fluids and electrolytes are present in body cells, in the tissue spaces between the cells, and in the blood that fills the vascular compartment. Body fluids serve to transport gases, nutrients, and wastes; help to generate the electrical activity needed to power body functions; take part in the transforming of food into energy; and otherwise maintain the overall function of the body. Although fluid volume and composition remain relatively constant in the presence of a wide range of changes in intake and output, conditions such as environmental stresses and disease can increase fluid loss, impair its intake, and otherwise interfere with mechanisms that regulate fluid volume, composition, and distribution.

COMPOSITION AND COMPARTMENTAL DISTRIBUTION OF BODY FLUIDS

Body fluids are distributed between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The ICF compartment consists of fluid contained within all of the billions of cells in the body. It is the larger of the two compartments, containing approximately two thirds of the body water in healthy adults. The remaining one third of body water is in the ECF compartment, which contains all the fluids outside the cells, including that in the interstitial or tissue spaces and blood vessels (Fig. 6-1). The ECF, including the plasma and interstitial fluids,

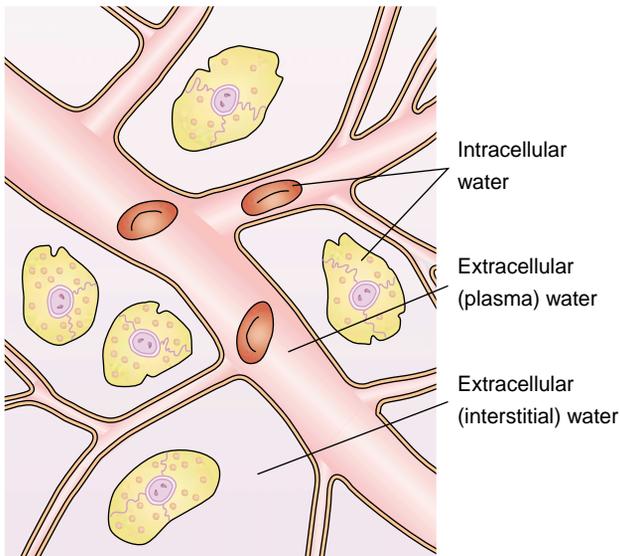


FIGURE 6-1 Distribution of body water. The extracellular space includes the vascular compartment (plasma water) and the interstitial spaces.

contain large amounts of sodium and chloride, moderate amounts of bicarbonate, but only small quantities of potassium. In contrast to the ECF fluid, the ICF contains small amounts of sodium, chloride, and bicarbonate and large amounts of potassium (Table 6-1). It is the ECF levels of electrolytes in the blood or blood serum that are measured clinically. Although blood levels usually are representative of the total body levels of an electrolyte, this is not always the case, particularly with potassium, which is approximately 28 times more concentrated inside the cell than outside.

The cell membrane serves as the primary barrier to the movement of substances between the ECF and ICF compartments. Lipid-soluble substances such as gases (*i.e.*, oxygen and carbon dioxide), which dissolve in the lipid bilayer of the cell membrane, pass directly through the membrane. Many ions, such as sodium (Na^+) and potassium (K^+), rely on transport

mechanisms such as the Na^+/K^+ -ATPase pump that is located in the cell membrane for movement across the membrane (see Chapter 1). Water crosses the cell membrane by osmosis using special protein channels.

Introductory Concepts

The electrolytes in body fluids are substances that dissociate in solution to form charged particles, or *ions*. For example, a sodium chloride (NaCl) molecule dissociates to form a positively charged Na^+ ion and a negatively charged Cl^- ion. Because of their attraction forces, positively charged cations are always accompanied by negatively charged anions. The distribution of electrolytes between body compartments is influenced by their electrical charge. However, one cation may be exchanged for another, providing it carries the same charge. For example, a positively charged H^+ ion may be exchanged for a positively charged K^+ and a negatively charged HCO_3^- ion may be exchanged for a negatively charged Cl^- anion.

Diffusion and Osmosis

Diffusion is the movement of charged or uncharged particles along a concentration gradient. All molecules and ions, including water and dissolved molecules, are in constant random motion. It is the motion of these particles, each colliding with one another, that supplies the energy for diffusion. Because there are more molecules in constant motion in a concentrated solution, particles move from an area of higher concentration to one of lower concentration.

Osmosis is the movement of water across a semipermeable membrane (*i.e.*, one that is permeable to water but impermeable to most solutes). As with solute particles, water diffuses down its concentration gradient, moving from the side of the membrane with the lesser number of particles and greater concentration of water to the side with the greater number of particles and lesser concentration of water (Fig. 6-2). As water moves across the semipermeable membrane, it generates a pressure, called the *osmotic pressure*. The osmotic pressure represents the pressure (measured in millimeters of mercury [mm Hg]) needed to oppose the movement of water across the membrane.

The osmotic activity that nondiffusible particles exert in pulling water from one side of the semipermeable membrane to the other is measured by a unit called an *osmole*. The osmole is derived from the gram molecular weight of a substance (*i.e.*, 1 gram molecular weight of a nondiffusible and non-ionizable substance is equal to 1 osmole). In the clinical setting, osmotic activity usually is expressed in milliosmoles (one thousandth of an osmole) per liter. Each nondiffusible particle, large or small, is equally effective in its ability to pull water through a semipermeable membrane. Thus, it is the number, rather than the size, of the nondiffusible particles that determines the osmotic activity of a solution.

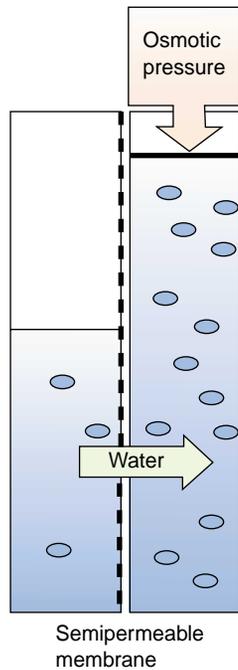
The osmotic activity of a solution may be expressed in terms of either its osmolarity or osmolality. *Osmolarity* refers to the osmolar concentration in 1 L of solution (mOsm/L) and *osmolality* to the osmolar concentration in 1 kg of water (mOsm/kg of H_2O). Osmolarity is usually used when referring to fluids outside the body and osmolality for describing fluids inside the body. Because 1 L of water weighs 1 kg, the terms *osmolarity* and *osmolality* are often used interchangeably.

TABLE 6-1 Concentrations of Extracellular and Intracellular Electrolytes in Adults

Electrolyte	Extracellular Concentration*	Intracellular Concentration*
Sodium	135–145 mEq/L	10–14 mEq/L
Potassium	3.5–5.0 mEq/L	140–150 mEq/L
Chloride	98–106 mEq/L	3–4 mEq/L
Bicarbonate	24–31 mEq/L	7–10 mEq/L
Calcium	8.5–10.5 mg/dL	<1 mEq/L
Phosphate/ phosphorus	2.5–4.5 mg/dL	4 mEq/kg [†]
Magnesium	1.8–3.0 mg/dL	40 mEq/kg [†]

*Values may vary among laboratories, depending on the method of analysis used.

[†]Values vary among various tissues and with nutritional status.



■ **FIGURE 6-2** ■ Movement of water across a semipermeable membrane. Water moves from the side that has fewer nondiffusible particles to the side that has more. The osmotic pressure is equal to the hydrostatic pressure needed to oppose water movement across the membrane.

Serum osmolality, which is largely determined by sodium and its attendant anions (chloride and bicarbonate), normally ranges between 275 and 295 mOsm/kg. Blood urea nitrogen (BUN) and glucose, which also are osmotically active, account for less than 5% of the total osmotic pressure in the ECF compartment. However, this can change, such as when blood glucose levels are elevated in persons with diabetes mellitus or when BUN levels change rapidly in persons with renal failure.

Tonicity. A change in water content causes cells to swell or shrink. The term *tonicity* refers to the tension or effect that the effective osmotic pressure of a solution with impermeable solutes exerts on cell size because of water movement across the cell membrane. An effective osmole is one that exerts an osmotic force and cannot permeate the cell membrane, whereas an ineffective osmole is one that exerts an osmotic force but crosses the cell membrane. Tonicity is determined solely by effective solutes such as glucose that cannot penetrate the cell membrane, thereby producing an osmotic force that pulls water into or out of the cell and causing it to change size.

Solutions to which body cells are exposed can be classified as isotonic, hypotonic, or hypertonic, depending on whether they cause cells to swell or shrink (Fig. 6-3). Cells placed in an isotonic solution, which has the same effective osmolality as the ICF (*i.e.*, 280 mOsm/L), neither shrink nor swell. An example of an isotonic solution is 0.9% sodium chloride. When cells are placed in a hypotonic solution, which has a lower effective osmolality than the ICF, they swell as water moves into the cell; when they are placed in a hypertonic solution, which has a greater effective osmolality than ICF, they shrink as water is pulled out of the cell.

Measurement Units

Laboratory measurements of electrolytes in body fluids are expressed as a concentration or amount of solute in a given volume of fluid, such as milligrams per deciliter (mg/dL), milliequivalents per liter (mEq/L), or millimoles per liter (mmol/L).

The use of *milligrams (mg) per deciliter* expresses the weight of the solute in one tenth of a liter (dL). The concentration of electrolytes, such as calcium, phosphate, and magnesium, is often expressed in mg/dL.

The *milliequivalent* is used to express the charge equivalency for a given weight of an electrolyte: 1 mEq of sodium has the same number of charges as 1 mEq of chloride, regardless of molecular weight. The number of milliequivalents of an electrolyte in a liter of solution can be derived from the following equation:

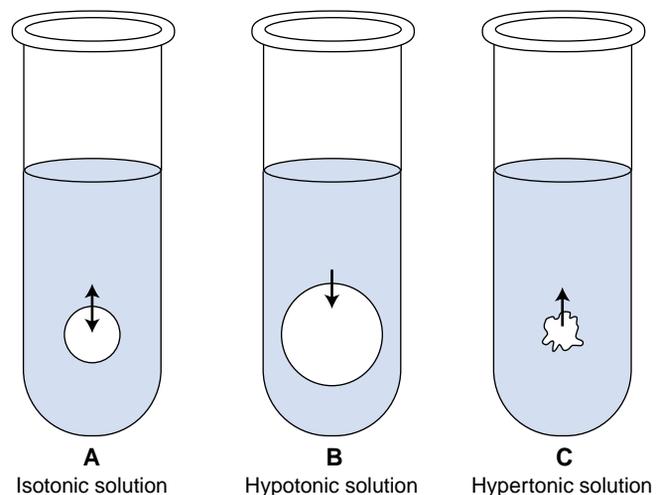
$$\text{mEq} = \frac{\text{mg}/100 \text{ mL} \times 10 \times \text{valence}}{\text{atomic weight}}$$

The *Système Internationale (SI)* units express electrolyte concentration in *millimoles per liter (mmol/L)*. A millimole is one thousandth of a mole, or the molecular weight of a substance expressed in milligrams. The number of millimoles of an electrolyte in a liter of solution can be calculated using the following equation:

$$\text{mmol/L} = \frac{\text{mEq/L}}{\text{valence}}$$

Compartmental Distribution of Body Fluids

Body water is distributed between the ICF and ECF compartments. In the adult, the fluid in the ICF compartment constitutes approximately 40% of body weight.¹ The fluid in the ECF compartment is further divided into two major subdivisions: the plasma compartment, which constitutes approximately 4%



■ **FIGURE 6-3** ■ **Tonicity.** Red cells undergo no change in size in isotonic solutions (A). They increase in size in hypotonic solutions (B) and decrease in size in hypertonic solutions (C).

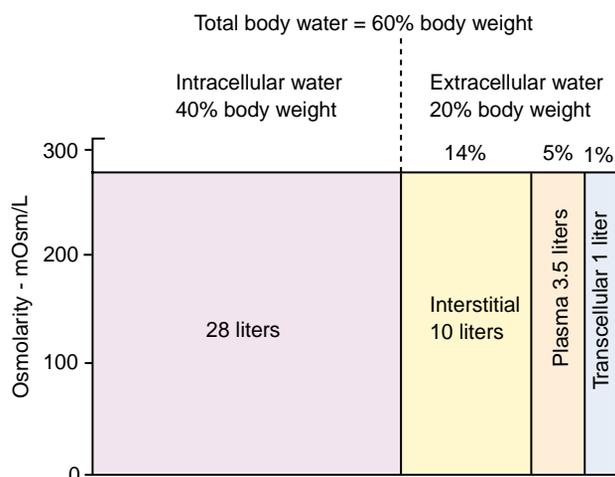
of body weight, and the interstitial fluid compartment, which constitutes approximately 15% of body weight (Fig. 6-4).

A third, usually minor, subdivision of the ECF compartment is the transcellular compartment. It includes the cerebrospinal fluid and fluid contained in the various body spaces, such as the peritoneal, pleural, and pericardial cavities; the joint spaces; and the gastrointestinal tract. Normally, only approximately 1% of ECF is in the transcellular space. This amount can increase considerably in conditions such as ascites, in which large amounts of fluid are sequestered in the peritoneal cavity. When the transcellular fluid compartment becomes considerably enlarged, it is referred to as a *third space*, because this fluid is not readily available for exchange with the rest of the ECF.

Intracellular Fluid Volume

The intracellular fluid volume is regulated by proteins and organic compounds in the ICF and by solutes that move between the ECF and ICF. The membrane in most cells is freely permeable to water; therefore, water moves between the ECF and ICF as a result of osmosis. In contrast, osmotically active proteins and other organic compounds cannot pass through the membrane. Water entry into the cell is regulated by these osmotically active substances as well as by solutes such as sodium and potassium that pass through the cell membrane. Many of the intracellular proteins are negatively charged and attract positively charged ions such as the K^+ ion, accounting for its higher concentration in the ICF. The Na^+ ion, which has a greater concentration in the ECF, tends to enter the cell by diffusion. The Na^+ ion is osmotically active, and its entry would, if left unchecked, pull water into the cell until it ruptured. The reason this does not occur is because the Na^+/K^+ -ATPase membrane pump continuously removes three Na^+ ions from the cell for every two K^+ ions that are moved back into the cell (see Chapter 1). Situations that impair the function of the Na^+/K^+ -ATPase pump, such as hypoxia, cause cells to swell because of an accumulation of Na^+ ions.

Intracellular volume is also affected by the concentration of osmotically active substances in the extracellular fluid that cannot cross the cell membrane. In diabetes mellitus, for example, glucose cannot enter the cell and its increased concentration in the ECF pulls water out of the cell.



■ **FIGURE 6-4** ■ Approximate size of body compartments in a 70-kg adult.

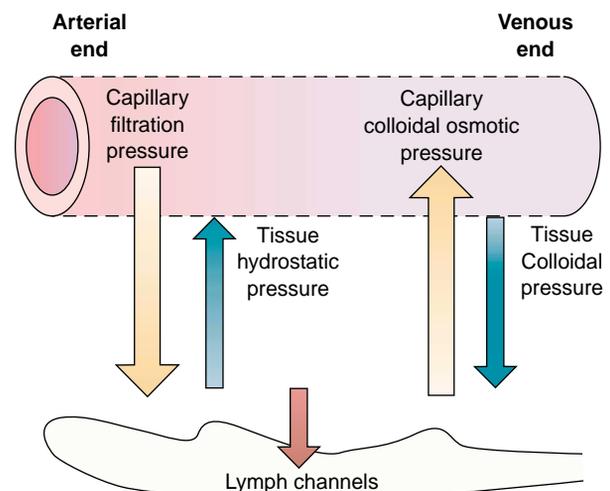
Extracellular Fluid Volume

The ECF is divided between the vascular and interstitial fluid compartments. The vascular compartment contains blood, which is essential to the transport of substances such as electrolytes, gases, nutrients, and waste products throughout the body. The fluid in the interstitial compartment acts as a transport vehicle for gases, nutrients, wastes, and other materials that move between the vascular compartment and body cells. The interstitial fluid compartment also provides a reservoir from which vascular volume can be maintained during periods of hemorrhage or loss of vascular volume. A tissue gel, which is a spongelike material composed of large quantities of mucopolysaccharides, fills the tissue spaces and aids in even distribution of interstitial fluid. Normally, most of the fluid in the interstitium is in gel form. The tissue gel is supported by collagen fibers that hold the gel in place. The tissue gel, which has a firmer consistency than water, opposes the outflow of water from the capillaries and prevents the accumulation of free water in the interstitial spaces.

Capillary/Interstitial Fluid Exchange

The transfer of water between the vascular and interstitial compartments occurs at the capillary level. Four forces control the movement of water between the capillary and interstitial spaces: (1) the capillary filtration pressure, which pushes water out of the capillary into the interstitial spaces; (2) the capillary colloidal osmotic pressure, which pulls water back into the capillary; (3) the interstitial hydrostatic pressure, which opposes the movement of water out of the capillary; and (4) the tissue colloidal osmotic pressure, which pulls water out of the capillary into the interstitial spaces (Fig. 6-5). Normally, the combination of these four forces is such that only a small excess of fluid remains in the interstitial compartment. This excess fluid is removed from the interstitium by the lymphatic system and returned to the systemic circulation.

Capillary filtration refers to the movement of water through capillary pores because of a mechanical, rather than an osmotic, force. The capillary filtration pressure, sometimes called the *capillary hydrostatic pressure*, is the pressure pushing water out of the capillary into the interstitial spaces. It reflects the



■ **FIGURE 6-5** ■ Exchange of fluid at the capillary level.

arterial and venous pressures, the precapillary (arterioles) and postcapillary (venules) resistances, and the force of gravity.² A rise in arterial or venous pressure increases capillary pressure. A decrease in arterial resistance or increase in venous resistance increases capillary pressure, and an increase in arterial resistance or decrease in venous resistance decreases capillary pressure. The force of gravity increases capillary pressure in the dependent parts of the body. In a person who is standing absolutely still, the weight of blood in the vascular column causes an increase of 1 mm Hg in pressure for every 13.6 mm of distance from the heart.² This pressure results from the weight of water and is therefore called *hydrostatic pressure*. In the adult who is standing absolutely still, the pressure in the veins of feet can reach 90 mm Hg. This pressure is then transmitted to the capillaries.

The *capillary colloidal osmotic pressure* is the osmotic pressure generated by the plasma proteins that are too large to pass through the pores of the capillary wall. The term *colloidal osmotic pressure* differentiates this type of osmotic pressure from the osmotic pressure that develops at the cell membrane from the presence of electrolytes and nonelectrolytes. Because plasma proteins do not normally penetrate the capillary pores and because their concentration is greater in the plasma than in the interstitial fluids, it is capillary colloidal osmotic pressure that pulls fluids back into the capillary.

The interstitial fluid pressure and the tissue colloidal osmotic pressure contribute to movement of water into and out of the interstitial spaces. The interstitial fluid pressure opposes the outward movement of water from the capillary into the interstitial spaces. The tissue colloidal osmotic pressure pulls water out of the capillary into the tissue spaces. It reflects the small amount of plasma proteins that normally escape from the capillary to enter the interstitial spaces.

Edema

Edema can be defined as palpable swelling produced by expansion of the interstitial fluid volume. Edema does not become evident until the interstitial fluid volume has been increased by 2.5 to 3 L.³

The physiologic mechanisms that contribute to edema formation include factors that: (1) increase the capillary filtration pressure, (2) decrease the capillary colloidal osmotic pressure, (3) increase capillary permeability, or (4) produce obstruction to lymph flow. The causes of edema are summarized in Chart 6-1.

Increased Capillary Filtration Pressure. As the capillary filtration pressure rises, the movement of vascular fluid into the interstitial spaces increases. Among the factors that increase capillary pressure are: (1) a decrease in the resistance to flow through the precapillary sphincters; (2) an increase in venous pressure or resistance to outflow at the postcapillary sphincters, and (3) capillary distention caused by increased vascular volume.

Edema can be either localized or generalized. The localized edema that occurs with urticaria (*i.e.*, hives) or other allergic or inflammatory conditions results from the release of histamine and other inflammatory mediators that cause dilation of the precapillary sphincters and arterioles that supply the swollen lesions. Thrombophlebitis obstructs venous flow, producing an elevation of venous pressure and edema of the affected part, usually one of the lower extremities.

CHART 6-1 Causes of Edema

Increased Capillary Pressure

Increased vascular volume
 Heart failure
 Kidney disease
 Premenstrual sodium retention
 Pregnancy
 Environmental heat stress
 Venous obstruction
 Liver disease with portal vein obstruction
 Acute pulmonary edema
 Venous thrombosis (thrombophlebitis)
 Decreased arteriolar resistance
 Calcium channel–blocking drug responses

Decreased Colloidal Osmotic Pressure

Increased loss of plasma proteins
 Protein-losing kidney diseases
 Extensive burns
 Decreased production of plasma proteins
 Liver disease
 Starvation, malnutrition

Increased Capillary Permeability

Inflammation
 Allergic reactions (*e.g.*, hives, angioneurotic edema)
 Malignancy (*e.g.*, ascites, pleural effusion)
 Tissue injury and burns

Obstruction of Lymphatic Flow

Malignant obstruction of lymphatic structures
 Surgical removal of lymph nodes

Generalized edema is common in conditions such as congestive heart failure that produce fluid retention and venous congestion. In right-sided heart failure, blood dams up throughout the entire venous system, causing organ congestion and edema of the dependent extremities. Decreased sodium and water excretion by the kidneys leads to an increase in ECF volume with an increase in capillary volume and pressure with subsequent movement of fluid into the tissue spaces. The swelling of hands and feet that occurs in healthy persons during hot weather results from vasodilation of superficial blood vessels along with sodium and water retention.

Because of the effects of gravity, edema resulting from increased capillary pressure commonly causes fluid to accumulate in the dependent parts of the body, a condition referred to as *dependent edema*. For example, edema of the ankles and feet becomes more pronounced during prolonged periods of standing.

Decreased Capillary Colloidal Osmotic Pressure. Plasma proteins exert the osmotic force needed to pull fluid back into the capillary from the tissue spaces. The plasma proteins constitute a mixture of proteins, including albumin, globulins, and fibrinogen. Albumin, the smallest of the plasma proteins, has a molecular weight of 69,000; globulins have molecular

weights of approximately 140,000; and fibrinogen has a molecular weight of 400,000.² Because of its lower molecular weight, 1 g of albumin has approximately twice as many osmotically active molecules as 1 g of globulin and almost six times as many osmotically active molecules as 1 g of fibrinogen. In addition, the concentration of albumin (approximately 4.5 g/dL) is greater than that of the globulins (2.5 g/dL) and fibrinogen (0.3 mg/dL).

Edema caused by decreased capillary colloidal osmotic pressure usually is the result of inadequate production or abnormal loss of plasma proteins, mainly albumin. The plasma proteins are synthesized in the liver. In persons with severe liver failure, impaired synthesis of albumin results in a decrease in colloidal osmotic pressure. In starvation and malnutrition, edema develops because there is a lack of the amino acids needed in plasma protein synthesis.

The most common site of plasma protein loss is the kidney. In kidney diseases such as nephrosis, the glomerular capillaries become permeable to the plasma proteins, particularly albumin, which is the smallest of the proteins. When this happens, large amounts of albumin are filtered out of the blood and lost in the urine. An excessive loss of plasma proteins also occurs when large areas of skin are injured or destroyed. Edema is a common problem during the early stages of a burn, resulting from capillary injury and loss of plasma proteins.

Because the plasma proteins are evenly distributed throughout the body and are not affected by the force of gravity, edema caused by decreased capillary colloidal osmotic pressure tends to affect tissues in nondependent as well as dependent parts of the body. There is swelling of the face as well as the legs and feet.

Increased Capillary Permeability. When the capillary pores become enlarged or the integrity of the capillary wall is damaged, capillary permeability is increased. When this happens, plasma proteins and other osmotically active particles leak into the interstitial spaces, increasing the tissue colloidal osmotic pressure and thereby contributing to the accumulation of interstitial fluid. Among the conditions that increase capillary permeability are burn injury, capillary congestion, inflammation, and immune responses.

Obstruction of Lymph Flow. Osmotically active plasma proteins and other large particles that cannot be reabsorbed through the pores in the capillary membrane rely on the lymphatic system for movement back into the circulatory system. Edema caused by impaired lymph flow is commonly referred to as *lymphedema*. Malignant involvement of lymph structures and removal of lymph nodes at the time of cancer surgery are common causes of lymphedema. Another cause of lymphedema is infection involving the lymphatic channels and lymph nodes.

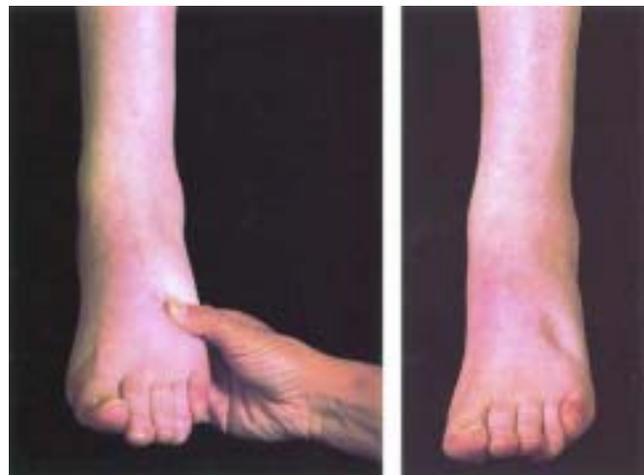
Manifestations. The effects of edema are determined largely by its location. Edema of the brain, larynx, or lungs is an acute, life-threatening condition. Although not life threatening, edema may interfere with movement by limiting joint motion. Swelling of the ankles and feet often is insidious in onset and may or may not be associated with disease. At the tissue level, edema increases the distance for diffusion of oxygen, nutrients, and wastes. Edematous tissues usually are more susceptible to

injury and the development of ischemic tissue damage, including pressure ulcers. Edema can also compress blood vessels. For example, the skin of a severely swollen finger can act as a tourniquet, shutting off the blood flow to the finger. Edema can also be disfiguring, causing psychological effects and disturbances in self-concept.

Assessment and Treatment. Methods for assessing edema include daily weight, visual assessment, measurement of the affected part, and application of finger pressure to assess for pitting edema. Daily weight performed at the same time each day with the same amount of clothing provides a useful index of water gain (1 L of water weighs 2.2 pounds) attributable to edema. Visual inspection and measurement of the circumference of an extremity can also be used to assess the degree of swelling. This is particularly useful when swelling is caused by thrombophlebitis. Pitting edema occurs when the accumulation of interstitial fluid exceeds the absorptive capacity of the tissue gel. In this form of edema, the tissue water becomes mobile and can be translocated with pressure exerted by a finger. Finger pressure can be used to assess the degree of pitting edema. If an indentation remains after the finger has been removed, pitting edema is identified. It is evaluated on a scale of +1 (minimal) to +4 (severe) (Fig. 6-6).

Treatment of edema usually is directed toward maintaining life when the swelling involves vital structures, correcting or controlling the cause, and preventing tissue injury. Diuretic therapy commonly is used to treat edema. Edema of the lower extremities may respond to simple measures such as elevating the feet.

Elastic support stockings and sleeves increase interstitial fluid pressure and resistance to outward movement of fluid from the capillary into the tissue spaces. These support devices typically are prescribed for patients with conditions such as lymphatic or venous obstruction and are most efficient if applied before the tissue spaces have filled with fluid, such as in the morning, before the effects of gravity have caused fluid to move into the ankles.



■ **FIGURE 6-6** ■ 3+ pitting edema of the left foot. (Used with permission from Bates B. [1999]. *Bates' guide to physical examination and history taking* [7th ed., p. 472]. Philadelphia: Lippincott Williams & Wilkins)

Third-Space Accumulation

Third spacing represents the loss or trapping of ECF in the transcellular space. The serous cavities are part of the transcellular compartment (*i.e.*, third space) located in strategic body areas where there is continual movement of body structures—the pericardial sac, the peritoneal cavity, and the pleural cavity. The exchange of ECF among the capillaries, the interstitial spaces, and the transcellular space of the serous cavity uses the same mechanisms as capillaries elsewhere in the body. The serous cavities are closely linked with lymphatic drainage systems. The milking action of the moving structures, such as the lungs, continually forces fluid and plasma proteins back into the circulation, keeping these cavities empty. Any obstruction to lymph flow causes fluid accumulation in the serous cavities. As with edema fluid, third-space fluids represent an accumulation or trapping of body fluids that contribute to body weight but not to fluid reserve or function.

The prefix *hydro-* may be used to indicate the presence of excessive fluid, as in *hydrothorax*, which means excessive fluid in the pleural cavity. The accumulation of fluid in the peritoneal cavity is called *ascites*. The transudation of fluid into the serous cavities is also referred to as *effusion*. Effusion can contain blood, plasma proteins, inflammatory cells (*i.e.*, pus), and ECF.

In summary, body fluids are distributed between the ICF and ECF compartments of the body. Two thirds of body fluids are contained in the body cells of the ICF compartment, and one third is contained in the vascular compartment, interstitial spaces, and third-space areas of the ECF compartment. Electrolytes and nonelectrolytes move by diffusion across cell membranes that separate the ICF and ECF compartments. Water moves by osmosis across semipermeable membranes, moving from the side of the membrane that has the lesser number of particles and greater concentration of water to the side that has the greater number of particles and lesser concentration of water. The osmotic tension or effect that a solution exerts on cell volume in terms of causing the cell to swell or shrink is called *tonicity*.

Intracellular volume is regulated by the large numbers of proteins and other inorganic solutes that cannot cross the cell's membrane and solutes such as sodium, potassium, and glucose that selectively move between the ICF and ECF dependent upon concentration gradients and transport mechanisms. ECF volume, which is distributed between the vascular and interstitial compartments, is regulated by the elimination of sodium and water by the kidney.

Edema represents an increase in interstitial fluid volume. The physiologic mechanisms that predispose to edema formation are increased capillary filtration pressure, decreased capillary colloidal osmotic pressure, increased capillary permeability, and obstruction of lymphatic flow. The effect that edema exerts on body function is determined by its location; cerebral edema can be a life-threatening situation, but swollen feet can be a normal discomfort that accompanies hot weather. Fluid can also accumulate in the transcellular compartment—the joint spaces, pericardial sac, the peritoneal cavity, and the pleural cavity. Because this fluid is not easily exchanged with the rest of the ECF, it is often referred to as third-space fluid.

SODIUM AND WATER BALANCE

The movement of body fluids between the ICF and ECF compartments occurs at the cell membrane and depends on regulation of ECF water and sodium. Water provides approximately 90% to 93% of the volume of body fluids and sodium salts approximately 90% to 95% of the ECF solutes. Normally, equivalent changes in sodium and water are such that the volume and osmolality of the ECF is maintained within a normal range. Because it is the concentration of sodium (in milligrams per liter) that controls ECF osmolality, changes in sodium are usually accompanied by proportionate changes in water volume.

Alterations of sodium and water balance can be divided into two main categories: (1) isotonic contraction or expansion of ECF volume and (2) hypotonic dilution (hyponatremia) or hypertonic concentration (hypernatremia) of sodium brought about by changes in extracellular water (Fig. 6-7). Isotonic disorders usually are confined to the ECF compartment producing a contraction (fluid volume deficit) or expansion (fluid volume excess) of the interstitial and vascular fluids. Disorders of sodium concentration produce a change in the osmolality of the ECF with movement of water from the ECF compartment into the ICF compartment (hyponatremia) or from the ICF compartment into the ECF compartment (hypernatremia) (Fig. 6-8).

Regulation of Sodium and Water Balance

Regulation of Sodium Balance

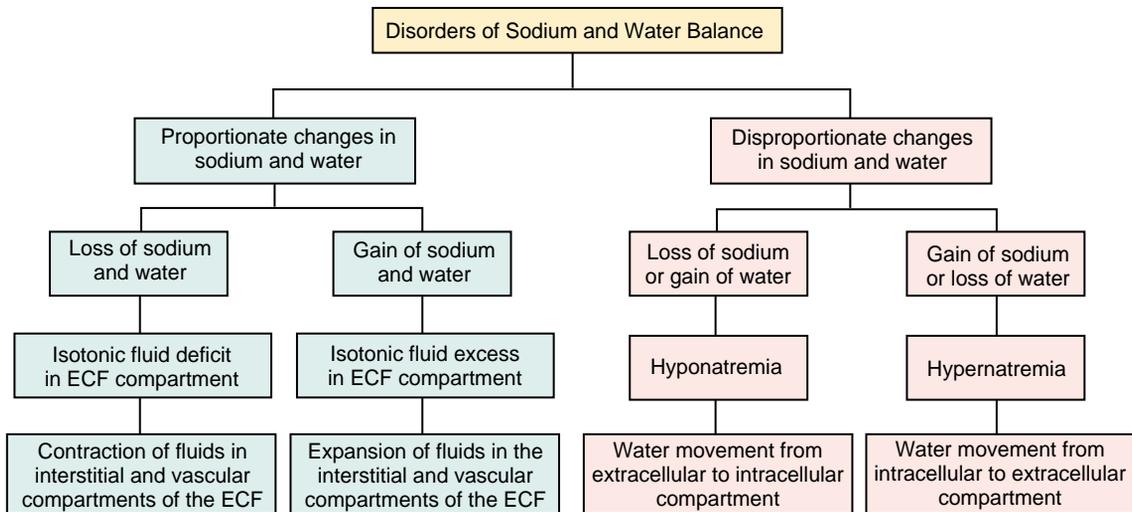
Sodium is the most abundant cation in the body, averaging approximately 60 mEq/kg of body weight.² Most of the body's sodium is in the ECF compartment (135 to 145 mEq/L), with only a small amount (10 to 14 mEq/L) located in the ICF compartment.

Sodium functions mainly in regulating extracellular fluid volume, including that in the vascular compartment. As the major cation in the ECF compartment, Na⁺ and its attendant anions (Cl⁻ and HCO₃⁻) account for most of the osmotic activity in the ECF. Because sodium is part of the sodium bicarbonate molecule, it is important in regulating acid-base balance. As a current-carrying ion, sodium contributes to the function of the nervous system and other excitable tissue.

Gains and Losses. Sodium normally enters the body through the gastrointestinal tract. Sodium intake normally is derived from dietary sources. Other sources of sodium are intravenous saline infusions and medications that contain sodium.

Sodium leaves the body through the kidney, gastrointestinal tract, and skin. Most sodium losses occur through the kidney. The kidneys are extremely efficient in regulating sodium output, and when sodium intake is limited or conservation of sodium is needed, the kidneys are able to reabsorb almost all the sodium that has been filtered by the glomerulus. This results in an essentially sodium-free urine. Conversely, urinary losses of sodium increase as intake increases.

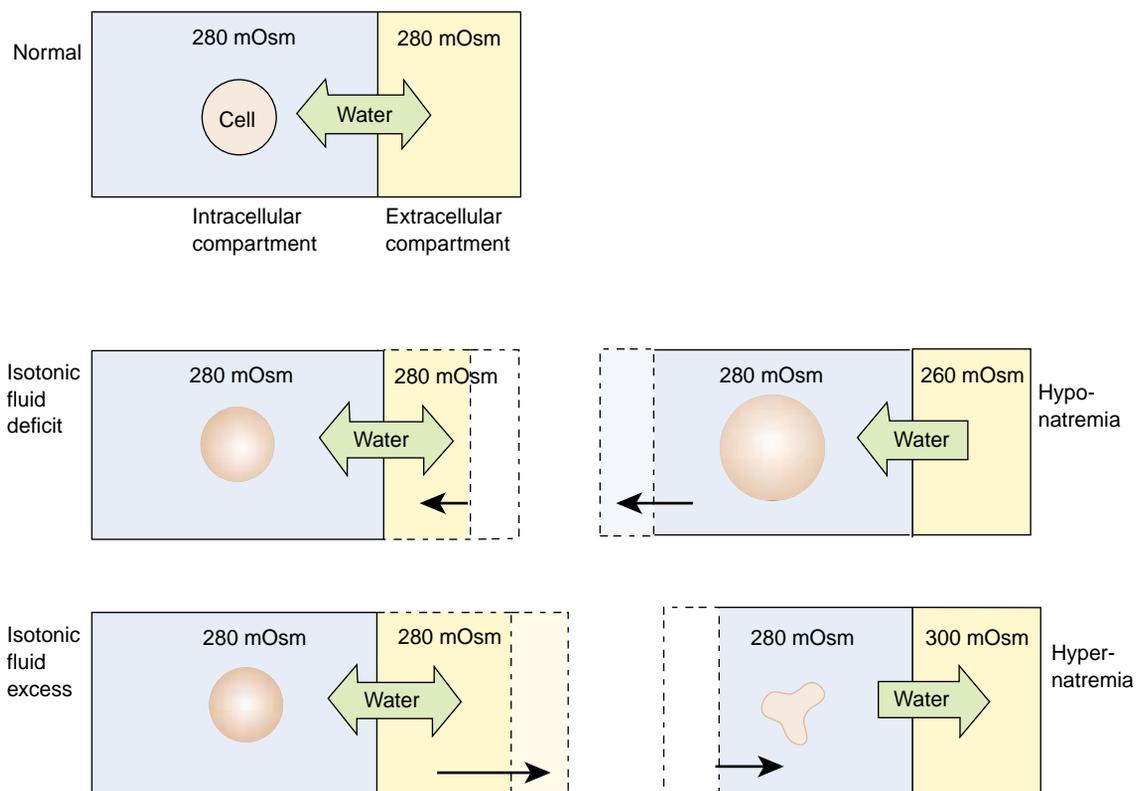
Usually less than 10% of sodium intake is lost through the gastrointestinal tract and skin. Sodium losses increase with conditions such as vomiting, diarrhea, fistula drainage, and



■ **FIGURE 6-7** ■ Effect of isotonic fluid volume deficit and excess and of hyponatremia and hypernatremia on ECF and ICF volume.

gastrointestinal suction that remove sodium from the upper gastrointestinal tract. Irrigation of gastrointestinal tubes with distilled water removes sodium from the gastrointestinal tract, as do repeated tap water enemas. Sweat losses, which usually are negligible, can increase greatly during exercise and periods of exposure to a hot environment. Loss of skin integrity, such as occurs in extensive burns, also leads to excessive skin losses of sodium.

Mechanisms of Sodium Regulation. The kidney is the main regulator of sodium. The kidney monitors arterial pressure and retains sodium when the arterial pressure is decreased and eliminates it when the arterial pressure is increased. The rate at which the kidney excretes or conserves sodium is coordinated by the sympathetic nervous system and the renin-angiotensin-aldosterone system. The sympathetic nervous system responds to changes in arterial pressure and blood volume by adjusting



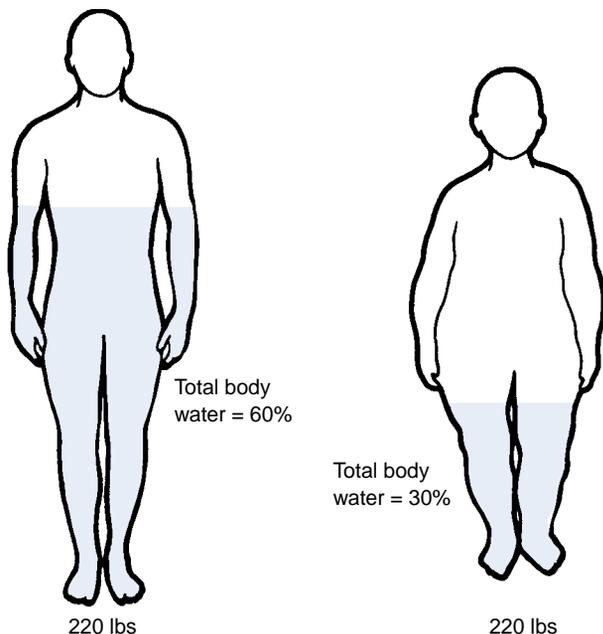
■ **FIGURE 6-8** ■ Effect of isotonic fluid volume excess and deficit and of hyponatremia and hypernatremia on extracellular and intracellular fluid volume.

the glomerular filtration rate and the rate at which sodium is filtered from the blood. Sympathetic activity also regulates tubular reabsorption of sodium and renin release. The renin-angiotensin-aldosterone system exerts its action through angiotensin II and aldosterone (see Chapter 16). Angiotensin II acts directly on the renal tubules to increase sodium reabsorption. It also acts to constrict renal blood vessels, thereby decreasing the glomerular filtration rate and slowing renal blood flow so that less sodium is filtered and more is reabsorbed. Angiotensin II is also a powerful regulator of aldosterone, a hormone secreted by the adrenal cortex. Aldosterone acts at the level of the cortical collecting tubules of the kidneys to increase sodium reabsorption while increasing potassium elimination.

Regulation of Water Balance

Total body water (TBW) varies with gender and weight. These differences can be explained by differences in body fat, which is essentially water free. In men, body water approximates 60% of body weight during young adulthood and decreases to approximately 50% in old age. In young women, it is approximately 50% and in elderly women, approximately 40%.³ Obesity produces further decreases in body water, sometimes reducing these levels to values as low as 30% to 40% of body weight in adults (Fig. 6-9).

Infants have a high TBW content. TBW constitutes approximately 75% to 80% of body weight in full-term infants and is even greater in premature infants. In addition to having proportionately more body water than adults, infants have relatively more water in their ECF compartment. Infants have more than half of their TBW in the ECF compartment, whereas adults have only approximately a third.⁴ The greater extracellular water content of an infant can be explained in terms of its higher metabolic rate, larger surface area in relation to its body mass, and its inability to concentrate its urine because of immature



■ **FIGURE 6-9** ■ Body composition of a lean and an obese individual. (Adapted with permission from Statland H. [1963]. *Fluids and electrolytes in practice*. [3rd ed.]. Philadelphia: J.B. Lippincott)

kidney structures. Because ECF is more easily lost from the body, infants are more vulnerable to fluid deficit than are older children and adults. As an infant grows older, TBW decreases, and by the second year of life, the percentages and distribution of body water approach those of an adult.⁵

Gains and Losses. Regardless of age, all healthy persons require approximately 100 mL of water per 100 calories metabolized for dissolving and eliminating metabolic wastes. This means that a person who expends 1800 calories for energy requires approximately 1800 mL of water for metabolic purposes. The metabolic rate increases with fever; it rises approximately 12% for every 1°C (7% for every 1°F) increase in body temperature.² Fever also increases the respiratory rate, resulting in additional loss of water vapor through the lungs.

The main source of water gain is through oral intake and metabolism of nutrients. Water, including that obtained from liquids and solid foods, is absorbed from the gastrointestinal tract. Metabolic processes also generate a small amount of water. The amount of water gained from these processes varies from 150 to 300 mL/day, depending on metabolic rate.

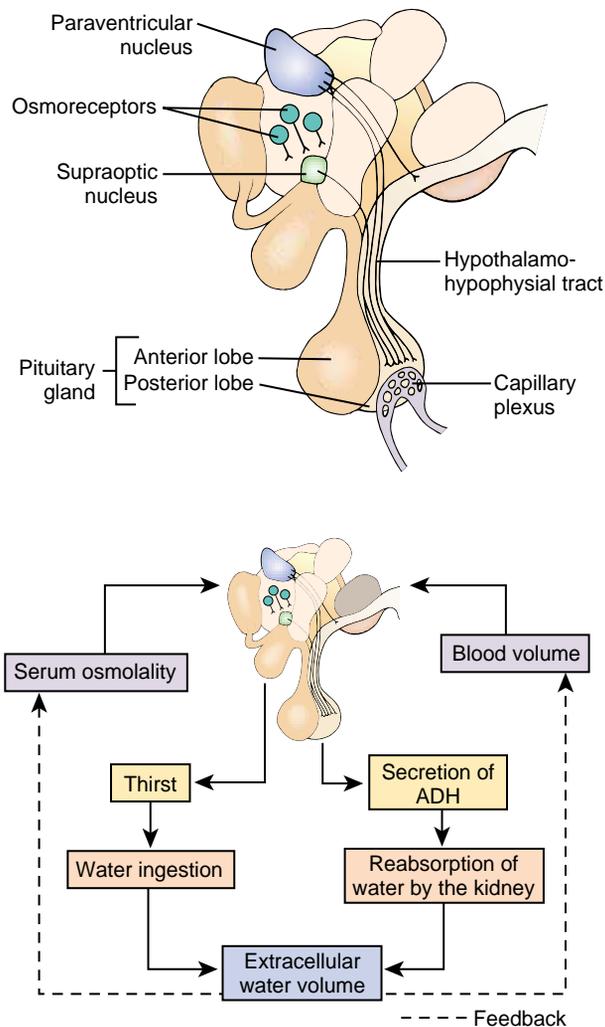
Normally, the largest loss of water occurs through the kidneys, with lesser amounts being lost through the skin, lungs, and gastrointestinal tract. Even when oral or parenteral fluids are withheld, the kidneys continue to produce urine as a means of ridding the body of metabolic wastes. The urine output that is required to eliminate these wastes is called the *obligatory urine output*. The obligatory urine loss is approximately 300 to 500 mL/day. Water losses that occur through the skin and lungs are referred to as *insensible water losses* because they occur without a person's awareness. The gains and losses of body water are summarized in Table 6-2.

Mechanisms of Regulation. There are two main physiologic mechanisms that assist in regulating body water: thirst and antidiuretic hormone (ADH). Thirst is primarily a regulator of water intake and ADH a regulator of water output. Both mechanisms respond to changes in extracellular osmolality and volume (Fig. 6-10).

Thirst. Thirst is controlled by the thirst center in the hypothalamus. There are two stimuli for true thirst based on water need: (1) cellular dehydration caused by an increase in extracellular osmolality and (2) a decrease in blood volume, which may or may not be associated with a decrease in serum osmolality. Sensory neurons, called *osmoreceptors*, which are located in or

TABLE 6-2 Sources of Body Water Gains and Losses in the Adult

Gains		Losses	
Oral intake		Urine	1500 mL
As water	1000 mL	Insensible losses	
In food	1300 mL	Lungs	300 mL
Water of oxidation	200 mL	Skin	500 mL
		Feces	200 mL
Total	2500 mL	Total	2500 mL



■ **FIGURE 6-10** ■ (Top) sagittal section through the pituitary and anterior hypothalamus. Antidiuretic hormone (ADH) is formed primarily in the supraoptic nucleus and to a lesser extent in the paraventricular nucleus of the hypothalamus. It is then transported down the hypothalamohypophysial tract and stored in secretory granules in the posterior pituitary, where it can be released into the blood. (Bottom) pathways for regulation of extracellular water volume by thirst and antidiuretic hormone.

near the thirst center in the hypothalamus, respond to changes in extracellular osmolality by stimulating the sensation of thirst (Fig. 6-10). Thirst normally develops when there is as little as a 1% to 2% change in serum osmolality.⁶ Stretch receptors in the vascular system that are sensitive to changes in arterial blood pressure and central blood volume also aid in the regulation of thirst. A third important stimulus for thirst is angiotensin II, which becomes increased in response to low blood volume and low blood pressure.

Dryness of the mouth produces a sensation of thirst that is not necessarily associated with the body's hydration status. Thirst sensation also occurs in those who breathe through their mouths, such as smokers and persons with chronic respiratory disease or hyperventilation syndrome.

Hypodipsia represents a decrease in the ability to sense thirst. There is evidence that thirst is decreased and water in-

take reduced in elderly persons, despite higher serum sodium and osmolality levels.^{7,8} The inability to perceive and respond to thirst is compounded in elderly persons who have had a stroke and may be further influenced by confusion and sensory disturbances.

Polydipsia, or excessive thirst, can be classified into three categories: (1) symptomatic or true thirst, (2) inappropriate or false thirst that occurs despite normal levels of body water and serum osmolality, and (3) compulsive water drinking. *Symptomatic thirst* develops when there is a loss of body water and resolves after the loss has been replaced. Among the most common causes of symptomatic thirst are water losses associated with diarrhea, vomiting, diabetes mellitus, and diabetes insipidus. *Inappropriate* or *excessive thirst* may persist despite adequate hydration. It is a common complaint in persons with renal failure and congestive heart failure. Although the cause of thirst in these persons is unclear, it may result from increased angiotensin levels. Thirst is also a common complaint in persons with dry mouth caused by decreased salivary function or treatment with drugs with an anticholinergic action (e.g., antihistamines, atropine) that lead to decreased salivary flow.

Psychogenic polydipsia involves compulsive water drinking and is usually seen in persons with psychiatric disorders, most commonly schizophrenia. Persons with the disorder drink large amounts of water and excrete large amounts of urine. The cause of excessive water drinking in these persons is uncertain. It has been suggested that the compulsive water drinking may share the same pathology as the psychosis because persons with the disorder often increase their water drinking during periods of exacerbation of their psychotic symptoms.⁹ The condition may be compounded by antipsychotic medications that increase ADH levels and interfere with water excretion by the kidneys. Cigarette smoking, which is common among persons with psychiatric disorders, also stimulates ADH secretion. Excessive water ingestion coupled with impaired water excretion (or rapid ingestion at a rate that exceeds renal excretion) in persons with psychogenic polydipsia can lead to water intoxication (see Hyponatremia). Treatment consists of water restriction and behavioral measures aimed at decreasing water consumption.¹⁰

Antidiuretic Hormone. The reabsorption of water by the kidneys is regulated by ADH, also known as vasopressin. ADH is synthesized by cells in the supraoptic and paraventricular nuclei of the hypothalamus; transported along a neural pathway (i.e., hypothalamohypophysial tract) to the neurohypophysis (i.e., posterior pituitary); and then released into the circulation (see Fig. 6-10).¹¹

As with thirst, ADH levels are controlled by extracellular volume and osmolality. Osmoreceptors in the hypothalamus sense changes in extracellular osmolality and stimulate the production and release of ADH. A small increase in serum osmolality of 1% is sufficient to cause ADH release. Likewise, stretch receptors (baroreceptors) that are sensitive to changes in blood pressure and central blood volume aid in the regulation of ADH release. A blood volume decrease of 5% to 10% produces a maximal increase in ADH levels.¹² As with many other homeostatic mechanisms, acute conditions produce greater changes in ADH levels than do chronic conditions; long-term changes in blood volume or blood pressure may exist without affecting ADH levels.

An abnormal increase in ADH synthesis and release occurs in a number of stress situations. Severe pain, nausea, trauma, surgery, certain anesthetic agents, and some narcotics (e.g., morphine and meperidine) increase ADH levels. Nausea is a potent stimulus of ADH secretion; it can increase ADH levels 10 to 1000 times those required for maximal diuresis.¹³ Among the drugs that affect ADH are nicotine, which stimulates its release, and alcohol, which inhibits it. Two important conditions alter ADH levels: diabetes insipidus and inappropriate secretion of ADH.

Diabetes insipidus (DI) is caused by a deficiency of or a decreased response to ADH. Persons with DI are unable to concentrate their urine during periods of water restriction; they excrete large volumes of urine, usually 3 to 20 L/day, depending on the degree of ADH deficiency or renal insensitivity to ADH. This large urine output is accompanied by excessive thirst. As long as the thirst mechanism is normal and fluid is readily available, there is little or no alteration in the fluid levels of persons with DI. The danger arises when the condition develops in someone who is unable to communicate the need for water or is unable to secure the needed water. In such cases, inadequate fluid intake rapidly leads to hypertonic dehydration and increased serum osmolality.

There are two types of DI: central or neurogenic and nephrogenic DI. Neurogenic DI occurs because of a defect in the synthesis or release of ADH and nephrogenic DI occurs because the kidneys do not respond to ADH.¹⁴ In neurogenic DI, loss of 75% to 80% of ADH-secretory neurons is necessary before polyuria becomes evident. Most persons with neurogenic DI have an incomplete form of the disorder and retain some ability to concentrate their urine. Temporary neurogenic DI may follow head injury or surgery near the hypophysial tract. Nephrogenic DI is characterized by impairment of the urine-concentrating ability of the kidney and free-water conservation. It may occur as a genetic trait that affects the ADH receptors in the kidney, as a side effect of drugs such as lithium,¹⁵ or as the result of electrolyte disorders such as potassium depletion or chronic hypercalcemia.

The *syndrome of inappropriate ADH* (SIADH) results from a failure of the negative feedback system that regulates the release and inhibition of ADH.¹⁶ In persons with this syndrome, ADH secretion continues even when serum osmolality is decreased, causing marked water retention and dilutional hyponatremia.

SIADH may occur as a transient condition, such as in a stress situation, or as a chronic condition, resulting from disorders such as a lung tumor. Stimuli, such as surgery, pain, stress, and temperature changes, are capable of stimulating ADH release through the central nervous system (CNS). Drugs induce SIADH in different ways; some drugs are thought to increase hypothalamic production and release of ADH, and others are believed to act directly on the renal tubules to enhance the action of ADH. More chronic forms of SIADH may be the result of lung tumors, chest lesions, and CNS disorders. Tumors, particularly bronchogenic carcinoma and cancers of the lymphoid tissues, prostate, and pancreas, are known to produce and release ADH independent of normal hypothalamic control mechanisms. Other intrathoracic conditions, such as advanced tuberculosis, severe pneumonia, and positive-pressure breathing, can also cause SIADH. The suggested mechanism for SIADH in positive-pressure ventilation is activation of baroreceptors (e.g., aortic baroreceptors, cardiopulmonary recep-

tors) that respond to marked changes in intrathoracic pressure. Human immunodeficiency virus (HIV) infection is emerging as a new cause of SIADH. It has been reported that as many as 35% of persons with acquired immunodeficiency syndrome (AIDS) who are admitted to the acute care setting will have SIADH related to *Pneumocystis carinii* pneumonia, central nervous system infections, or malignancies.¹⁷

The manifestations of SIADH are those of dilutional hyponatremia. Urine output decreases despite adequate or increased fluid intake. Urine osmolality is high, and serum osmolality is low. Hematocrit and the serum sodium and BUN levels are all decreased because of the expansion of the ECF volume. The severity of symptoms usually is proportional to the extent of sodium depletion and water intoxication.

Alterations in Isotonic Fluid Volume

Isotonic fluid volume disorders represent an expansion or contraction of the ECF brought about by proportionate changes in both sodium and water.

Isotonic Fluid Volume Deficit

Fluid volume deficit is characterized by a decrease in ECF, including circulating blood volume. The term *isotonic fluid volume deficit* is used to differentiate fluid deficit in which there are proportionate losses in sodium and water from water deficit and the hyperosmolar state associated with hypernatremia. Unless other fluid and electrolyte imbalances are present, the concentration of serum electrolytes remains essentially unchanged. When the effective circulating blood volume is compromised, the condition is often referred to as *hypovolemia*.

Causes. Isotonic fluid volume deficit results when water and electrolytes are lost in isotonic proportions. It is almost always caused by a loss of body fluids and is often accompanied by a

KEY CONCEPTS

SODIUM AND WATER BALANCE

- It is the amount of water and its effect on sodium concentration in the ECF that serves to regulate the distribution of fluid between the ICF and the ECF compartments.
- Isotonic changes in body fluids that result from proportionate gains or losses of sodium and water are largely confined to the ECF compartment. Many of the manifestations of isotonic fluid deficit or excess reflect changes in vascular and interstitial fluid volume.
- Hyponatremia or hypernatremia brought about by disproportionate losses or gains in sodium or water exert their effects on the ICF compartment, causing water to move in or out of body cells. Many of the manifestations of changes in sodium concentration reflect changes in the intracellular volume of cells, particularly those in the nervous system.

decrease in fluid intake. It can occur because of a loss of gastrointestinal fluids, polyuria, or sweating caused by fever and exercise. Third-space losses cause sequestering of ECF in the serous cavities, extracellular spaces in injured tissues, or lumen of the gut.

In a single day, 8 to 10 L of ECF is secreted into the gastrointestinal tract. Most of it is reabsorbed in the ileum and proximal colon, and only about 150 to 200 mL per day is eliminated in the feces. Vomiting and diarrhea interrupt the reabsorption process and, in some situations, lead to increased secretion of fluid into the intestinal tract. Gastrointestinal suction, fistulas, and drainage tubes can remove large amounts of fluid from the gastrointestinal tract.

Excess sodium and water losses can also occur through the kidney. Certain forms of kidney disease are characterized by salt wasting caused by impaired sodium reabsorption. Fluid volume deficit also can result from osmotic diuresis or injudicious use of diuretic therapy. Glucose in the urine filtrate prevents reabsorption of water by the renal tubules, causing a loss of sodium and water. In Addison's disease, a condition of chronic adrenocortical insufficiency, there is unregulated loss of sodium in the urine with a resultant loss of ECF volume (see Chapter 31).

The skin acts as an exchange surface for heat and as a vapor barrier to prevent water from leaving the body. Body surface losses of sodium and water increase when there is excessive sweating or when large areas of skin have been damaged. Hot weather and fever increase sweating. The respiratory rate and sweating usually are increased as body temperature rises. Burns are another cause of excess fluid loss.

Manifestations. The manifestations of fluid volume deficit reflect a decrease in ECF volume. They include thirst, signs of water conservation by the kidney, loss of body weight, im-

paired temperature regulation, and signs of reduced interstitial and vascular volume (Table 6-3).

Thirst is a common symptom of fluid deficit, although it is not always present during early stages of isotonic fluid deficit. It develops as the effective circulating volume decreases to a point sufficient to stimulate the thirst mechanism. Urine output decreases and urine osmolality and specific gravity increase as ADH levels rise because of a decrease in vascular volume. Although there is an isotonic loss of sodium and water from the vascular compartment, other substances such as hematocrit and BUN become more concentrated.

A loss in fluid volume is accompanied by a decrease in body weight. One liter of water weighs 1 kg (2.2 lb). A mild ECF deficit exists when weight loss equals 2% of body weight.⁵ In a person who weighs 68 kg (150 lb.), this percentage of weight loss equals 1.4 L of water. A moderate deficit equates to a 5% loss in weight and a severe deficit to an 8% or greater loss in weight.⁵ To be accurate, weight must be measured at the same time each day with the person wearing the same amount of clothing. Because the fluid is trapped within the body in persons with third-space losses, their body weight may not decrease.

The fluid content of body tissues decreases as fluid is removed from the interstitial spaces. The eyes assume a sunken appearance and feel softer than normal as the fluid content in the anterior chamber of the eye is decreased. Fluids add resiliency to the skin and underlying tissues that is referred to as *skin* or *tissue turgor*.⁵ Pinching a fold of skin between the thumb and forefinger provides a means for assessing tissue turgor. The skin should immediately return to its original configuration when the fingers are released. A loss of 3% to 5% of body water in children causes the resiliency of the skin to be lost. Decreased tissue turgor is less predictive of fluid deficit in older persons (>65 years) because of the loss of tissue elasticity. In

TABLE 6-3 Manifestations of Isotonic Fluid Volume Deficit and Excess

Fluid Volume Deficit	Fluid Volume Excess
<p>Acute Weight Loss (% body weight) Mild fluid volume deficit: 2% Moderate fluid volume deficit: 5% Severe fluid volume deficit: >8%</p> <p>Signs of Compensatory Mechanisms Increased thirst Increased ADH: oliguria and high urine-specific gravity</p> <p>Decreased Interstitial Fluid Volume Decreased skin and tissue turgor Dry mucous membranes Sunken and soft eyeballs Depressed fontanel in infants</p> <p>Decreased Vascular Volume Postural hypotension Weak rapid pulse Decreased vein filling Hypotension and shock (severe deficit)</p>	<p>Acute Weight Gain (% body weight) Mild fluid volume excess: 2% Moderate fluid volume excess: 5% Severe fluid volume excess: >8%</p> <p>Increased Interstitial Fluid Volume Dependent and generalized edema</p> <p>Increased Vascular Volume Full and bounding pulse Venous distention Pulmonary edema (severe excess) Shortness of breath Crackle Dyspnea Cough</p>

infants fluid deficit may be evidenced by depression of the anterior fontanel because of a decrease in cerebrospinal fluid.

Arterial and venous volumes decline during periods of fluid deficit, as does filling of the capillary circulation. As the volume in the arterial system declines, the blood pressure decreases, the heart rate increases, and the pulse becomes weak and thready. Postural hypotension (a drop in blood pressure upon standing) is an early sign of fluid deficit. On the venous side of the circulation, the veins become less prominent, and venous refill time increases. Body temperature may be subnormal because of decreased metabolism.⁵ When volume depletion becomes severe, signs of hypovolemic shock and vascular collapse appear (see Chapter 18).

Diagnosis and Treatment. Treatment of fluid volume deficit consists of fluid replacement and measures to correct the underlying cause. Usually, isotonic electrolyte solutions are used for fluid replacement. Acute hypovolemia and hypovolemic shock can cause renal damage; therefore, prompt assessment of the degree of fluid deficit and adequate measures to resolve the deficit and treat the underlying cause are essential.

Isotonic Fluid Volume Excess

Fluid volume excess represents an isotonic expansion of the ECF compartment with increases in both interstitial and vascular volumes. Although increased fluid volume is usually the result of a disease condition, this is not always true. For example, a compensatory isotonic expansion of body fluids can occur in healthy persons during hot weather as a mechanism for increasing body heat loss.

Causes. Isotonic fluid volume excess almost always results from an increase in total body sodium that is accompanied by a proportionate increase in body water. Although it can occur as the result of excessive sodium intake, it is most commonly caused by a decrease in sodium and water elimination by the kidney. Among the causes of decreased sodium and water elimination are disorders of renal function, heart failure, liver failure, and corticosteroid excess.

Heart failure produces a decrease in renal blood flow and a compensatory increase in sodium and water retention (Chapter 18). Persons with severe congestive heart failure maintain a precarious balance between sodium and water intake and output. Even small increases in sodium intake can precipitate a state of fluid volume excess and a worsening of heart failure. Liver failure impairs aldosterone metabolism and alters renal perfusion, leading to increased salt and water retention. Corticosteroid hormones increase sodium reabsorption by the kidney. Persons taking corticosteroid medications and those with Cushing's syndrome (see Chapter 31) often have problems with sodium retention.

Manifestations. Isotonic fluid volume excess is characterized by an increase in interstitial and vascular fluids. It is manifested by weight gain over a short period of time. A mild fluid volume excess represents a 2% weight gain; moderate fluid volume excess, a 5% weight gain; and severe fluid volume excess, a weight gain of 8% or more (Table 6-3).⁵ The presence of edema is characteristic of isotonic fluid volume excess. When the excess fluid accumulates gradually, as often happens in debilitating diseases and starvation, edema fluid may mask the loss of tissue

mass. As the vascular volume increases, the neck veins become distended, the pulse becomes full and bounding, and the central venous pressure becomes elevated. The BUN and hematocrit may be decreased as a result of the expanded plasma volume. When excess fluid accumulates in the lungs (*i.e.*, pulmonary edema), there is shortness of breath, complaints of difficult breathing, respiratory crackles, and a productive cough (see Chapter 18). Ascites and pleural effusion may occur with severe fluid volume excess.

Diagnosis and Treatment. The treatment of fluid volume excess focuses on providing a more favorable balance between sodium intake and output. A sodium-restricted diet is often prescribed. Diuretic therapy may be used to increase sodium elimination.

Alterations in Sodium Concentration

The normal serum sodium ranges from 135 to 145 mEq/L (135 to 145 mmol/L). Serum sodium values, expressed in mEq/L, reflect the concentration or dilution of sodium by water, rather than its absolute value. Because sodium and its attendant anions account for 90% to 95% of the osmolality of the ECF (normal range, 275 to 295 mOsm/kg), changes in serum sodium generally are accompanied by changes in serum osmolality.

Hyponatremia

Hyponatremia represents a serum sodium concentration below 135 mEq/L (135 mmol/L). Because of the effects of other osmotically active particles in the ECF, such as glucose, hyponatremia may be associated with high or low tonicity.¹⁷⁻¹⁹

Hypertonic (translocational) hyponatremia results from an osmotic shift of water from ICF to the ECF, such as occurs with hyperglycemia. In this case, the sodium in the ECF becomes diluted as water moves out of cells in response to the osmotic effects of the elevated blood glucose level.

Hypotonic (dilutional) is by far the most common form of hyponatremia. It is caused by water retention and characterized by a decrease in serum osmolality. Dilutional hyponatremia can present as a hypervolemic, euvolemic, or hypovolemic condition. Hypervolemic hyponatremia involves an increase in ECF volume and is seen when hyponatremic conditions are accompanied by edema-forming disorders such as congestive heart failure, cirrhosis, and advanced kidney disease.

Euvolemic hyponatremia represents a retention of water with dilution of sodium while maintaining the ECF volume within a normal range. It is usually the result of inappropriate thirst or SIADH. Hypovolemic hyponatremia occurs when water is lost along with sodium but to a lesser extent. It occurs with diuretic use, excessive sweating in hot weather, and vomiting and diarrhea.

Causes. The most common causes of acute dilutional hyponatremia in adults are drug therapy (diuretics and drugs that increase ADH levels), inappropriate fluid replacement during heat exposure or after heavy exercise, SIADH, and polydipsia in persons with psychotic disorder.

Among the causes of hypovolemic hyponatremia are excessive sweating in hot weather, particularly during heavy exercise, which leads to loss of salt and water; hyponatremia develops

when water, rather than electrolyte-containing liquids, is used to replace fluids lost in sweating. Another potential cause of hypovolemic hyponatremia is the loss of sodium from the gastrointestinal tract caused by repeated tap water enemas or frequent gastrointestinal irrigations with distilled water. Iso-osmotic fluid loss, such as occurs in vomiting or diarrhea, does not usually lower serum sodium levels unless these losses are replaced with disproportionate amounts of orally ingested or parenterally administered water. Gastrointestinal fluid loss and ingestion of excessively diluted formula are common causes of acute hyponatremia in infants and children.

Hypovolemic hyponatremia is a common complication of adrenal insufficiency and is attributable to the effects of aldosterone and cortisol deficiency (see Chapter 31). A lack of aldosterone increases renal losses of sodium, and a cortisol deficiency leads to increased release of ADH with water retention.

The risk of euvolemic hyponatremia is increased during the postoperative period. During this time ADH levels are often high, producing an increase in water reabsorption by the kidney (see SIADH). Although these elevated levels usually resolve in about 72 hours, they can persist for as long as 5 days. The hyponatremia becomes exaggerated when electrolyte-free fluids (*e.g.*, 5% glucose in water) are used for fluid replacement.

Manifestations. The manifestations of hyponatremia will vary dependent upon the serum osmolality, the ECF fluid volume status, the rapidity of onset, and the severity of the sodium dilution (Table 6-4). The signs and symptoms may be acute, as in severe water intoxication, or more insidious in onset and less severe, as in chronic hyponatremia. Because of water movement, hypotonic hyponatremia causes intracellular hypo-osmolality, which is responsible for many of the clinical manifestations of the disorder.¹⁹ Fingerprint edema is a sign of excess intracellular water. This phenomenon is demonstrated by pressing the finger firmly over the bony surface of the sternum for 15 to 30 seconds. When excess intracellular water is present, a fingerprint similar to that observed when pressing on a piece of modeling clay is seen.

Muscle cramps, weakness, and fatigue reflect the hypo-osmolality of skeletal muscle cells and are often early signs of hyponatremia. These effects commonly are observed in persons with hyponatremia that occurs during heavy exercise in hot weather. Gastrointestinal manifestations such as nausea and vomiting, abdominal cramps, and diarrhea may develop.

The brain and nervous system are the most seriously affected by pronounced increases in intracellular water. Symptoms include apathy, lethargy, and headache, which can progress to disorientation, confusion, gross motor weakness, depression of

TABLE 6-4 Manifestations of Hyponatremia and Hypernatremia

Hyponatremia (Hypotonic)	Hypernatremia
<p>Laboratory Values</p> <p>Serum sodium <135 mEq/L</p> <p>Decreased serum osmolality</p> <p>Dilutional decrease in blood components, including hematocrit, blood urea nitrogen</p>	<p>Laboratory Values</p> <p>Serum sodium >145 mEq/L</p> <p>Increased serum osmolality</p> <p>Increase in blood components, including hematocrit, blood urea nitrogen</p>
<p>Increased Intracellular Fluid</p> <p>Fingerprint edema</p>	<p>Compensatory Mechanisms</p> <p>Increased thirst</p> <p>Increased ADH with oliguria and high urine-specific gravity</p>
<p>Hypo-osmolality and Movement of Water Into Muscle, Neural, and Gastrointestinal Tract Tissue</p> <p><i>Muscle</i></p> <p>Muscle cramps and weakness</p> <p><i>Central Nervous System</i></p> <p>Headache</p> <p>Apprehension, feeling of impending doom</p> <p>Personality changes</p> <p>Lethargy</p> <p>Stupor and coma (severe)</p> <p><i>Gastrointestinal Tract</i></p> <p>Anorexia, nausea, vomiting</p> <p>Abdominal cramps, diarrhea</p>	<p>Decreased Intracellular Fluid</p> <p>Dry skin and mucous membranes</p> <p>Decreased tissue turgor</p> <p>Decreased salivation and lacrimation</p>
	<p>Hyperosmolality and Movement of Water Out of Neural Tissue</p> <p>Headache</p> <p>Disorientation and agitation</p> <p>Decreased reflexes</p> <p>Seizures and coma (severe)</p>
	<p>Decreased Vascular Volume</p> <p>Weak rapid pulse</p> <p>Possible impaired temperature regulation with fever</p> <p>Decreased blood pressure</p> <p>Vascular collapse (severe)</p>

deep tendon reflexes. Seizures and coma occur when serum sodium levels reach extremely low levels. These severe effects, which are caused by brain swelling, may be irreversible.¹⁹ If the condition develops slowly, signs and symptoms do not develop until serum sodium levels approach 125 mEq/L. The term “water intoxication” is often used to describe the neurologic effects of acute hyponatremia.

Treatment. The treatment of hyponatremia with water excess focuses on the underlying cause. When hyponatremia is caused by water intoxication, limiting water intake or discontinuing medications that contribute to SIADH may be sufficient. The administration of saline solution orally or intravenously may be needed in severe hyponatremia caused by sodium deficiency.

Hypertatremia

Hypertatremia implies a serum sodium level above 145 mEq/L and a serum osmolality greater than 295 mOsm/kg. Because sodium is functionally an impermeable solute, it contributes to the tonicity and movement of water across cell membranes. Hypertatremia is characterized by hypertonicity of the ECF and almost always causes cellular dehydration.²⁰

Causes. Hypertatremia represents a deficit of water in relation to the body’s sodium levels. It can be caused by net gain of sodium or net loss of water. Rapid ingestion or infusion of sodium with insufficient time or opportunity for water ingestion can produce a disproportionate gain in sodium. A defect in thirst or inability to obtain or drink water can interfere with water replacement.

Hypertatremia also occurs when there is an excess loss of body fluids that have a lower than normal concentration of sodium so that water is lost in excess of sodium. This can result from increased losses from the respiratory tract during fever or strenuous exercise, from watery diarrhea, or when osmotically active tube feedings are given with inadequate amounts of water. With pure water loss, each body fluid compartment loses an equal percentage of its volume. Because approximately one third of the water is in the ECF compartment, compared with the two thirds in the ICF compartment, more actual water volume is lost from the ICF than the ECF compartment.⁵

Normally, water deficit stimulates thirst and increases water intake. Therefore, hypertatremia is more likely to occur in infants and in persons who cannot express their thirst or obtain water to drink. With hypodipsia, or impaired thirst, the need for fluid intake does not activate the thirst response. Hypodipsia is particularly prevalent among the elderly. In persons with diabetes insipidus, hypertatremia can develop when thirst is impaired or access to water is impeded.

Manifestations. The clinical manifestations of hypertatremia caused by water loss are largely those of ECF fluid loss and cellular dehydration (Table 6-4). The severity of signs and symptoms is greatest when the increase in serum sodium is large and occurs rapidly. Body weight is decreased in proportion to the amount of water that has been lost. Because blood plasma is roughly 90% to 93% water, the concentrations of blood cells, hematocrit, BUN, and other solutes increase as ECF water decreases.

Thirst is an early symptom of water deficit, occurring when water losses are equal to 0.5% of body water. Urine output is decreased and urine osmolality increased because of renal water-conserving mechanisms. Body temperature frequently is elevated, and the skin becomes warm and flushed. As the vascular volume decreases, the pulse becomes rapid and thready, and the blood pressure drops. Hypertatremia produces an increase in serum osmolality and results in water being pulled out of body cells. As a result, the skin and mucous membranes become dry, and salivation and tearing of the eyes are decreased. The mouth becomes dry and sticky, and the tongue becomes rough and fissured. Swallowing is difficult. The subcutaneous tissues assume a firm, rubbery texture. Most significantly, water is pulled out of the cells in the CNS, causing decreased reflexes, agitation, headache, and restlessness. Coma and seizures may develop as hypertatremia progresses.

Treatment. The treatment of hypertatremia includes measures to treat the underlying cause of the disorder and fluid replacement therapy to treat the accompanying dehydration. Replacement fluids can be given orally or intravenously. The oral route is preferable. Oral glucose–electrolyte replacement solutions are available for the treatment of infants with diarrhea.²¹ Until recently, these solutions were used only early in diarrheal illness or as a first step in re-establishing oral intake after parenteral replacement therapy. These solutions are now widely available in grocery stores and pharmacies for use in the treatment of diarrhea and other dehydrating disorders in infants and young children.

In summary, body fluids are distributed between the ICF and ECF compartments. Regulation of fluid volume, solute concentration, and distribution between the two compartments depends on water and sodium balance. Water provides approximately 90% to 93% of fluid volume and sodium salts, approximately 90% to 95% of extracellular solutes. Body water is regulated by thirst, which controls water intake, and ADH, which controls urine concentration and renal output. Sodium is ingested in the diet and eliminated by the kidneys under the influence of the sympathetic nervous system and the renin-angiotensin-aldosterone system.

Isotonic fluid disorders result from contraction or expansion of ECF volume brought about by proportionate losses of sodium and water. *Isotonic fluid volume deficit* is characterized by a decrease in ECF volume. It causes thirst, decreased vascular volume and circulatory function, decreased urine output, and increased urine specific gravity. *Isotonic fluid volume excess* is characterized by an increase in ECF volume. It is manifested by signs of increased vascular volume and edema.

Alterations in extracellular sodium concentration are brought about by a disproportionate gain (hyponatremia) or loss (hypertatremia) of water. As the major cation in the ECF compartment, sodium controls the ECF osmolality and its effect on cell volume. Hypotonic hyponatremia is characterized by water being pulled into the cell from the extracellular compartment, causing cells to swell. It is manifested by muscle cramps and weakness; nausea, vomiting, abdominal cramps, and diarrhea; and CNS signs such as lethargy, headache, depression of deep tendon reflexes, and in severe cases seizure

and coma. Hyponatremia is characterized by intracellular water being pulled into the extracellular compartment, causing cells to shrink. It is manifested by thirst and decreased urine output; dry mouth and decreased tissue turgor; signs of decreased vascular volume (tachycardia, weak and thready pulse); and CNS signs, such as decreased reflexes, agitation, headache, and in severe cases seizures and coma.

POTASSIUM BALANCE

Potassium is the second most abundant cation in the body and the major cation in the ICF compartment. Approximately 98% of body potassium is contained within body cells, with an intracellular concentration of 140 to 150 mEq/L.²² The potassium content of ECF (3.5 to 5.0 mEq/L) is considerably less. Because potassium is an intracellular ion, total body stores of potassium are related to body size and muscle mass. Approximately 65% to 75% of potassium is in muscle.²³ Thus, total body potassium declines with age, mainly as a result of a decrease in muscle mass.

As the major intracellular cation, potassium is critical to many body functions. It is involved in a wide range of body functions, including the maintenance of the osmotic integrity of cells, acid-base balance, and the kidney's ability to concentrate urine. Potassium is necessary for growth, and it contributes to the intricate chemical reactions that transform carbohydrates into energy, change glucose into glycogen, and convert amino acids to proteins.

Potassium also plays a critical role in conducting nerve impulses and the excitability of skeletal, cardiac, and smooth muscle (see Chapter 1). It does this by regulating: (1) the rest-

ing membrane potential, (2) the opening of the sodium channels that control the flow of current during the action potential, and (3) the rate of repolarization. Changes in nerve and muscle excitability are particularly important in the heart, where alterations in serum potassium can produce serious dysrhythmias and conduction defects. Changes in serum potassium also affect skeletal muscles and the smooth muscle in blood vessels and the gastrointestinal tract.

The *resting membrane potential* is determined by the ratio of intracellular to extracellular potassium. A decrease in serum potassium causes the resting membrane potential to become more negative (hyperpolarization), moving further from the threshold for excitation (Fig. 6-11). Thus, it takes a greater stimulus to reach threshold and open the sodium channels that are responsible for the action potential. An increase in serum potassium has the opposite effect; it causes the resting membrane potential to become more positive (hypopolarized), moving closer to threshold. This produces an initial increase in excitability. Activation and opening of the sodium channels that control the flow of current during an action potential are also affected by potassium levels. With severe hyperkalemia, the sodium channels become inactivated, producing a net decrease in excitability. The *rate of repolarization* also varies with serum potassium levels.¹¹ It is more rapid in hyperkalemia and delayed in hypokalemia. The rate of repolarization is important clinically because it predisposes to conduction defects and dysrhythmias in the heart.

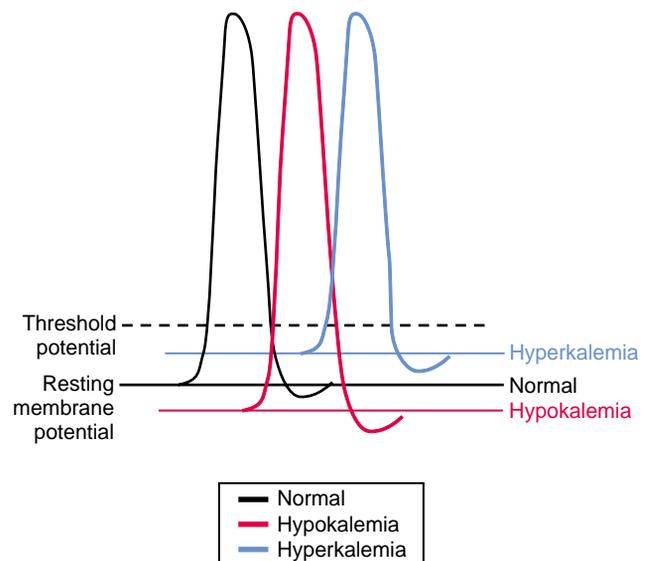
Regulation of Potassium Balance

Potassium intake is normally derived from dietary sources. In healthy persons, potassium balance usually can be maintained by a daily dietary intake of 50 to 100 mEq. Additional amounts of potassium are needed during periods of trauma and stress. The kidneys are the main source of potassium loss. Approximately 80% to 90% of potassium losses occur in the urine, with the remainder being lost in stools or sweat.

KEY CONCEPTS

POTASSIUM BALANCE

- Most of the body's potassium is contained in the ICF, with only a small, but vital, amount being present in the ECF.
- Two major mechanisms function in the control of serum potassium: (1) renal mechanisms that conserve or eliminate potassium, and (2) transcellular buffer systems that remove potassium from and release it into the serum as needed.
- The distribution of potassium between the ICF and ECF compartments regulates electrical membrane potentials controlling the excitability of nerve and muscle cells as well as contractility of skeletal, cardiac, and smooth muscle tissue. Many of the manifestations of potassium deficit or excess are related to potassium's effect on membrane potentials in cardiac, skeletal, and smooth muscle in the gastrointestinal tract.



■ FIGURE 6-11 ■ Effect of changes in serum hypokalemia (red) and hyperkalemia (blue) on the resting membrane potential.

Mechanisms of Regulation. Normally, the ECF concentration of potassium is precisely regulated at about 4.2 mEq/ml. The precise control is necessary because many cell functions are sensitive to even small changes in ECF potassium levels. An increase in serum potassium levels of only maybe 0.3 to 0.4 mEq/L can cause serious cardiac dysrhythmias and even death.

Serum potassium levels are largely regulated through two mechanisms: (1) renal mechanisms that conserve or eliminate potassium, and (2) a transcellular shift of potassium between the ICF and ECF compartments. Normally, it takes 6 to 8 hours to eliminate 50% of potassium intake.³ To avoid an increase in extracellular potassium levels during this time, excess potassium is temporarily shifted into red blood cells and other cells such as those of muscle, liver, and bone.

Renal Regulation. The kidney provides the major route for potassium elimination. Potassium is filtered in the glomerulus, reabsorbed along with sodium and water in the proximal tubule and with sodium and chloride in the thick ascending loop of Henle, and then secreted into the late distal and cortical collecting tubules for elimination in the urine. The latter mechanism serves to “fine-tune” the concentration of potassium in the ECF.

Aldosterone plays an essential role in regulating potassium elimination by the kidney (see Chapter 22). In the presence of aldosterone, sodium is transported back into the blood and potassium is secreted into the tubular filtrate for elimination in the urine. There is also a potassium-hydrogen exchange system in the collecting tubules of the kidney. When serum potassium levels are increased, potassium is secreted into the urine and hydrogen is reabsorbed into the blood, producing a decrease in pH and metabolic acidosis. Conversely, when potassium levels are low, potassium is reabsorbed and hydrogen is secreted into the urine, leading to metabolic alkalosis.

Extracellular-Intracellular Shifts. The movement of potassium between the ECF and ICF allows potassium to move into body cells when serum levels are high and move out when serum levels are low. Among the factors that alter potassium distribution between the ECF and ICF are insulin, β -adrenergic stimulation, serum osmolality, and acid-base disorders. Both insulin and the β -adrenergic catecholamines (*e.g.*, epinephrine) increase cellular uptake of potassium. Insulin increases the cellular uptake of potassium after a meal. The potassium content of a single meal is often as high as 50 mEq; the actions of insulin prevent a rise in serum potassium to life-threatening levels. The catecholamines, particularly epinephrine, facilitate the movement of potassium into muscle tissue during periods of physiologic stress.

Extracellular osmolality and pH also influence the movement of potassium between the ICF and ECF. Acute increases in serum osmolality cause potassium to move out of cells. When serum osmolality is increased because of the presence of impermeable solutes such as glucose (without insulin), water leaves the cell. The loss of cell water produces an increase in intracellular potassium, causing it to move out of the cell into the ECF. Acid-base disorders are often accompanied by a change in serum potassium. Both the hydrogen and potassium ions are positively charged, and both ions move freely between the ICF and ECF compartments. In metabolic acidosis, hydrogen ions move into body cells for buffering; this causes potassium to

leave the cells and move into the ECF. Metabolic alkalosis has the opposite effect.

Exercise can also produce compartmental shifts in potassium. Repeated muscle contraction releases potassium into the ECF. Although the increase usually is small with modest exercise, it can be considerable during exhaustive exercise. Even the repeated clenching and unclenching of the fist during a blood draw can cause potassium to move out of cells and artificially elevate serum potassium levels.

Hypokalemia

Hypokalemia refers to a serum potassium level below 3.5 mEq/L (3.5 mmol/L). Because of transcellular shifts, temporary changes in serum K^+ may occur as the result of movement between the ICF and ECF compartments.

Causes. The causes of potassium deficit can be grouped into three categories: (1) inadequate intake; (2) excessive losses through the kidney, skin, and gastrointestinal tract; and (3) redistribution between the ICF and ECF compartments.

Inadequate intake is a frequent cause of hypokalemia. A potassium intake of at least 10 to 30 mEq/day is needed to compensate for obligatory urine losses.^{4,23} A person on a potassium-free diet continues to lose approximately 5 to 15 mEq of potassium daily. Insufficient dietary intake may result from the inability to obtain or ingest food or from a diet that is low in potassium-containing foods.

Excessive renal losses can occur with diuretic use, metabolic alkalosis, magnesium depletion, trauma and stress, and increased levels of aldosterone. Diuretic therapy, with the exception of potassium-sparing diuretics, is the most common cause of hypokalemia. Both thiazide and loop diuretics increase the loss of potassium in the urine. The degree of hypokalemia is directly related to diuretic dose and is greater when sodium intake is higher.²³ Magnesium depletion causes renal potassium wasting. Magnesium deficiency often coexists with potassium depletion because of diuretic therapy or disease processes such as diarrhea. Importantly, the ability to correct potassium deficiency is impaired when magnesium deficiency is present.

The kidneys do not have the homeostatic mechanisms needed to conserve potassium during periods of stress or insufficient intake. After trauma and in stress situations, urinary losses of potassium are greatly increased, sometimes approaching levels of 150 to 200 mEq/L.²⁴ Renal losses of potassium are accentuated by aldosterone and cortisol. Trauma and surgery produce a stress-related increase in these hormones. Primary aldosteronism, caused by an aldosterone-secreting tumor of the adrenal cortex, can produce severe urinary losses of potassium. Cortisol binds to aldosterone receptors and exerts aldosterone-like effects on potassium elimination.

Although potassium losses from the gastrointestinal tract and the skin usually are minimal, these losses can become excessive under certain conditions. The gastrointestinal tract is one of the most common sites for acute potassium losses. Vomiting and gastrointestinal suction lead to hypokalemia, partly because of actual potassium losses and because of renal losses associated with metabolic alkalosis (see section on metabolic alkalosis under acid-base balance). Because intestinal secretions are high in potassium content, diarrhea and intestinal suction can also cause large losses of potassium. Excessive skin losses occur with loss of the protective skin surface

and sweating. Burns and other types of skin injury increase the loss of potassium through wound drainage. Losses caused by sweating increase in persons who are acclimating to a hot climate, partly because increased secretion of aldosterone during heat acclimatization increases the loss of potassium in urine and sweat.

Because of the high ratio of intracellular to extracellular potassium, a redistribution of potassium from the ECF to the ICF compartment can produce a marked decrease in the serum concentration. One cause of potassium redistribution is insulin. Because insulin increases the movement of glucose and potassium into cells, potassium deficit often develops during treatment of diabetic ketoacidosis. β -adrenergic agonist drugs, such as pseudoephedrine and albuterol, can have a similar effect on potassium distribution.

Manifestations. The manifestations of hypokalemia include the effect of altered membrane potentials on cardiovascular, neuromuscular and gastrointestinal function (see Table 6-5). The signs and symptoms of potassium deficit seldom develop until the serum potassium level has fallen to less than 3.0 mEq/L. They are typically gradual in onset, so the disorder may go undetected for some time.

The most serious effects of hypokalemia are those affecting cardiovascular function. Postural hypotension is common. Most persons with a serum potassium level of less than 3.0 mEq/L demonstrate electrocardiographic (ECG) changes typical of hypokalemia. These changes include prolongation

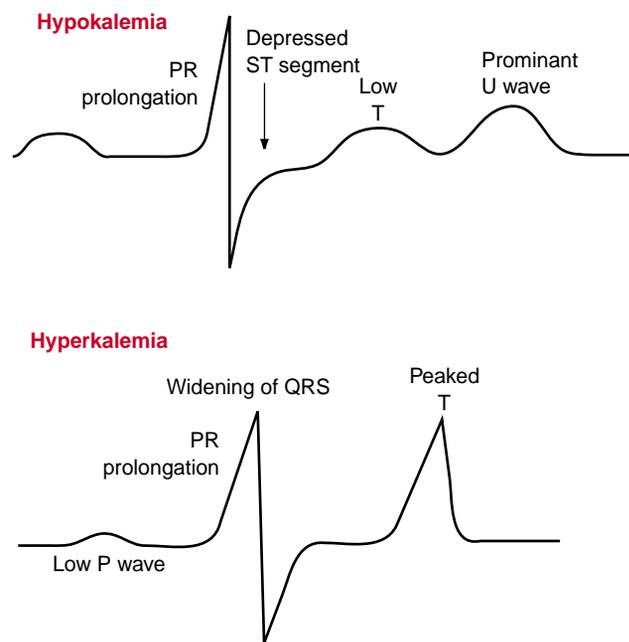
of the PR interval, depression of the ST segment, flattening of the T wave, and appearance of a prominent U wave (Fig. 6-12). Although these ECG changes usually are not serious, they may predispose to sinus bradycardia and ectopic ventricular dysrhythmias (see Chapter 17). Digitalis toxicity can be provoked in persons treated with this drug, and there is an increased risk of ventricular dysrhythmias, particularly in persons with underlying heart disease. Potassium and digitalis compounds compete for binding to sites on the Na^+/K^+ -ATPase membrane pump. In hypokalemia, more sites are available for digitalis to bind to and exert its action. The dangers associated with digitalis toxicity are compounded in persons who are receiving diuretics that increase urinary losses of potassium.

Complaints of weakness, fatigue, and muscle cramps, particularly during exercise, are common in moderate hypokalemia (serum potassium 3.0 to 2.5 mEq/L). Muscle paralysis with life-threatening respiratory insufficiency can occur with severe hypokalemia (serum potassium <2.5 mEq/L). Leg muscles, particularly the quadriceps, are most prominently affected. Some persons report muscle tenderness and paresthesias, rather than weakness. In chronic potassium deficiency, muscle atrophy may contribute to muscle weakness.

There are numerous signs and symptoms associated with altered gastrointestinal function, including anorexia, nausea, and vomiting. Atony of the gastrointestinal smooth muscle can cause constipation, abdominal distention, and, in severe hypokalemia, paralytic ileus. When gastrointestinal symptoms occur

TABLE 6-5 Manifestations of Hypokalemia and Hyperkalemia

Hypokalemia	Hyperkalemia
<p>Laboratory Values Serum potassium <3.5 mEq/L</p> <p>Thirst and Urine Increased thirst Inability to concentrate urine with polyuria and urine with low specific gravity</p> <p>Effects of Changes in Membrane Potentials on Neural and Muscle Function <i>Gastrointestinal</i> Anorexia, nausea, vomiting Abdominal distention Paralytic ileus (severe hypokalemia) <i>Neuromuscular</i> Muscle weakness, flabbiness, fatigue Muscle cramps and tenderness Paresthesias Paralysis (severe hypokalemia) <i>Central Nervous System</i> Confusion, depression <i>Cardiovascular</i> Postural hypotension Predisposition to digitalis toxicity Electrocardiogram changes Cardiac dysrhythmias</p> <p>Acid-Base Balance Metabolic alkalosis</p>	<p>Laboratory Values Serum potassium >5.0 mEq/L</p> <p>Effects of Changes in Membrane Potentials on Neural and Muscle Function <i>Gastrointestinal</i> Nausea, vomiting Intestinal cramps Diarrhea <i>Neuromuscular</i> Weakness, dizziness Muscle cramps Paresthesias Paralysis (severe hyperkalemia) <i>Cardiovascular</i> Electrocardiogram changes Risk of cardiac arrest with severe hyperkalemia</p>



■ FIGURE 6-12 ■ Electrocardiographic changes with hyperkalemia and hypokalemia.

gradually and are not severe, they often impair potassium intake and exaggerate the condition.

The renal processes that conserve potassium during hypokalemia interfere with the kidney's ability to concentrate urine. As a result, urine output and serum osmolality are increased, urine specific gravity is decreased, and polyuria, nocturia, and thirst are common. Metabolic alkalosis and renal chloride wasting are signs of severe hypokalemia.

Treatment. When possible, hypokalemia caused by potassium deficit is treated by increasing the intake of foods high in potassium content. Oral potassium supplements are prescribed for persons whose intake of potassium is insufficient in relation to losses. This is particularly true of persons who are receiving diuretic therapy and those who are taking digitalis.

Potassium may be given intravenously when the oral route is not tolerated or when rapid replacement is needed. Magnesium deficiency may impair potassium correction; in such cases, magnesium replacement is indicated.²⁵ The rapid infusion of a concentrated potassium solution can cause death from cardiac arrest. Health personnel who assume responsibility for administering potassium-containing intravenous solutions should be fully aware of all the precautions pertaining to potassium dilution and flow rate.

Hyperkalemia

Hyperkalemia refers to an increase in serum levels of potassium in excess of 5.0 mEq/L (5.0 mmol/L). It seldom occurs in healthy persons because the body is extremely effective in preventing excess potassium accumulation in the ECF.

Causes. The three major causes of potassium excess are (1) decreased renal elimination, (2) excessively rapid administration, and (3) movement of potassium from the ICF to ECF compartment.

The most common cause of hyperkalemia is decreased renal function. Chronic hyperkalemia is almost always associated with renal failure. Usually, the glomerular filtration rate must decline to less than 10 mL/minute before hyperkalemia develops. Some renal disorders, such as sickle cell nephropathy, lead nephropathy, and systemic lupus nephritis, can selectively impair tubular secretion of potassium without causing renal failure. As discussed previously, acidosis diminishes potassium elimination by the kidney. Persons with acute renal failure accompanied by lactic acidosis or ketoacidosis are at increased risk for the development of hyperkalemia. Correcting the acidosis usually helps to correct the hyperkalemia.²⁶

Aldosterone acts at the level of the distal tubular sodium/potassium exchange system to increase potassium excretion while facilitating sodium reabsorption. A decrease in aldosterone-mediated potassium elimination can result from adrenal insufficiency (*i.e.*, Addison's disease), depression of aldosterone release caused by a decrease in renin or angiotensin II, or impaired ability of the kidneys to respond to aldosterone. Potassium-sparing diuretics (*e.g.*, spironolactone, amiloride, triamterene) can produce hyperkalemia by means of the latter mechanism. Because of their ability to decrease aldosterone levels, angiotensin-converting enzyme inhibitors also can produce an increase in serum potassium levels.

Potassium excess can result from excessive oral ingestion or intravenous administration of potassium. It is difficult to increase potassium intake to the point of causing hyperkalemia when renal function is adequate and the aldosterone sodium/potassium exchange system is functioning. An exception to this rule is the intravenous route of administration. In some cases, severe and fatal incidents of hyperkalemia have occurred when intravenous potassium solutions were infused too rapidly. Because the kidneys control potassium elimination, the administration of potassium-containing intravenous solutions should not be initiated until urine output has been assessed and renal function has been deemed to be adequate.

The movement of potassium out of body cells into the ECF also can lead to elevated serum potassium levels. Tissue injury, such as that caused by burns and crushing injuries, causes release of intracellular potassium into the ECF compartment. The same injuries often diminish renal function, which contributes to the development of hyperkalemia. Transient hyperkalemia may be induced during extreme exercise or seizures, when muscle cells are permeable to potassium.

Manifestations. The signs and symptoms of potassium excess are closely related to the alterations in neuromuscular excitability (see Table 6-5). The neuromuscular manifestations of potassium excess usually are absent until the serum concentration exceeds 6 mEq/L. The first symptom associated with hyperkalemia typically is paresthesia. There may be complaints of generalized muscle weakness or dyspnea secondary to respiratory muscle weakness.

The most serious effect of hyperkalemia is on the heart. As potassium levels increase, disturbances in cardiac conduction occur. The earliest changes are peaked, narrow T waves and widening of the QRS complex. If serum levels continue to rise, the PR interval becomes prolonged and is followed by the disappearance of P waves (see Fig. 6-12). The heart rate may be slow. Ventricular fibrillation and cardiac arrest are terminal events. Detrimental effects of hyperkalemia on the heart

are most pronounced when the serum potassium level rises rapidly.

Treatment. The treatment of potassium excess varies with the severity of the disturbance and focuses on decreasing or curtailing intake or absorption, increasing renal excretion, and increasing cellular uptake. Decreased intake can be achieved by restricting dietary sources of potassium. The major ingredient in most salt substitutes is potassium chloride, and such substitutes should not be given to patients with renal problems.

Increasing potassium output often is more difficult. People with renal failure may require hemodialysis or peritoneal dialysis to reduce serum potassium levels. Most emergency methods focus on measures that cause serum potassium to move into the ICF compartment. An intravenous infusion of insulin and glucose is often used for this purpose.

In summary, potassium, which is the major intracellular cation, contributes to the maintenance of intracellular osmolality, is necessary for normal neuromuscular function, and influences acid-base balance. Potassium levels are influenced by dietary intake and elimination by the kidney. A transcellular shift can produce a redistribution of potassium between the ECF and ICF compartments, causing blood levels to increase or decrease.

Hypokalemia represents a serum potassium level below 3.5 mEq/L. It can result from inadequate intake, excessive losses, or redistribution between the ICF and ECF compartments. The manifestations of potassium deficit include alterations in renal, skeletal muscle, gastrointestinal, and cardiovascular function, reflecting the crucial role of potassium in cell metabolism and neuromuscular function. *Hyperkalemia* represents an increase in serum potassium in excess of 5.0 mEq/L. It seldom occurs in healthy persons because the body is extremely effective in preventing excess potassium accumulation in the ECF. The major causes of potassium excess are decreased renal elimination of potassium, excessively rapid intravenous administration of potassium, and a transcellular shift of potassium out of the cell to the ECF compartment. The most serious effect of hyperkalemia is cardiac arrest.

CALCIUM AND MAGNESIUM BALANCE

Calcium Balance

Calcium is one of the major divalent cations in the body. Approximately 99% of body calcium is found in bone, where it provides the strength and stability for the skeletal system and serves as an exchangeable source to maintain extracellular calcium levels. Most of the remaining calcium (approximately 1%) is located inside cells, and only 0.1%–0.2% is present in the ECF.

Serum calcium exists in three forms: (1) protein bound, (2) complexed, and (3) ionized. Approximately 40% of serum calcium is bound to plasma proteins, mostly albumin, and cannot diffuse or pass through the capillary wall to leave the vascular compartment (Fig. 6-13). Another 10% is complexed (*i.e.*, chelated) with substances such as citrate, phosphate, and

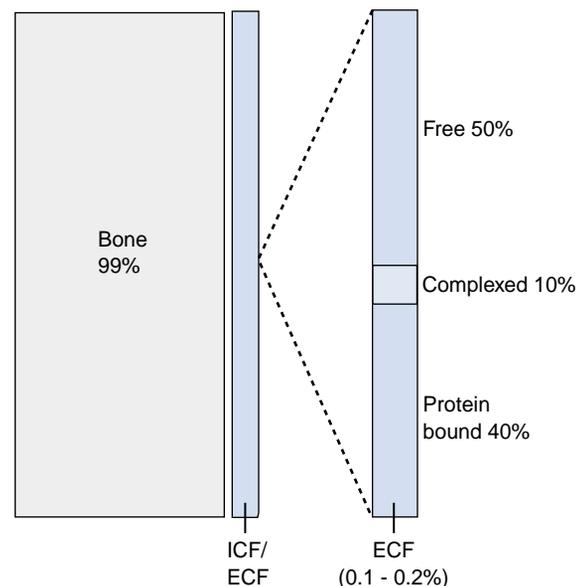
KEY CONCEPTS

CALCIUM BALANCE

- About 99% of body calcium is stored in bone; 1% is located inside cells; and 0.1% is found in the ECF.
- ECF calcium levels are made up of free (ionized), complexed, and protein-bound fractions. Only the ionized calcium ions play an essential role in neuromuscular and cardiac excitability.
- Serum calcium levels are regulated by parathyroid hormone and by renal mechanisms in which serum levels of calcium and phosphate are reciprocally regulated to prevent the damaging deposition of calcium phosphate crystals in the soft tissues of the body.

sulfate. This form is not ionized. The remaining 50% of serum calcium is present in the ionized form. It is the ionized form of calcium that is free to leave the vascular compartment and participate in cellular functions. The total serum calcium level fluctuates with changes in serum albumin and pH.

Ionized calcium serves a number of functions. It participates in many enzyme reactions; exerts an important effect on membrane potentials and neuronal excitability; is necessary for contraction in skeletal, cardiac, and smooth muscle; participates in the release of hormones, neurotransmitters, and other chemical messengers; influences cardiac contractility and automaticity by way of slow calcium channels; and is essential for blood clotting. The use of calcium channel-blocking drugs in circulatory disorders demonstrates the importance of the calcium ion



■ **FIGURE 6-13** ■ Distribution of body calcium between the bone and the intracellular and extracellular fluids. The percentages of free, complexed, and protein-bound calcium in extracellular fluids are indicated.

in the normal function of the heart and blood vessels. Calcium is required for all but the first two steps of the intrinsic pathway for blood coagulation. Because of its ability to bind calcium, citrate often is used to prevent clotting in blood that is to be used for transfusions.

Regulation of Serum Calcium

Calcium enters the body through the gastrointestinal tract, is absorbed from the intestine under the influence of vitamin D, is stored in bone, and is excreted by the kidney. The major sources of calcium are milk and milk products. Only 30% to 50% of dietary calcium is absorbed from the duodenum and upper jejunum; the remainder is eliminated in the stool.

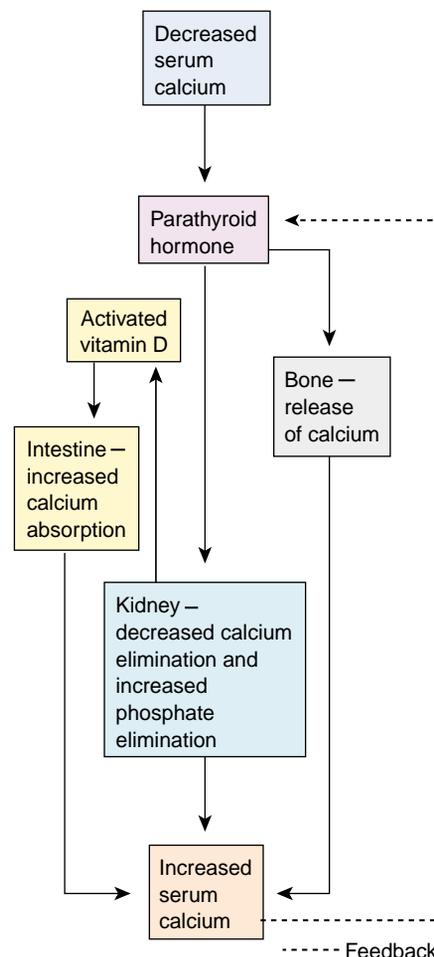
Calcium is filtered in the glomerulus of the kidney and then selectively reabsorbed back into the blood. Approximately 60% to 65% of filtered calcium is passively reabsorbed in the proximal tubule, driven by the reabsorption of sodium chloride; 15% to 20% is reabsorbed in the thick ascending loop of Henle, driven by the $\text{Na}^+/\text{K}^+ / 2\text{Cl}^-$ cotransport system; and 5% to 10% is reabsorbed in the distal convoluted tubule (see Chapter 22). The distal convoluted tubule is an important regulatory site for controlling the amount of calcium that enters the urine. PTH and possibly vitamin D stimulate calcium reabsorption in this segment of the nephron. Other factors that may influence calcium reabsorption in the distal convoluted tubule are phosphate levels and glucose and insulin levels. Thiazide diuretics, which exert their effects in the distal convoluted tubule, enhance calcium reabsorption.

Serum calcium, which is responsible for the physiologic functions of calcium, is directly or indirectly regulated by parathyroid hormone (PTH) and vitamin D. Calcitonin, a hormone produced by C cells in the thyroid, is thought to act on the kidney and bone to remove calcium from the circulation. The regulation of serum calcium is also strongly influenced by serum phosphate levels. The role of PTH, calcitonin, and vitamin D on skeletal function is discussed in Chapter 44.

Parathyroid hormone, a major regulator of serum calcium and phosphate, is secreted by the parathyroid glands. The response to a decrease in serum calcium is prompt, occurring within seconds. The main function of PTH is to maintain the calcium concentration of the ECF (Fig. 6-14). It performs this function by promoting the release of calcium from bone, increasing the activation of vitamin D as a means of enhancing intestinal absorption of calcium, and stimulating calcium conservation by the kidney while increasing phosphate excretion (see Chapter 31).

Vitamin D, although classified as a vitamin, functions as a hormone. Vitamin D_3 , the precursor of the active form of vitamin D, is synthesized in the skin or obtained from foods in the diet, many of which are fortified with vitamin D. Vitamin D_3 is hydroxylated in the liver and is transformed to its active form in the kidney. The major action of the activated form of vitamin D is to increase the absorption of calcium from the intestine.

The extracellular concentrations of calcium and phosphate are reciprocally regulated such that calcium levels fall when phosphate levels are high and vice versa. Normal serum levels of calcium (8.5 to 10.5 mg/dL in adults) and phosphate (2.5 to 4.5 mg/dL in adults) are regulated so that the product of the two concentrations ($[\text{Ca}^{2+}] \times [\text{PO}_4^{2-}]$) is normally maintained at less than 70.²⁷ Maintenance of the calcium-phosphate prod-



■ **FIGURE 6-14** ■ Regulation of serum calcium concentration by parathyroid hormone.

uct within this range is important in preventing the deposition of CaPO_4 salts in soft tissue, damaging the kidneys, blood vessels, and lungs.

Hypocalcemia

Hypocalcemia represents a serum calcium level of less than 8.5 mg/dL. Hypocalcemia occurs in many forms of critical illness and has affected as many as 70% to 90% of patients in intensive care units.²⁷

Causes. The causes of hypocalcemia can be divided into three categories: (1) impaired ability to mobilize calcium bone stores, (2) abnormal losses of calcium from the kidney, and (3) increased protein binding or chelation such that greater proportions of calcium are in the nonionized form. A pseudo-hypocalcemia is caused by hypoalbuminemia. It results in a decrease in protein-bound, rather than ionized, calcium and usually is asymptomatic.²⁸ Calcium deficit caused by dietary deficiency exerts its effects on bone stores, rather than extracellular calcium levels.

Serum calcium exists in a dynamic equilibrium with calcium in bone. The ability to mobilize calcium from bone depends on adequate levels of PTH. Decreased levels of PTH may result from primary or secondary forms of hypoparathyroid-

ism (see Chapter 31). Suppression of PTH release may also occur when vitamin D levels are elevated. Magnesium deficiency inhibits PTH release and impairs the action of PTH on bone resorption. This form of hypocalcemia is difficult to treat with calcium supplementation alone and requires correction of the magnesium deficiency.

Phosphate elimination is impaired in renal failure. Because of the inverse relation between calcium and phosphate, serum calcium levels fall as phosphate levels rise in renal failure. Hypocalcemia and hyperphosphatemia occur when the glomerular filtration rate falls to less than 25 to 30 mL/minute (normal is 100 to 120 mL/minute).

Only the ionized form of calcium is able to leave the capillary and participate in body functions. A change in pH alters the proportion of calcium that is in the bound and ionized forms. An acid pH decreases binding of calcium to protein, causing a proportionate increase in ionized calcium, whereas total serum calcium remains unchanged. An alkaline pH has the opposite effect. As an example, hyperventilation sufficient to cause respiratory alkalosis can produce tetany because of increased protein binding of calcium. Free fatty acids increase binding of calcium to albumin, causing a reduction in ionized calcium. Elevations in free fatty acids sufficient to alter calcium binding may occur during stressful situations that cause elevations of epinephrine, glucagon, growth hormone, and adrenocorticotropin levels.

Hypocalcemia is a common finding in a patient with acute pancreatitis. Inflammation of the pancreas causes release of pro-

teolytic and lipolytic enzymes. It is thought that the calcium ion combines with free fatty acids released by lipolysis in the pancreas, forming soaps and removing calcium from the circulation.

Manifestations. Hypocalcemia can manifest as an acute or chronic condition. The manifestations of acute hypocalcemia reflect the increased neuromuscular excitability and cardiovascular effects of a decrease in ionized calcium (see Table 6-6). Ionized calcium stabilizes neuromuscular excitability, thereby making nerve cells less sensitive to stimuli. Nerves exposed to low ionized calcium levels show decreased thresholds for excitation, repetitive responses to a single stimulus, and, in extreme cases, continuous activity. The severity of the manifestations depends on the underlying cause, rapidity of onset, accompanying *electrolyte disorders, and extracellular pH*. Increased neuromuscular excitability can manifest as paresthesias (i.e., tingling around the mouth and in the hands and feet) and tetany (i.e., muscle spasms of the muscles of the face, hands, and feet). Severe hypocalcemia can lead to laryngeal spasm, seizures, and even death.

The cardiovascular effects of acute hypocalcemia include hypotension, cardiac insufficiency, cardiac dysrhythmias (particularly heart block and ventricular fibrillation), and failure to have a response to drugs such as digitalis, norepinephrine, and dopamine that act through calcium-mediated mechanisms.

Chronic hypocalcemia is often accompanied by skeletal manifestations and skin changes. There may be bone pain, fragility, deformities, and fractures. The skin may be dry and

TABLE 6-6 Manifestations of Hypocalcemia and Hypercalcemia

Hypocalcemia	Hypercalcemia
<p>Laboratory Serum calcium <8.5 mg/dL</p>	<p>Laboratory Serum calcium >10.5 mg/dL</p>
<p>Neural and Muscle Effects (Increased Excitability) Paresthesias, especially numbness and tingling Skeletal muscle cramps Abdominal muscle spasms and cramps Hyperactive reflexes Carpopedal spasm Tetany Laryngeal spasm</p>	<p>Inability to Concentrate Urine and Exposure of Kidney to Increased Concentration of Calcium Polyuria Increased thirst Flank pain Signs of acute renal insufficiency Signs of kidney stones</p>
<p>Cardiovascular Effects Hypotension Signs of cardiac insufficiency Decreased response to drugs that act by calcium-mediated mechanisms Prolongation of the QT interval predisposes to ventricular dysrhythmias</p>	<p>Neural and Muscle Effects (Decreased Excitability) Muscle weakness Ataxia, loss of muscle tone Lethargy Personality and behavioral changes Stupor and coma</p>
<p>Skeletal Effects (Chronic Deficiency) Osteomalacia Bone pain</p>	<p>Cardiovascular Effects Hypertension Shortening of the QT interval Atrioventricular block</p> <p>Gastrointestinal Effects Anorexia Nausea, vomiting Constipation</p>

scaling, the nails brittle, and hair dry. The development of cataracts is common. A person with chronic hypocalcemia may also present with mild diffuse brain disease mimicking depression, dementia, or psychoses.

Diagnosis and Treatment. Chvostek's and Trousseau's tests can be used to assess for an increase in neuromuscular excitability and tetany.⁵ *Chvostek's sign* is elicited by tapping the face just below the temple at the point where the facial nerve emerges. Tapping the face over the facial nerve causes spasm of the lip, nose, or face when the test result is positive. An inflated blood pressure cuff is used to test for *Trousseau's sign*. The cuff is inflated above systolic blood pressure for 3 minutes. Contraction of the fingers and hands (*i.e.*, carpopedal spasm) indicates the presence of tetany.

Acute hypocalcemia is an emergency situation, requiring prompt treatment. An intravenous infusion containing calcium is used when tetany or acute symptoms are present or anticipated because of a decrease in the serum calcium level.

Chronic hypocalcemia is treated with oral intake of calcium. One glass of milk contains approximately 300 mg of calcium. Oral calcium supplements may be used. In some cases, long-term treatment may require the use of vitamin D preparations. The active form of vitamin D is administered when the liver or kidney mechanisms needed for hormone activation are impaired.

Hypercalcemia

Hypercalcemia represents a total serum calcium concentration greater than 10.5 mg/dL. Falsely elevated levels of calcium can result from prolonged drawing of blood with an excessively tight tourniquet. Increased plasma proteins (*e.g.*, hyperalbuminemia, hyperglobulinemia) may elevate the total serum calcium but not affect the ionized calcium concentration

Causes. A serum calcium excess (*i.e.*, hypercalcemia) results when calcium movement into the circulation overwhelms the calcium regulatory hormones or the ability of the kidney to remove excess calcium ions. The most common causes of hypercalcemia are increased bone resorption caused by neoplasms or hyperparathyroidism. Hypercalcemia is a common complication of cancer, occurring in approximately 10% to 20% of persons with advanced disease.²⁹ A number of malignant tumors, including carcinoma of the lungs, have been associated with hypercalcemia. Some tumors destroy the bone, but others produce humoral agents that stimulate osteoclastic activity, increase bone resorption, or inhibit bone formation.

Less common causes of hypercalcemia are prolonged immobilization, increased intestinal absorption of calcium, and excessive doses of vitamin D. Prolonged immobilization and lack of weight bearing cause demineralization of bone and release of calcium into the bloodstream. Intestinal absorption of calcium can be increased by excessive doses of vitamin D or as a result of a condition called the *milk-alkali syndrome*. The milk-alkali syndrome is caused by excessive ingestion of calcium (often in the form of milk) and absorbable antacids. Because of the advent of nonabsorbable antacids, the condition is seen less frequently than in the past, but it may occur in women who are overzealous in taking calcium preparations for osteoporosis prevention.

A variety of drugs elevate calcium levels. The use of lithium to treat bipolar disorders has caused hypercalcemia and hyper-

parathyroidism. The thiazide diuretics increase calcium reabsorption in the distal convoluted tubule of the kidney. Although the thiazide diuretics seldom cause hypercalcemia, they can unmask hypercalcemia from other causes such as underlying bone disorders and conditions that increase bone resorption.

Manifestations. The signs and symptoms associated with calcium excess originate from three sources: (1) changes in neural excitability, (2) alterations in smooth and cardiac muscle function, and (3) exposure of the kidneys to high concentrations of calcium (see Table 6-6).

Neural excitability is decreased in patients with hypercalcemia. There may be a dulling of consciousness, stupor, weakness, and muscle flaccidity. Behavioral changes may range from subtle alterations in personality to acute psychoses.

The heart responds to elevated levels of calcium with increased contractility and ventricular dysrhythmias. Digitalis accentuates these responses. Gastrointestinal symptoms reflect a decrease in smooth muscle activity and include constipation, anorexia, nausea, and vomiting. Pancreatitis is another potential complication of hypercalcemia and is probably related to stones in the pancreatic ducts.

High calcium concentrations in the urine impair the ability of the kidneys to concentrate urine by interfering with the action of ADH. This causes salt and water diuresis and an increased sensation of thirst. Hypercalciuria also predisposes to the development of renal calculi.

Hypercalcemic crisis describes an acute increase in the serum calcium level.²⁹ Malignant disease and hyperparathyroidism are major causes of hypercalcemic crisis. In hypercalcemic crisis, polyuria, excessive thirst, volume depletion, fever, altered levels of consciousness, azotemia (*i.e.*, nitrogenous wastes in the blood), and a disturbed mental state accompany other signs of calcium excess. Symptomatic hypercalcemia is associated with a high mortality rate; death often is caused by cardiac arrest.

Treatment. The treatment of calcium excess usually is directed toward rehydration and measures to increase urinary excretion of calcium and inhibit release of calcium from bone. Fluid replacement is needed in situations of volume depletion. The excretion of sodium is accompanied by calcium excretion. Diuretics and sodium chloride can be administered to increase urinary elimination of calcium after the ECF volume has been restored. Loop diuretics commonly are used, rather than thiazide diuretics, which increase calcium reabsorption.

The initial lowering of calcium levels is followed by measures to inhibit bone reabsorption. Drugs that are used to inhibit calcium mobilization include bisphosphonates, calcitonin, and the glucocorticosteroids. The bisphosphonates are a relatively new group of drugs that act mainly by inhibiting osteoclastic activity. Calcitonin inhibits osteoclastic activity, thereby decreasing resorption. The glucocorticosteroids inhibit bone resorption and are used to treat hypercalcemia associated with cancer.

Magnesium Balance

Magnesium is the second most abundant intracellular cation. The average adult has approximately 24 g of magnesium distributed throughout the body.³⁰ Of the total magnesium content, approximately 50% to 60% is stored in bone, 39% to 49% is contained in the body cells, and the remaining 1% is dis-

persed in the ECF.³¹ Approximately 20% to 30% of the extracellular magnesium is protein bound, and only a small fraction of intracellular magnesium (15% to 30%) is exchangeable with the ECF. The normal serum concentration of magnesium is 1.8 to 2.7 mg/dL.

Only recently has the importance of magnesium to the overall function of the body been recognized.³¹ Magnesium acts as a cofactor in many intracellular enzyme reactions, including those related to transfer of phosphate groups. It is essential to all reactions that require ATP, for every step related to replication and transcription of DNA, and for the translation of messenger RNA. It is required for cellular energy metabolism, functioning of the sodium-potassium membrane pump, membrane stabilization, nerve conduction, ion transport, and calcium channel activity. Magnesium binds to calcium receptors, and it has been suggested that alterations in magnesium levels may exert their effects through calcium-mediated mechanisms. Magnesium may bind competitively to calcium binding sites, producing the appropriate response; it may compete with calcium for a binding site but not exert an effect; or it may alter the distribution of calcium by interfering with its movement across the cell membrane.

Regulation of Magnesium

Magnesium is ingested in the diet, absorbed from the intestine, and excreted by the kidneys. Intestinal absorption is not closely regulated, and approximately 25% to 65% of dietary magnesium is absorbed. Magnesium is contained in all green vegetables, grains, nuts, meats, and seafood. Magnesium is also present in much of the groundwater in North America.

The kidney is the principal organ of magnesium regulation. Magnesium is a unique electrolyte in that only approximately 30% to 40% of the filtered amount is reabsorbed in the proximal tubule. The greatest quantity, approximately 50% to 70%, is reabsorbed in the thick ascending loop of Henle. The distal tubule, which reabsorbs a small amount of magnesium, is the major site of magnesium regulation. Magnesium reabsorption is decreased in the presence of increased serum levels, stimulated by PTH, and inhibited by increased calcium levels. The major driving force for magnesium absorption in the thick ascending loop of Henle is the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransport system (see Chapter 22). Inhibition of this transport system by loop diuretics lowers magnesium reabsorption.

Hypomagnesemia

Hypomagnesemia represents a serum magnesium concentration of less than 1.8 mg/dL (Table 6-7).³² It is seen in conditions that limit intake or increase intestinal or renal losses, and it is a common finding in emergency department and critical care patients.

Causes. Magnesium deficiency can result from insufficient intake, excessive losses, or movement between the ECF and ICF compartments. It can result from conditions that directly limit intake, such as malnutrition, starvation, or prolonged maintenance of magnesium-free parenteral nutrition. Other conditions, such as diarrhea, malabsorption syndromes, prolonged nasogastric suction, or laxative abuse can serve to decrease intestinal absorption. Excessive calcium intake impairs intestinal absorption of magnesium by competing for the same transport site. Another common cause of magnesium deficiency is chronic alcoholism. There are many factors that contribute to hypomagnesemia in alcoholism, including low intake and gastrointestinal losses from diarrhea.

Although the kidneys are able to defend against hypermagnesemia, they are less able to conserve magnesium and prevent hypomagnesemia. Urine losses are increased in diabetic ketoacidosis, hyperparathyroidism, and hyperaldosteronism. Some drugs increase renal losses of magnesium, including diuretics (particularly loop diuretics) and nephrotoxic drugs such as aminoglycoside antibiotics, cyclosporine, cisplatin, and amphotericin B.

A relative hypomagnesemia may also develop in conditions that promote movement of magnesium between the ECF and ICF compartments, including rapid administration of glucose, insulin-containing parenteral solutions, and alkalosis. Although transient, these conditions can cause serious alterations in body function.

Manifestations. Signs of magnesium deficiency are not usually apparent until the serum magnesium is less than 1 mEq/dL. Hypomagnesemia is characterized by an increase in neuromuscular excitability as evidenced by muscle weakness and tremors. Other manifestations may include hyperactive deep tendon reflexes, paresthesias (*e.g.*, numbness, pricking, tingling sensation), muscle fasciculations, and tetanic muscle contractions. A positive Chvostek's or Trousseau's may be present,

TABLE 6-7 Manifestations of Hypomagnesemia and Hypermagnesemia

Hypomagnesemia	Hypermagnesemia
Laboratory Values Serum magnesium <1.8 mg/dL	Laboratory Values Serum magnesium >2.7 mg/dL
Neural and Muscle Effects Personality changes Athetoid or choreiform movements Nystagmus Tetany	Neural and Muscle Effects Lethargy Hyporeflexia Confusion Coma
Cardiovascular Effects Tachycardia Hypertension Cardiac dysrhythmias	Cardiovascular Effects Hypotension Cardiac dysrhythmias Cardiac arrest

particularly if hypocalcemia is present. Because decreased serum magnesium increases irritability in nervous tissue, seizures may occur. Other manifestations may include ataxia, vertigo, disorientation, depression, and psychotic symptoms.

Cardiovascular manifestations include tachycardia, hypertension, and ventricular dysrhythmias. There may be ECG changes such as widening of the QRS complex, appearance of peak T waves, prolongation of the PR interval, T-wave inversion, and appearance of U waves. Ventricular dysrhythmias, particularly in the presence of digitalis, may be difficult to treat unless magnesium levels are normalized.

Magnesium deficiency often occurs in conjunction with hypocalcemia and hypokalemia, producing a number of related neurologic and cardiovascular manifestations. Hypocalcemia is typical of severe hypomagnesemia. Most persons with hypomagnesemia-related hypocalcemia have decreased PTH levels, probably as a result of impaired magnesium-dependent mechanisms that control PTH release and synthesis. Hypokalemia also is a typical feature of hypomagnesemia. It leads to a reduction in intracellular potassium and impairs the ability of the kidney to conserve potassium. When hypomagnesemia is present, hypokalemia is unresponsive to potassium replacement therapy.

Treatment. Hypomagnesemia is treated with magnesium replacement. The route of administration depends on the severity of the condition. Symptomatic, moderate to severe magnesium deficiency is treated by parenteral administration. Treatment must be continued for several days to replace stored and serum levels. In conditions of chronic intestinal or renal loss, maintenance support with oral magnesium may be required. Patients with any degree of renal failure must be carefully monitored to prevent magnesium excess. Magnesium often is used therapeutically to treat cardiac arrhythmia, myocardial infarct, angina, and pregnancy complicated by preeclampsia or eclampsia. Caution to prevent hypermagnesemia is essential.

Hypermagnesemia

Hypermagnesemia represents a serum magnesium concentration in excess of 2.7 mg/dL. Because of the ability of the normal kidney to excrete magnesium, hypermagnesemia is rare.

When hypermagnesemia does occur, it usually is related to renal insufficiency and the injudicious use of magnesium-containing medications such as antacids, mineral supplements, or laxatives. The elderly are particularly at risk because they have age-related reductions in renal function and tend to consume more magnesium-containing medications. Magnesium sulfate is used to treat toxemia of pregnancy and premature labor; in these cases, careful monitoring for signs of hypermagnesemia is essential.

Hypermagnesemia affects neuromuscular and cardiovascular function (see Table 6-7). The signs and symptoms occur only when serum magnesium levels exceed 4.9 mg/dL.³²

Hypermagnesemia diminishes neuromuscular transmission, causing hyporeflexia, muscle weakness, and confusion. Magnesium decreases acetylcholine release at the myoneural junction and may cause neuromuscular blockade and respiratory paralysis. Cardiovascular effects are related to the calcium channel-blocking effects of magnesium. Blood pressure is decreased, and the ECG shows an increase in the PR interval, a shortening of the QT interval, T-wave abnormalities, and prolongation of

the QRS and PR intervals. Hypotension caused by vasodilation and cardiac dysrhythmias can occur with moderate hypermagnesemia (≥ 5 to 10 mg/dL), and confusion and coma can occur with severe hypermagnesemia (≥ 10 mg/dL). Very severe hypermagnesemia (≥ 15 mg/dL) may cause cardiac arrest.

The treatment of hypermagnesemia includes cessation of magnesium administration. Calcium is a direct antagonist of magnesium, and intravenous administration of calcium may be used. Peritoneal dialysis or hemodialysis may be required.

In summary, calcium is one of the major divalent ions in the body. Approximately 99% of body calcium is found in bone; about 1% is in the ICF and 0.1% to 0.2% is in the ECF. The calcium in bone is in dynamic equilibrium with extracellular calcium. Of the three forms of ECF calcium (*i.e.*, protein bound, complexed, and ionized), only the ionized form can cross the cell membrane and contribute to cellular function. Ionized calcium has a number of functions. It contributes to neuromuscular function, plays a vital role in the blood clotting process, and participates in a number of enzyme reactions. Alterations in ionized calcium levels produce neural effects; neural excitability is increased in hypocalcemia and decreased in hypercalcemia.

Magnesium is the second most abundant intracellular cation. It acts as a cofactor in many enzyme reactions and affects neuromuscular function in the same manner as the calcium ion. Magnesium deficiency can result from insufficient intake, excessive losses, or movement between the ECF and ICF compartments. The manifestations of hypomagnesemia are characterized by a decrease in neuromuscular excitability as evidenced by paresthesias and hyperactive reflexes. Cardiovascular effects include tachycardia, hypertension, and ventricular dysrhythmias. Hypermagnesemia usually is related to renal insufficiency and the injudicious use of magnesium-containing medications such as antacids, mineral supplements, or laxatives. It diminishes neuromuscular transmission leading to hyporeflexia, muscle weakness, and confusion.

ACID-BASE BALANCE

Metabolic activities of the body require the precise regulation of acid-base balance, which is reflected by the pH of ECF. Membrane excitability, enzyme systems, and chemical reactions depend on pH being regulated within a narrow physiologic range. Many conditions, pathologic or otherwise, can alter body pH.

Introductory Concepts

Normally, the concentration of body acids and bases is regulated so that the pH of extracellular body fluids is maintained within a very narrow range of 7.35 to 7.45. This balance is maintained through mechanisms that generate, buffer, and eliminate acids and bases.

Acid-Base Chemistry

An *acid* is a molecule that can release a hydrogen ion (H^+), and a *base* is a molecule that can accept or combine with an H^+ ion. Most of the body's acids and bases are weak acids and

bases; the most important are *carbonic acid* (H_2CO_3), which is a weak acid derived from carbon dioxide (CO_2), and *bicarbonate* (HCO_3^-), which is a weak base.

The concentration of H^+ ions in body fluids is low compared with other ions. For example, the Na^+ ion is present at a concentration approximately 1 million times that of the H^+ ion. Because of its low concentration in body fluids, the H^+ ion concentration is commonly expressed in terms of pH. Specifically, *pH* represents the negative logarithm (p) of the H^+ ion concentration in mEq/L. A pH value of 7.0 implies a H^+ ion concentration of 10^{-7} (0.0000001 mEq/L). Because the pH is inversely related to the H^+ ion concentration, a low pH indicates a high concentration of H^+ ions and a high pH, a low concentration.²

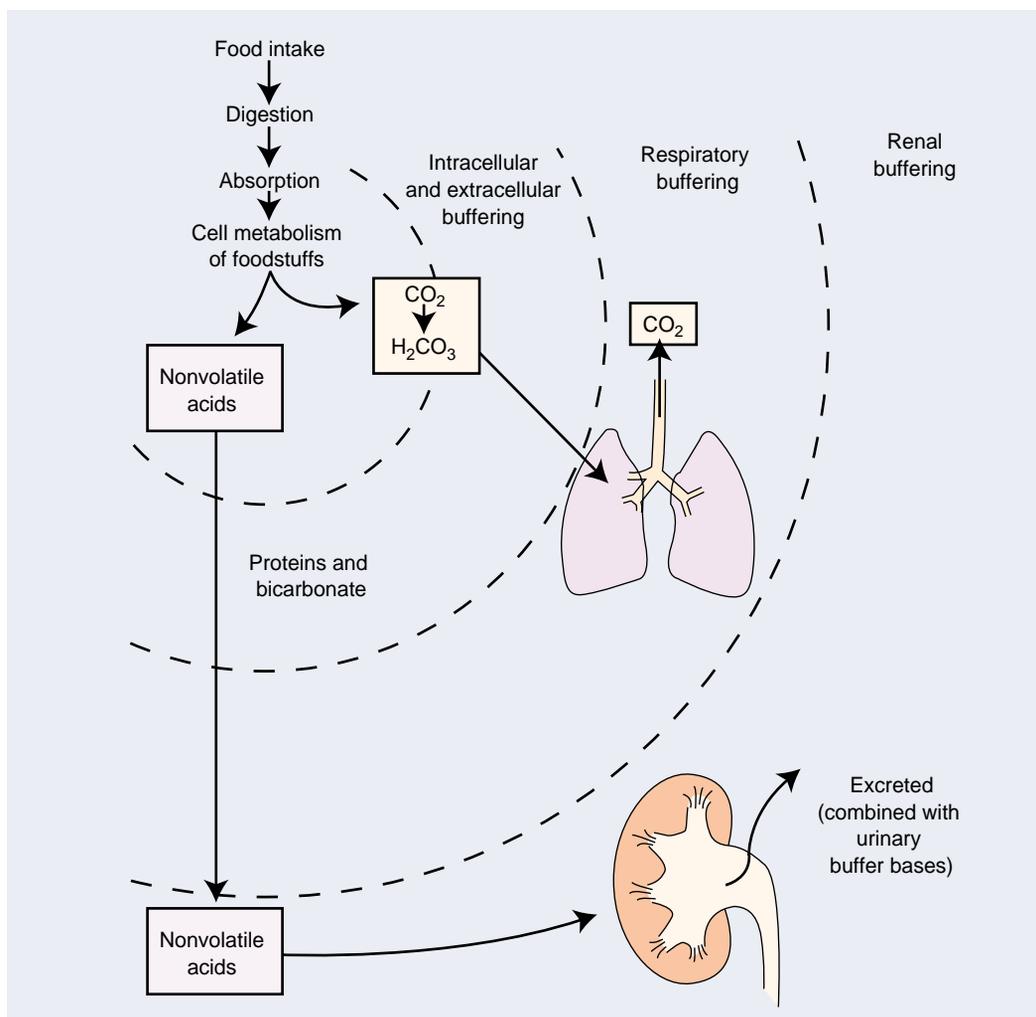
Metabolic Acid and Bicarbonate Production

Acids are continuously generated as by-products of metabolic processes. Physiologically, these acids fall into two groups: the volatile acid carbonic acid and all other nonvolatile or fixed acids (Fig. 6-15).

KEY CONCEPTS

MECHANISMS OF ACID-BASE BALANCE

- The pH is determined by the ratio of the HCO_3^- base to CO_2 (H_2CO_3). At a pH of 7.4, the ratio is normally 20 to 1.
- The HCO_3^- part of the pH equation reflects the generation of nonvolatile metabolic acids that are buffered in intracellular and extracellular buffers and eliminated by the kidney.
- The H_2CO_3 or volatile acid part of the equation represents the level of dissolved CO_2 ($\text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3$) in the blood. It is regulated by the elimination of CO_2 by the lungs.



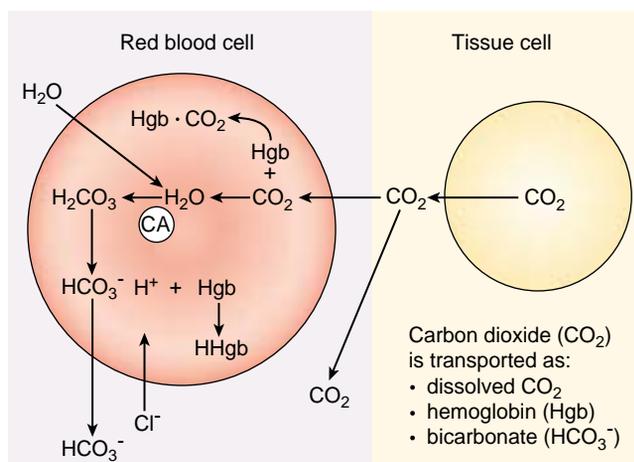
■ **FIGURE 6-15** ■ The role of intracellular and extracellular buffer, respiratory, and renal mechanisms in maintaining normal blood pH. (Rhoades R.A., Tanner G.A. [1996]. *Medical physiology* [p. 468]. Boston: Little, Brown)

The difference between the two types of acids arises because H_2CO_3 is in equilibrium with the volatile CO_2 , which leaves the body by way of the lungs. Therefore, the H_2CO_3 concentration is determined by the lungs and their respiratory capacity. The *noncarbonic acids* (e.g., sulfuric, hydrochloric, phosphoric) are *nonvolatile* and are not eliminated by the lungs. Instead, they are buffered by body proteins or extracellular buffers, such as HCO_3^- , and then excreted by the kidney.

Carbon Dioxide and Bicarbonate Production. Body metabolism results in the production of approximately 15,000 mmol of CO_2 each day.³³ Carbon dioxide is transported in the circulation in three forms: (1) attached to hemoglobin, (2) as dissolved CO_2 (i.e., PCO_2), and as (3) HCO_3^- (Fig. 6-16). Collectively, dissolved CO_2 and HCO_3^- constitute approximately 77% of the CO_2 that is transported in the ECF; the remaining CO_2 travels attached to hemoglobin. Although CO_2 is not an acid, a small percentage of the gas combines with water in the bloodstream to form H_2CO_3 ($\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$). The reaction between CO_2 and water is catalyzed by an enzyme, called *carbonic anhydrase*, which is present in large quantities in red blood cells, renal tubular cells, and other tissues in the body.

Because it is almost impossible to measure H_2CO_3 , dissolved CO_2 measurements are commonly substituted when calculating pH. The H_2CO_3 content of the blood can be calculated by multiplying the partial pressure of the CO_2 in the blood by its solubility coefficient, which is 0.03. This means that the concentration of H_2CO_3 in venous blood, which normally has a PCO_2 of approximately 45 mm Hg, is 1.35 mEq/L ($45 \times 0.03 = 1.35$).

Production of Metabolic Acids. The metabolism of dietary proteins is the major source of strong *inorganic acids*—sulfuric acid, hydrochloric acid, and phosphoric acid.^{33, 34} Oxidation of the sulfur-containing amino acids (e.g., methionine, cysteine, cystine) results in the production of sulfuric acid. Oxidation of arginine and lysine produces hydrochloric acid, and oxidation of phosphorus-containing nucleic acids yields phosphoric acid. Incomplete oxidation of glucose results in the formation of lactic acid, and incomplete oxidation of fats results in the production of ketoacids. The major source of base is the metabolism of amino acids such as aspartate and glutamate and the



■ FIGURE 6-16 ■ Mechanisms of carbon dioxide transport.

metabolism of certain organic anions (e.g., citrate, lactate, acetate). Acid production normally exceeds base production, with the net effect being the addition of approximately 1 mmol/kg body weight of nonvolatile acid to the body each day.³³ A vegetarian diet, which contains large amounts of organic anions, results in the net production of base.

Calculation of pH. The pH is calculated with the *Henderson-Hasselbalch equation* using the dissociation constant for the bicarbonate buffer system (6.1) and the HCO_3^- to H_2CO_3 ratio.

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3}$$

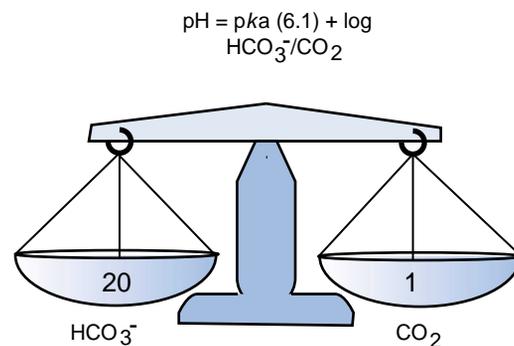
The log of 20 is 1.3. Thus, when the ratio is 20 to 1, the pH is within the normal range at 7.4 (Fig. 6-17). Because the ratio is used, a change in HCO_3^- will have little or no effect on pH, as long as there are accompanying changes in H_2CO_3 . The generation of metabolic acids and the availability of bicarbonate to buffer these acids control the HCO_3^- part of the equation. The H_2CO_3 part of the equation is regulated by the lungs and their ability to eliminate CO_2 . The kidney functions in the generation and reabsorption of HCO_3^- and contributes to control of the metabolic part of the equation.

Regulation of pH

The pH of body fluids is regulated by three major mechanisms: (1) ICF and ECF buffering systems, (2) the lungs, which control the elimination of CO_2 , and (3) the kidneys, which eliminate H^+ and regulate the elimination of HCO_3^- .

Intracellular and Extracellular Buffer Systems. The moment-by-moment regulation of pH depends on the ICF and ECF buffer systems. A *buffer system* consists of a weak acid and the base salt of that acid or of a weak base and its acid salt. In the process of preventing large changes in pH, the system trades a strong acid for a weak acid or a strong base for a weak base.

The three major buffer systems that protect the pH of body fluids are (1) proteins, (2) the HCO_3^- buffer system, and (3) the transcellular H^+/K^+ exchange system.² These buffer systems are immediately available to combine with excess acids or bases and prevent large changes in pH from occurring during the time it takes for the respiratory and renal mechanisms to become effective. Bone also represents an important site for the buffering of acids and bases.³³ The role of bone buffers is even greater in chronic acid-base disorders. One consequence of



■ FIGURE 6-17 ■ The Henderson-Hasselbalch equation expressed as a simple scale.

bone buffering is the release of calcium from bone and increased renal excretion of calcium. In addition to causing demineralization of bone, it also predisposes to kidney stones.

Proteins are the largest buffer system in the body. Proteins are *amphoteric*, meaning that they can function as either acids or bases. They contain many ionizable groups that can release or bind H^+ . The protein buffers are largely located within cells, and H^+ ions and CO_2 diffuse across cell membranes for buffering by intracellular proteins. Albumin and plasma globulins are the major protein buffers in the vascular compartment.

The *bicarbonate buffer system* uses H_2CO_3 as its weak acid and HCO_3^- as its weak base. It substitutes the weak H_2CO_3 for a strong acid such as hydrochloric acid or the weak HCO_3^- base for a strong base such as sodium hydroxide. The HCO_3^-/H_2CO_3 buffer system is a particularly efficient system because the buffer components can be readily added or removed from the body.³⁴ Metabolism provides an ample supply of CO_2 , which can replace any H_2CO_3 that is lost when excess base is added, and CO_2 can be readily eliminated when excess acid is added. Likewise, the kidney can form new HCO_3^- when excess acid is added, and it can excrete HCO_3^- when excess base is added.

The *transcompartmental exchange* of the K^+ and H^+ ions is important in the regulation of acid-base balance. Both ions are positively charged, and both ions move freely between the ICF and ECF compartments. When excess H^+ is present in the ECF, it moves into the body cells in exchange for K^+ . Likewise, when excess K^+ is present in the ECF, it moves into the cell in exchange for H^+ . On the average, serum K^+ rises by approximately 0.6 mEq/L for every 0.1 unit fall in pH.³³ Thus, alterations in K^+ levels can affect acid-base balance, and changes in acid-base balance can influence K^+ levels. Potassium shifts tend to be more pronounced in acidemia than alkalemia and are greater in metabolic acidosis than respiratory acidosis.⁵ Metabolic acidosis caused by an accumulation of nonorganic acids (*e.g.*, hydrochloric acid that occurs in diarrhea, phosphoric acid that occurs in renal failure) produces a greater increase in K^+ than does acidosis caused by an accumulation of organic acids (*e.g.*, lactic acid, ketoacids).

An important implication of the K^+ and H^+ transcompartmental exchange is its effect on the resting membrane potential of neurons and other excitable tissue. In acidosis, increased levels of serum K^+ cause the resting membrane potential to become less negative and in alkalosis, decreased levels cause the resting membrane potential to become more negative. Changes in neural excitability are further influenced by alterations in ionized calcium. In acidosis, the ionized portion of the extracellular calcium is increased, making neurons less excitable, and in alkalosis, the amount of ionized calcium is reduced, making neurons more excitable.

Respiratory Control Mechanisms. The respiratory system provides for the elimination of CO_2 into the air and plays a major role in acid-base regulation. The respiratory control of pH is rapid, occurring within minutes, and is maximal within 12 to 24 hours.³³ However, it does not return the pH to normal.

Renal Control Mechanisms. The kidneys regulate acid-base balance by excreting acidic or alkaline urine. Excreting an acidic urine reduces the amount of acid in the ECF, and excreting an alkaline urine removes base from the ECF. The renal mechanisms for regulating acid-base balance cannot adjust the pH

within minutes, as respiratory mechanisms can, but they continue to function for days until the pH has returned to normal or near-normal range.

The kidneys filter HCO_3^- in the glomerulus and then reabsorb it in the tubules as a means of maintaining ECF levels. Bicarbonate ions do not readily cross the membranes of renal tubular cells; therefore, HCO_3^- that has been filtered in the glomerulus cannot be directly reabsorbed. Instead, the HCO_3^- ions are reabsorbed in a special process in which they first combine with H^+ ions that have been secreted into the tubular fluid to form H_2CO_3 , which is converted to CO_2 and water (Fig. 6-18). The resulting CO_2 can readily cross the tubular membrane and enter the tubular cell, where it combines with water, under the influence of carbonic anhydrase, to generate a new H_2CO_3 molecule. The newly formed H_2CO_3 , in turn, dissociates to form a HCO_3^- and a H^+ ion. The HCO_3^- that is formed moves out of the tubular cell into the bloodstream and the H^+ is secreted into the tubular fluid.

The HCO_3^- reabsorption system serves a dual purpose—it buffers the H^+ ions that have been secreted from the blood into the tubular fluid, and it conserves the HCO_3^- ions that have been filtered from the blood into the tubular fluid. Normally, only a few of the secreted H^+ ions remain in the tubular fluid because the secretion of H^+ ions is roughly equivalent to the number of HCO_3^- ions that are filtered in the glomerulus. When the number of H^+ ions secreted into the tubular fluid exceeds the amount of filtered HCO_3^- ions, the urine filtrate becomes acidic.

The elimination of H^+ is accomplished through secretion into the urine filtrate by the cells in the renal tubules. Because extremely acidic urine would be damaging to structures in the urinary tract, the pH of the urine is maintained within a range from 4.5 to 8.0. This limits the number of unbuffered H^+ ions that can be excreted by the kidney. When the number of free H^+ ions secreted into the tubular fluid threatens to cause the urine to become too acidic, the H^+ ions must be carried in

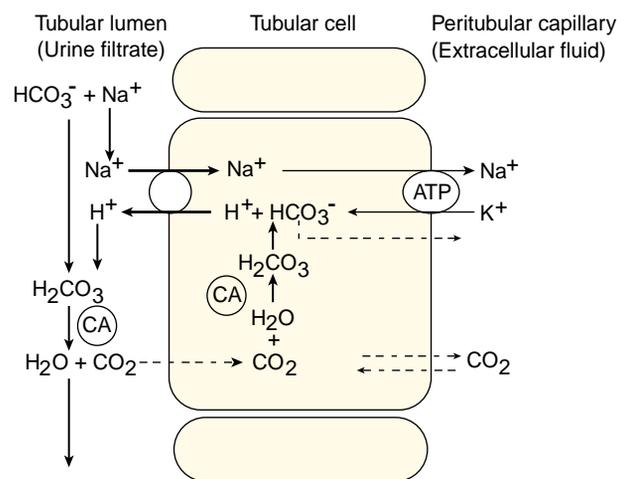


FIGURE 6-18 Hydrogen ion (H^+) secretion and bicarbonate ion (HCO_3^-) reabsorption in a renal tubular cell. Carbon dioxide (CO_2) diffuses from the blood or urine filtrate into the tubular cell, where it combines with water in a carbonic anhydrase-catalyzed reaction that yields carbonic acid (H_2CO_3). The H_2CO_3 dissociates to form H^+ and HCO_3^- . The H^+ is secreted into the tubular fluid in exchange for Na^+ . The Na^+ and HCO_3^- enter the extracellular fluid.

some other form. This is accomplished by combining the H^+ ions with intratubular buffers before being excreted in the urine. There are two important intratubular buffer systems: the phosphate buffer system and the ammonia buffer system.

The *phosphate buffer system* uses HPO_4^{2-} and $H_2PO_4^-$ that are present in the tubular filtrate to buffer H^+ . The combination of H^+ with HPO_4^{2-} to form $H_2PO_4^-$ allows the kidneys to increase their secretion of H^+ ions. Because they are poorly reabsorbed, the phosphates become more concentrated as they move through the tubules. This system works best when the renal tubular fluid contains a high concentration of H^+ ions.

Another important but more complex buffer system is the *ammonia buffer system*. Renal tubular cells are able to use the amino acid glutamine to synthesize ammonia (NH_3) and secrete it into the tubular fluid. The H^+ ions then combine with the NH_3 to form an ammonium ion (NH_4^+). The NH_4^+ ions combine with Cl^- ions (Cl^-), which are present in the tubular fluid, to form ammonium Cl^- (NH_4Cl), which is then excreted in the urine.

Plasma potassium levels influence renal elimination of H^+ ions and vice versa. When plasma potassium levels fall, there is movement of K^+ ions from tubular cells into the plasma and a reciprocal movement of H^+ ions from the plasma into tubular cells. Potassium depletion also produces a reduction in Cl^- reabsorption in the distal tubule. The result is increased reabsorption of the filtered bicarbonate and development of metabolic alkalosis. An elevation in serum potassium has the opposite effect.

Aldosterone also influences H^+ ion elimination by the kidney. It acts in the collecting duct to indirectly stimulate H^+ ion secretion, while increasing Na^+ ion reabsorption and K^+ secretion. Hyperaldosteronism tends to lead to a decrease in serum K^+ levels and increased pH and alkalosis caused by increased H^+ ion secretion. Hypoaldosteronism has the opposite effect. It leads to increased K^+ levels, decreased H^+ ion secretion, and acidosis.

One of the mechanisms that the kidneys use in regulating the pH of the ECF is the conservation or elimination of HCO_3^- ions; in the process, it often is necessary to shuffle anions. Chloride is the most abundant anion in the ECF and can substitute for HCO_3^- when an anion shift is needed. As an example, serum HCO_3^- levels normally increase as hydrochloric acid (HCl) is secreted into the stomach after a heavy meal, causing what is called the *postprandial alkaline tide*. Later, as the Cl^- ion is reabsorbed in the small intestine, the pH returns to normal. *Hypochloremic alkalosis* refers to an increase in pH that is induced by a decrease in serum Cl^- levels and *hyperchloremic acidosis* to a decrease in pH that occurs when excess levels of Cl^- are present.

Laboratory Tests

Laboratory tests that are used in assessing acid-base balance include arterial blood gas measurements, carbon dioxide content and bicarbonate levels, base excess or deficit, and the anion gap.

Arterial blood gases provide a means of assessing the respiratory component of acid-base balance. H_2CO_3 levels are determined from arterial CO_2 levels and the solubility coefficient for CO_2 (normal arterial PCO_2 is 38 to 42 mm Hg). Arterial blood gases are used because *venous blood gases* are highly variable, depending on metabolic demands of the various tissues that empty into the vein from where the sample is being drawn.

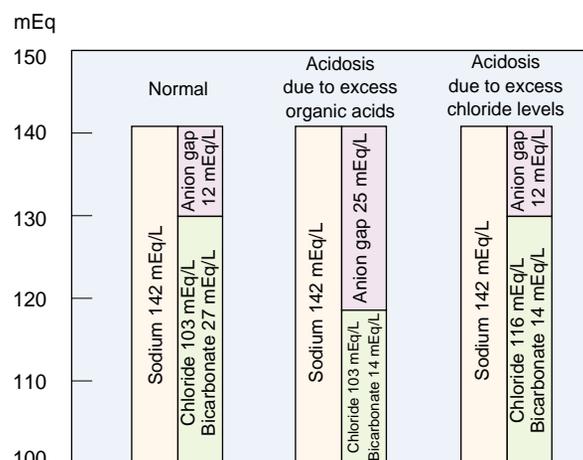
Laboratory measurements of electrolytes include the CO_2 content and bicarbonate levels. The *CO_2 content* refers to the total CO_2 content of blood, including that contained in bicarbonate. It is determined by adding a strong acid to a plasma sample and measuring the amount of CO_2 generated. More than 70% of the CO_2 in the blood is in the form of bicarbonate.² The serum *bicarbonate* is then determined from the total CO_2 content of the blood.

Base excess or deficit is a measurement of bicarbonate excess or deficit. It describes the amount of a fixed acid or base that must be added to a blood sample to achieve a pH of 7.4 (normal ± 3.0 mEq/L).³³ A base excess indicates metabolic alkalosis, and a base deficit indicates metabolic acidosis.

The *anion gap* describes the difference between the plasma concentration of the major measured cation (Na^+) and the sum of the measured anions (Cl^- and HCO_3^-). This difference represents the concentration of unmeasured anions, such as phosphates, sulfates, organic acids, and proteins (Fig. 6-19). Normally, the anion gap ranges between 8 and 12 mEq/L (a value of 16 mEq is normal if Na^+ and K^+ concentrations are used in the calculation). The anion gap is increased in conditions such as lactic acidosis and ketoacidosis that result from elevated levels of metabolic acids. A low anion gap is found in conditions that produce a fall in unmeasured anions (primarily albumin) or rise in unmeasured cations. An increase in unmeasured anions can occur in hyperkalemia, hypercalcemia, hypermagnesemia, lithium intoxication, or multiple myeloma, in which an abnormal immunoglobulin is produced.³⁴

Alterations in Acid-Base Balance

The terms *acidosis* and *alkalosis* describe the clinical conditions that arise as a result of changes in dissolved CO_2 and HCO_3^- concentrations. An alkali represents a combination of one or more alkali metals such as sodium or potassium with a highly basic ion such as a hydroxyl ion (OH^-). Sodium bicarbonate ($NaHCO_3$) is the main alkali in the ECF. Although the definitions differ somewhat, the terms *alkali* and *base* are often used



■ **FIGURE 6-19** ■ The anion gap in acidosis due to excess metabolic acids and excess serum chloride levels. Unmeasured anions such as phosphates, sulfates, and organic acids increase the anion gap because they replace bicarbonate. This assumes there is no change in sodium content.

KEY CONCEPTS**ACID-BASE DISORDERS**

- The manifestations of acid-base disorders can be divided into three groups: (1) those due to the primary cause of the imbalance, (2) those due to the changed pH, and (3) those due to the elicited compensatory mechanisms.
- Metabolic acidosis represents a decrease in HCO_3^- that is caused by an excess of nonvolatile acids or loss of bicarbonate, and metabolic alkalosis represents an increase in HCO_3^- caused by a decrease in nonvolatile acids or increase in HCO_3^- intake or generation.
- Respiratory acidosis represents an increase in H_2CO_3 that is caused by respiratory conditions that interfere with the elimination of CO_2 , and respiratory alkalosis represents a decrease in H_2CO_3 that is caused by excess elimination of CO_2 .

interchangeably. Thus, the term *alkalosis* has come to mean the opposite of *acidosis*.

Metabolic Versus Respiratory Acid-Base Disorders

There are two types of acid-base disorders: metabolic and respiratory. Metabolic disorders produce an alteration in bicarbonate concentration and result from the addition or loss of nonvolatile acid or alkali to or from the ECF. A decrease in pH caused by a decrease in bicarbonate is called *metabolic acidosis*, and an elevated pH caused by increased bicarbonate levels is called *metabolic alkalosis*. Respiratory disorders involve changes in the CO_2 , reflecting an increase or decrease in alveolar ventilation. *Respiratory acidosis* is characterized by a decrease in pH, reflecting a decrease in ventilation and an increase in CO_2 . *Respiratory alkalosis* involves an increase in pH, resulting from an increase in alveolar ventilation and a decrease in CO_2 .

Primary Versus Compensatory Mechanisms

Acidosis and alkalosis typically involve a *primary* or *initiating event* and a *compensatory state* that results from homeostatic mechanisms that attempt to correct or prevent large changes in

pH. For example, a person may have a primary metabolic acidosis as a result of overproduction of ketoacids and respiratory alkalosis because of a compensatory increase in ventilation (see Table 6-8).

Compensatory mechanisms adjust the pH toward a more normal level without correcting the underlying cause of the disorder. Often, compensatory mechanisms are interim measures that permit survival while the body attempts to correct the primary disorder. Compensation requires the use of mechanisms that are different from those that caused the primary disorder. In other words, the lungs cannot compensate for respiratory acidosis that is caused by lung disease, nor can the kidneys compensate for metabolic acidosis that occurs because of renal failure. Compensatory mechanisms often become more effective with time; thus, there are differences between the level of pH change that occurs with acute and chronic acid-base disorders.

Metabolic Acidosis

Metabolic acidosis involves a primary deficit in base bicarbonate along with a decrease in plasma pH. In metabolic acidosis, the body compensates for the decrease in pH by increasing the respiratory rate in an effort to decrease CO_2 and H_2CO_3 levels.

Causes. Metabolic acidosis can be caused by one of four mechanisms: (1) increased production of nonvolatile metabolic acids, (2) decreased acid secretion by the kidney, (3) excessive loss of bicarbonate, or (4) an increase in chloride. Metabolic acids increase when there is an accumulation of lactic acid, overproduction of ketoacids, or ingestion of drugs (*e.g.*, aspirin and salicylates) or chemicals (*e.g.*, methanol or ethylene glycol) that results in production of metabolic acids or an inability of the kidneys to excrete metabolic acids or conserve bicarbonate. The anion gap is often useful in determining the cause of the metabolic acidosis (Chart 6-2). The presence of excess metabolic acids produces an increase in the anion gap as sodium bicarbonate is replaced by the sodium salt of the offending acid (*e.g.*, sodium lactate). When acidosis results from increased chloride levels (*e.g.*, hyperchloremic acidosis), the anion gap remains within normal levels.

Acute lactic acidosis is one of the most common types of metabolic acidosis. Lactic acid is produced by the anaerobic metabolism of glucose. Lactic acidosis develops when there is excess production of lactic acid or diminished lactic acid removal from the blood. Most cases of lactic acidosis are caused by inadequate oxygen delivery, as in shock or cardiac arrest. These conditions

TABLE 6-8 Summary of Acid-Base Imbalances

Acid-Base Imbalance	Primary Disturbance	Respiratory Compensation	Renal Compensation
Metabolic acidosis	Decrease in bicarbonate	Hyperventilation to decrease PCO_2	If no renal disease, increased H^+ excretion and increased HCO_3^- reabsorption
Metabolic alkalosis	Increase in bicarbonate	Hypoventilation to increase PCO_2	If no renal disease, decreased H^+ excretion and decreased HCO_3^- reabsorption
Respiratory acidosis	Increase in PCO_2	None	Increased H^+ excretion and increased HCO_3^- reabsorption
Respiratory alkalosis	Decrease in PCO_2	None	Decreased H^+ excretion and decreased HCO_3^- reabsorption

CHART 6-2 The Anion Gap in Differential Diagnosis of Metabolic Acidosis

Decreased Anion Gap (<8 mEq/L)

Hypoalbuminemia (decrease in unmeasured anions)
Multiple myeloma (increase in unmeasured cationic IgG paraproteins)
Increased unmeasured cations (hyperkalemia, hypercalcemia, hypermagnesemia, lithium intoxication)

Increased Anion Gap (>12 mEq/L)

Presence of unmeasured metabolic anion
Diabetic ketoacidosis
Alcoholic ketoacidosis
Lactic acidosis
Starvation
Renal insufficiency
Presence of drug or chemical anion
Salicylate poisoning
Methanol poisoning
Ethylene glycol poisoning

Normal Anion Gap (8–12 mEq/L)

Loss of bicarbonate
Diarrhea
Pancreatic fluid loss
Ileostomy (unadapted)
Chloride retention
Renal tubular acidosis
Ileal loop bladder
Parenteral nutrition (arginine and lysine)

increase lactic acid production, and they impair lactic acid clearance because of poor liver perfusion. Excess lactate also is produced with vigorous exercise or grand mal seizures (*i.e.*, convulsions), during which there is a local disproportion between oxygen supply and demand in the contracting muscles.

Lactic acidosis is also associated with disorders in which tissue hypoxia does not appear to be present. It has been reported in patients with leukemia, lymphomas, or other cancers and in patients with severe liver failure. The mechanisms causing lactic acidosis in these conditions are poorly understood. Some conditions such as neoplasms may produce local increases in tissue metabolism and lactate production or may interfere with blood flow delivery to noncancerous cells.

Ketoacids (*i.e.*, acetoacetic and β -hydroxybutyric acid), produced in the liver from fatty acids, are the source of fuel for many body tissues. An overproduction of ketoacids occurs when carbohydrate stores are inadequate or when the body cannot use available carbohydrates as a fuel. Under these conditions, fatty acids are mobilized from adipose tissue and delivered to the liver, where they are converted to ketones. Ketoacidosis develops when ketone production exceeds tissue use.

The most common cause of ketoacidosis is uncontrolled diabetes mellitus, in which an insulin deficiency leads to the release of fatty acids from adipose cells with subsequent production of excess ketoacids (see Chapter 32). Ketoacidosis may also develop as the result of fasting or food deprivation, during which the lack of carbohydrates produces a self-limited state of

ketoacidosis (self-limited because the resultant decrease in insulin release suppresses the release of fatty acids for fat cells). Ketones are also formed during the oxidation of alcohol, a process that occurs in the liver. A condition called *alcoholic ketoacidosis* can develop in persons who engage in excess alcohol consumption.³⁵ It usually follows prolonged alcohol ingestion, particularly if accompanied by decreased food intake and vomiting that results in using fatty acids as an energy source.

Kidney failure is the most common cause of chronic metabolic acidosis. The kidneys normally conserve HCO_3^- and secrete H^+ ions into the urine as a means of regulating acid-base balance. In renal failure, there is loss of glomerular and tubular function, with retention of nitrogenous wastes and metabolic acids. In a condition called *renal tubular acidosis*, glomerular function is normal, but the tubular secretion of H^+ or reabsorption of HCO_3^- is abnormal.

Increased HCO_3^- losses occur with the loss of bicarbonate-rich body fluids or with impaired conservation of HCO_3^- by the kidney. Intestinal secretions have a high HCO_3^- concentration. Consequently, excessive losses of HCO_3^- ions occur with severe diarrhea; small bowel, pancreatic, or biliary fistula drainage; ileostomy drainage; and intestinal suction. In diarrhea of microbial origin, HCO_3^- is secreted into the bowel to neutralize the metabolic acids produced by the microorganisms causing the diarrhea.

Hyperchloremic acidosis occurs when serum Cl^- ion levels are increased. Because Cl^- and HCO_3^- are anions, the serum HCO_3^- ion concentration decreases when there is an increase in Cl^- ions. Hyperchloremic acidosis can occur as the result of abnormal absorption of chloride by the kidneys or as a result of treatment with chloride-containing medications (*i.e.*, sodium chloride, amino acid-chloride hyperalimentation solutions, and ammonium chloride). The administration of intravenous sodium chloride or parenteral hyperalimentation solutions that contain an amino acid-chloride combination can cause acidosis in a similar manner.³⁶ With hyperchloremic acidosis, the anion gap is within the normal range, but the chloride levels are increased and bicarbonate levels are decreased.

Manifestations. Metabolic acidosis is characterized by a decrease in pH (<7.35) and a decrease in serum HCO_3^- levels (<24 mEq/L). Acidosis typically produces a compensatory increase in respiratory rate with a decrease in PCO_2 and H_2CO_3 (see Table 6-9).

The manifestations of metabolic acidosis fall into three categories: (1) signs and symptoms of the disorder causing the acidosis, (2) alterations in function resulting from the decreased pH, and (3) changes in body function related to recruitment of compensatory mechanisms. The signs and symptoms of metabolic acidosis usually begin to appear when the plasma HCO_3^- concentration falls to 20 mEq/L or less. Metabolic acidosis is seldom a primary disorder; the manifestations of the disorder are frequently superimposed on the symptoms of the contributing health problem. With diabetic ketoacidosis, which is a common cause of metabolic acidosis, there is an increase in blood and urine glucose and a characteristic smell of ketones to the breath. In metabolic acidosis that accompanies renal failure, blood urea nitrogen levels are elevated, and tests of renal function yield abnormal results.

Changes in pH have a direct effect on body function that can produce signs and symptoms common to most types of meta-

TABLE 6-9 Manifestations of Metabolic Acidosis and Alkalosis

Metabolic Acidosis	Metabolic Alkalosis
<p>Laboratory Tests</p> <p>pH decreased Bicarbonate (primary) decreased PCO₂ (compensatory) decreased</p> <p>Signs of Compensation</p> <p>Increased respirations (rate and depth) Hyperkalemia Acid urine Increased ammonia in urine</p> <p>Gastrointestinal Effects</p> <p>Anorexia Nausea and vomiting Abdominal pain</p> <p>Nervous System Effects</p> <p>Weakness Lethargy Confusion Stupor Coma Depression of vital functions</p> <p>Cardiovascular Effects</p> <p>Peripheral vasodilation Decreased heart rate Cardiac dysrhythmias</p> <p>Skin</p> <p>Warm and flushed</p> <p>Skeletal System Effects</p> <p>Bone disease (chronic acidosis)</p>	<p>Laboratory Tests</p> <p>pH increased Bicarbonate (primary) increased PCO₂ (compensatory) increased</p> <p>Signs of Compensation</p> <p>Decreased respirations (rate and depth) with various degrees of hypoxia and respiratory acidosis</p> <p>Nervous System Effects</p> <p>Hyperactive reflexes Tetany Confusion Seizures</p> <p>Cardiovascular Effects</p> <p>Hypotension Cardiac dysrhythmias</p>

bolic acidosis, regardless of cause. A person with metabolic acidosis often reports weakness, fatigue, general malaise, and a dull headache. Anorexia, nausea, vomiting, and abdominal pain also may be reported. The skin is warm and flushed, and there is a decrease in tissue turgor when fluid deficit accompanies acidosis. In persons with undiagnosed diabetes mellitus, the nausea, vomiting, and abdominal symptoms may be misinterpreted as being caused by gastrointestinal flu or other abdominal disease, such as appendicitis.

Neural activity becomes depressed as body pH declines. Acidosis directly depresses membrane excitability, and it decreases binding of calcium to plasma proteins so that more free calcium is available to decrease neural activity. As acidosis progresses, the level of consciousness declines, and stupor and coma develop. The skin becomes warm and flushed as the cutaneous blood vessels become less responsive to sympathetic stimulation and lose tone.

When the pH falls to 7.0, cardiac contractility and cardiac output decrease, the heart becomes less responsive to catecholamines (*i.e.*, epinephrine and norepinephrine), and dysrhythmias, including fatal ventricular dysrhythmias, can develop.

Metabolic acidosis also is accompanied by signs and symptoms related to the recruitment of compensatory mechanisms. In situations of acute metabolic acidosis, the respiratory system

compensates for a decrease in pH by increasing ventilation to reduce PCO₂; this is accomplished through deep and rapid respirations. There may be complaints of dyspnea with exertion; with severe acidosis, dyspnea may be present even at rest.

When kidney function is normal, net acid excretion increases promptly in response to acidosis, and the urine becomes more acid. Most of the initial acid secretion into the urine is facilitated through use of the phosphate buffer system. Over several days, ammonia production by the kidney increases and becomes the most important mechanism for excreting excess H⁺ ions.

Chronic acidemia, as in renal failure, can lead to a variety of skeletal problems, some of which result from the release of calcium and phosphate during bone buffering of excess H⁺ ions.³⁷ Of particular importance is impaired growth in children. In infants and children, acidemia may be associated with a variety of nonspecific symptoms such as anorexia, weight loss, muscle weakness, and listlessness.^{33,37}

Treatment. The treatment of metabolic acidosis focuses on correcting the condition that caused the disorder and restoring the fluids and electrolytes that have been lost from the body. The treatment of diabetic ketoacidosis is discussed in Chapter 32.

Metabolic Alkalosis

Metabolic alkalosis involves a primary excess of base bicarbonate along with an increased plasma pH. It can be caused by a gain in HCO_3^- or loss of H^+ ions. The body compensates for the increase in pH by decreasing the respiratory rate as a means of increasing PCO_2 and H_2CO_3 levels.

Causes. Metabolic alkalosis can occur because of (1) ingestion or administration of excess NaHCO_3 or other alkali, (2) excess H^+ , Cl^- , and K^+ loss, or (3) ECF volume contraction.

Excessive alkali ingestion, as in the use of bicarbonate-containing antacids or sodium bicarbonate administration during cardiopulmonary resuscitation, can cause metabolic alkalosis. Other sources of alkali intake are acetate in hyperalimentation solutions and lactate in parenteral solutions such as Ringer's lactate. A condition called the milk-alkali syndrome may develop in persons who consume excessive amounts of milk (Ca^{++} source) along with alkaline antacids. In this case metabolic alkalosis develops as a consequence of vomiting (volume depletion and K^+ loss), hypercalcemia (increased HCO_3^- reabsorption), and reduced glomerular filtration rate (increased HCO_3^- reabsorption).^{34,38}

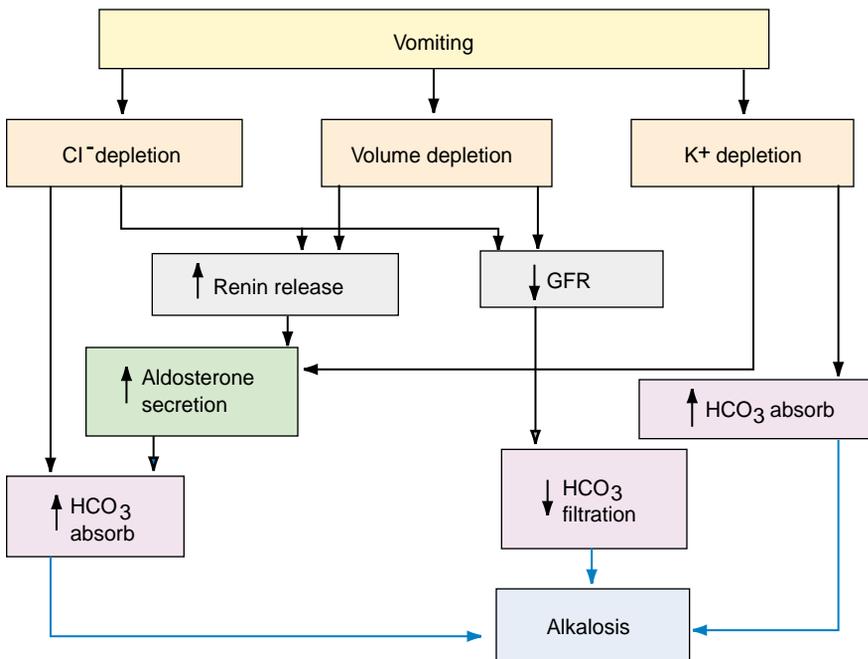
Vomiting, removal of gastric secretion through use of nasogastric suction, and low serum potassium levels resulting from hyperaldosteronism or diuretic therapy are the most common causes of metabolic alkalosis in hospitalized patients. The binge-purge syndrome, or self-induced vomiting, is also associated with metabolic alkalosis.³⁸ Gastric secretions contain high concentrations of HCl and lesser concentrations of K^+ . As Cl^- is taken from the blood and secreted into the stomach with H^+ , it is replaced by HCO_3^- . Normally, the increase in serum HCO_3^- concentration is only transient because the entry of acid into the duodenum stimulates an equal secretion of pancreatic HCO_3^- . However, the continued loss of H^+ and Cl^- ions from the stomach because of vomiting or gastric suction stimulates continued production of gastric acid and thus the addition of more bicarbonate into the blood.

Metabolic alkalosis can also result from the use of diuretics (*e.g.*, loop and thiazide diuretics) and other conditions that cause excessive loss of potassium in the urine. Hypokalemia produces a compensatory increase in K^+ reabsorption and H^+ secretion by the kidney, along with a simultaneous increase in HCO_3^- reabsorption.³⁴ The adrenocorticosteroid hormone, aldosterone, increases H^+ ion secretion as it increases Na^+ and HCO_3^- ion reabsorption. In hyperaldosteronism, the concurrent loss of K^+ in the urine serves to perpetuate the alkalosis.

Chronic respiratory acidosis produces a compensatory loss of H^+ and Cl^- ions in the urine along with HCO_3^- retention. When respiratory acidosis is corrected abruptly, as with mechanical ventilation, a "posthypercapnic" metabolic alkalosis may develop because of a rapid drop in PCO_2 , while the HCO_3^- concentration, which requires renal elimination, remains elevated.

Vomiting results in the loss of water, Na^+ , Cl^- , and K^+ . The resultant volume depletion, hypochloremia, and hypokalemia produce a metabolic alkalosis by increasing renal reabsorption of HCO_3^- (Fig. 6-20). Volume depletion and hypokalemia also increase the activity of the renin-angiotensin-aldosterone system, with increased Na^+ reabsorption. Na^+ reabsorption requires a concomitant anion reabsorption. Because of a Cl^- deficit, HCO_3^- is reabsorbed along with Na^+ , contributing to the development of metabolic alkalosis.

Manifestations. Metabolic alkalosis is characterized by a plasma pH greater than 7.45, plasma HCO_3^- level greater than 29 mEq/L, and base excess greater than 3.0 mEq/L (Table 6-9). Persons with metabolic alkalosis often have no symptoms or have signs related to volume depletion or hypokalemia. The neurologic signs (*e.g.*, hyperexcitability) occur less frequently with metabolic alkalosis than with other acid-base disorders because the HCO_3^- ion enters the cerebrospinal fluid more slowly than does CO_2 . When neurologic manifestations occur, as in acute and severe metabolic alkalosis, they include mental confusion, hyperactive reflexes, tetany, and carpopedal spasm. Metabolic alkalosis also leads to a compensatory hypoventila-



■ **FIGURE 6-20** ■ The mechanisms by which vomiting maintains metabolic alkalosis. See text for explanation. (Adapted from Galla J.H., Luke R.G. [1987]. Pathophysiology of metabolic alkalosis. *Hospital Practice* 22 [10], 130)

tion, with the development of various degrees of hypoxemia and respiratory acidosis. Significant morbidity occurs with severe metabolic alkalosis (pH >7.55), including respiratory failure, dysrhythmias, seizures, and coma.

Treatment. The treatment of metabolic alkalosis usually is directed toward correcting the cause of the condition. A chloride deficit requires correction. Potassium chloride usually is the treatment of choice for metabolic alkalosis when there is an accompanying potassium deficit. When potassium chloride is used as a therapy, the chloride anion replaces the bicarbonate anion, and the administration of potassium corrects the potassium deficit and allows the kidneys to conserve H^+ while eliminating the K^+ . Fluid replacement with normal saline or one-half normal saline often is used in the treatment of patients with volume contraction alkalosis.

Respiratory Acidosis

Respiratory acidosis involves an increase in PCO_2 and H_2CO_3 along with a decrease in pH. Acute respiratory failure is associated with severe acidosis and only a small change in serum bicarbonate levels. Within a day or so, renal compensatory mechanisms begin to conserve and generate HCO_3^- ions. In chronic respiratory acidosis, there is a compensatory increase in bicarbonate levels.³⁹

Causes. Respiratory acidosis occurs in conditions that impair alveolar ventilation and cause an increase in PCO_2 . It can occur as an acute or chronic disorder. Because renal compensatory mechanisms take time to exert their effects, blood pH tends to drop sharply in persons with acute respiratory acidosis.

Acute respiratory acidosis can be caused by impaired function of the respiratory center in the medulla (as in narcotic

overdose), lung disease, chest injury, weakness of the respiratory muscles, or airway obstruction. Acute respiratory acidosis can also result from breathing air with a high CO_2 content. Almost all persons with acute respiratory acidosis are hypoxemic if they are breathing room air. In many cases, signs of hypoxemia develop before those of respiratory acidosis because CO_2 diffuses across the alveolar capillary membrane 20 times more rapidly than does oxygen.^{33,34}

Chronic respiratory acidosis is associated with chronic lung diseases such as chronic bronchitis and emphysema (see Chapter 21). In people with these disorders, the persistent elevation of PCO_2 stimulates renal H^+ ion secretion and HCO_3^- reabsorption. The effectiveness of these compensatory mechanisms can often return the pH to near-normal values as long as oxygen levels are maintained within a range that does not unduly suppress the chemoreceptor-mediated control of ventilation.

An acute episode of respiratory acidosis can develop in persons with chronic lung disease who receive oxygen therapy at a flow-rate sufficient to raise the PO_2 to a level that produces a decrease in ventilation. In these persons, the respiratory center has become adapted to the elevated levels of CO_2 and no longer responds to increases in PCO_2 . Instead, the oxygen content of their blood becomes the major stimulus for respiration. If oxygen is administered at a flow rate that is sufficient to suppress this stimulus, the rate and depth of respiration decrease, and the CO_2 content of the blood increases.

Manifestations. Respiratory acidosis is associated with a plasma pH less than 7.35 and an arterial PCO_2 greater than 50 mm Hg (Table 6-10). The signs and symptoms of respiratory acidosis depend on the rapidity of onset and whether the condition is acute or chronic. Because respiratory acidosis often

TABLE 6-10 Manifestations of Respiratory Acidosis and Alkalosis

Respiratory Acidosis	Respiratory Alkalosis
<p>Laboratory Tests</p> <p>pH decreased</p> <p>PCO_2 (primary) increased</p> <p>Bicarbonate (compensatory) increased</p> <p>Signs of Compensation</p> <p>Acid urine</p> <p>Nervous System Effects</p> <p>Dilation of cerebral vessels and decreased neuronal activity</p> <ul style="list-style-type: none"> Headache Behavioral changes <ul style="list-style-type: none"> Confusion Depression Paranoia Hallucinations Weakness Tremors Paralysis Stupor and coma <p>Skin</p> <p>Warm and flushed</p>	<p>Laboratory Tests</p> <p>pH increased</p> <p>PCO_2 (primary) decreased</p> <p>Bicarbonate (compensatory) decreased</p> <p>Signs of Compensation</p> <p>Alkaline urine</p> <p>Nervous System Effects</p> <p>Constriction of cerebral vessels and increased neuronal activity</p> <ul style="list-style-type: none"> Dizziness, panic, light-headedness Tetany Numbness and tingling of fingers and toes Seizures (severe) <p>Cardiovascular Effects</p> <p>Cardiac dysrhythmias</p>

is accompanied by hypoxemia, the manifestations of respiratory acidosis often are intermixed with those of oxygen deficit.

Sudden elevations in arterial CO_2 can cause headache, blurred vision, an increase in heart rate and blood pressure, warm and flushed skin, irritability, muscle twitching, and psychological disturbances. Carbon dioxide readily crosses the blood-brain barrier, exerting its effects by changing the pH of brain fluids. Elevated levels of CO_2 produce vasodilation of cerebral blood vessels. If the condition is severe and prolonged, it can cause an increase in cerebrospinal fluid pressure and papilledema. Impaired consciousness, ranging from lethargy to coma, develops as the PCO_2 rises. Paralysis of extremities may occur, and there may be respiratory depression.

Treatment. The treatment of acute and chronic respiratory acidosis is directed toward improving ventilation (see Chapter 21). In severe cases, mechanical ventilation may be necessary.

Respiratory Alkalosis

Respiratory alkalosis involves a decrease in PCO_2 and a primary deficit in carbonic acid (H_2CO_3) along with an increase in pH. Because respiratory alkalosis can occur suddenly, a compensatory decrease in HCO_3^- may not occur before respiratory correction has been accomplished. The increase in pH is less in chronic compensated respiratory alkalosis, and the fall in HCO_3^- is greater.

Causes. Respiratory alkalosis is caused by hyperventilation or a respiratory rate in excess of that needed to maintain normal PCO_2 levels. One of the most common causes of respiratory alkalosis is the hyperventilation syndrome, which is characterized by recurring episodes of overbreathing often associated with anxiety. Persons experiencing panic attacks frequently present in the emergency room with acute respiratory alkalosis. Other causes of hyperventilation are fever, hypoxemia, early salicylate toxicity, and encephalitis. Hyperventilation can also occur during anesthesia or with use of mechanical ventilatory devices. Hypoxemia exerts its effect through stimulation of the peripheral chemoreceptors. Salicylate toxicity and encephalitis produce hyperventilation by directly stimulating the respiratory center in the brain stem.

Manifestations. Respiratory alkalosis is characterized by a pH greater than 7.45, arterial PCO_2 less than 35 mm Hg, and serum HCO_3^- levels less than 24 mEq/L (Table 6-10). The signs and symptoms of respiratory alkalosis are mainly associated with hyperexcitability of the nervous system and a decrease in cerebral blood flow. Alkalosis increases protein binding of serum calcium. This reduces ionized serum calcium levels, causing an increase in neuromuscular excitability. A decrease in the CO_2 content of the blood causes constriction of cerebral blood vessels. Because CO_2 crosses the blood-brain barrier rather quickly, the manifestations of acute respiratory alkalosis often are of sudden onset. The person often experiences light-headedness, dizziness, tingling, and numbness of the fingers and toes. These manifestations may be accompanied by sweating, palpitations, panic, air hunger, and dyspnea. Chvostek's and Trousseau's signs may be positive, and tetany and convulsions may occur. Because CO_2 provides the stimulus for short-term regulation of respiration, short periods of apnea may occur in persons with acute episodes of hyperventilation.

Treatment. The treatment of respiratory alkalosis focuses on measures to increase the PCO_2 . Attention is directed toward correcting the disorder that caused the overbreathing. Rebreathing of small amounts of expired air (breathing into a paper bag) may prove useful in restoring PCO_2 levels in persons with anxiety-produced respiratory alkalosis.

In summary, normal body function depends on the precise regulation of acid-base balance to maintain a pH within the narrow physiologic range of 7.35 to 7.45. Metabolic processes produce volatile and nonvolatile metabolic acids that must be buffered and eliminated from the body. The volatile acid H_2CO_3 is in equilibrium with dissolved CO_2 , which is eliminated through the lungs. The nonvolatile metabolic acids, most of which are excreted by the kidneys, are derived mainly from protein metabolism and incomplete carbohydrate and fat metabolism. It is the ratio of the bicarbonate ion concentration to dissolved CO_2 (carbonic acid concentration) that determines body pH. When this ratio is 20:1, the pH is 7.4. The ability of the body to maintain pH within the normal physiologic range depends on respiratory and renal mechanisms and on intracellular and extracellular buffers; the most important of these is the bicarbonate buffer system. The respiratory regulation of pH is rapid but does not return pH completely to normal. The kidney aids in regulation of pH by eliminating H^+ ions or conserving HCO_3^- ions. In the process of eliminating H^+ ions, it uses the phosphate and ammonia buffer systems. Body pH is also affected by the distribution of exchangeable cations (K^+ and H^+) and anions (Cl^- and HCO_3^-). Metabolic acidosis is defined as a decrease in HCO_3^- , and metabolic alkalosis as an increase in HCO_3^- . Metabolic acidosis is caused by an excessive production and accumulation of metabolic acids or an excessive loss of HCO_3^- .

Metabolic alkalosis is caused by an increase in HCO_3^- or from a decrease in H^+ or Cl^- , with a resultant increase in renal reabsorption of HCO_3^- . Respiratory acidosis reflects a decrease in pH that is caused by conditions that produce hypoventilation, with a resultant increase in PCO_2 levels. Respiratory alkalosis reflects an increase in pH that is caused by conditions that produce hyperventilation, with a resultant decrease in PCO_2 levels.

The signs and symptoms of acidosis and alkalosis reflect alterations in body function associated with the disorder causing the acid-base disturbance, the effect of the change of pH on body function, and the body's attempt to correct and maintain the pH within a normal physiologic range. In general, neuromuscular excitability is decreased in acidosis and increased in alkalosis.

REVIEW QUESTIONS

- Describe factors that control fluid exchange between the vascular and interstitial fluid compartments and relate them to the development of edema and third spacing of extracellular fluids.
- Compare and contrast the causes, manifestations, and treatment of isotonic fluid volume deficit, isotonic fluid volume excess, hyponatremia with water excess, and hypernatremia with water deficit.

- Characterize the distribution of potassium in the body and explain how extracellular potassium levels are regulated in relation to body gains and losses.
- Persons with severe hyperkalemia are at risk for cardiac arrest. Explain the effects of potassium on membrane potentials that are responsible for this risk.
- A person may have hypocalcemia according to laboratory reports but have no clinical signs of the disorder. Explain.
- Persons with renal failure experience both hyperphosphatemia and hypocalcemia. Explain.
- Describe the three forms of carbon dioxide transport and their contribution to acid-base balance.
- Use the Henderson-Hasselbalch equation to calculate pH and compare compensatory mechanisms for regulating pH.
- Describe a clinical situation involving an acid-base disorder in which primary and compensatory mechanisms might be active.
- Define metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis.
- Explain the use of the plasma anion gap in differentiating types of metabolic acidosis.



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