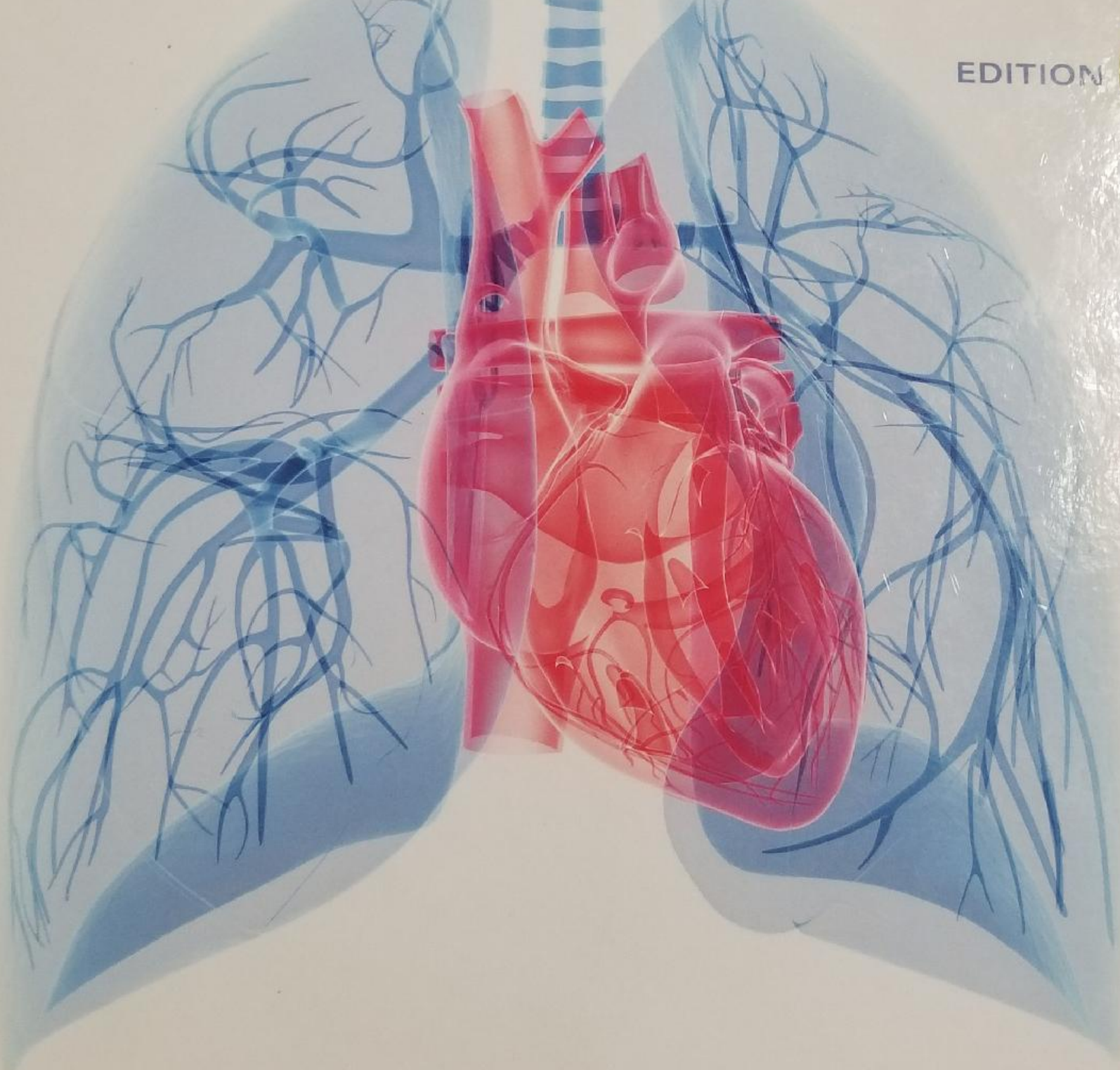
EGAN'S

Fundamentals OF Respiratory Care

EDITION 11



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Diluting a solution increases its volume without changing the amount of solute it contains, and this reduces the concentration of the solution. The amount of solute in a solution can be expressed as volume times concentration. For example, 50 ml of a 10% solution (10 g/dl) contains 50×0.1, or 5 g. In the dilution of a solution, initial volume (V_1) multiplied by initial concentration (C_1) equals final volume multiplied by final concentration. This can be expressed as follows:

$$V_1C_1 = V_2C_2$$

This equation is sometimes referred to as the **dilution equation.** Whenever three of the variables are known, the fourth can be calculated as in the following examples:

1. Diluting 10 ml of a 2% (0.02) solution to a concentration of 0.5% (0.005) requires finding the new volume (V_2) by rearranging the dilution equation as follows:

$$V_2 = V_1C_1/C_2$$
$$V_2 = 10\text{ ml} \times 0.02/0.005$$
$$V_2 = 40\text{ ml}$$

2. If 50 ml of water is added to 150 ml of a 3% (0.03) solution, the new concentration is calculated by rearranging the dilution equation to find C_2 as follows:

$$C_2 = V_1C_1/V_2$$
$$C_2 = 150\text{ ml} \times 0.02/(50\text{ ml} + 150\text{ ml})$$
$$C_2 = 0.0225 \text{ or } (2.25\%)$$

3. To dilute 50 ml of a 0.33 normal (N) solution to a 0.1 N concentration, concentration is given as normality, but it can be used similar to a percentage. The new volume (V_2) can be calculated by rearranging the dilution equation as follows:

$$V_2 = V_1C_1/C_2$$
$$V_2 = 50\text{ ml} \times 0.33/0.1$$
$$V_2 = 165\text{ ml}$$

In the last example, the volume needed to produce a 0.1 N solution would be 165 ml – 50 ml (the original volume), or 115 ml. In other words, 115 ml of solvent would have to be added to the original 50 ml of 0.33 N solution to produce the desired concentration. The added solvent is called the **diluent** because it dilutes the original concentration to a lower concentration.

ELECTROLYTIC ACTIVITY AND ACID-BASE BALANCE

Acid-base balance depends on the concentration and activity of electrolytic solutes in the body. Clinical application of acid-base homeostasis is discussed in detail in Chapter 14.

Characteristics of Acids, Bases, and Salts

Acids

The term **acid** refers to either compounds that can donate [H^+] (Brönsted-Lowry acid) or any compound that accepts an electron pair (Lewis acid). Although these two theories of acids differ in which is being transferred, both theories attempt to describe how reactive groups perform within an aqueous solution[7,8]:

$$NH_4Cl + NaOH \rightarrow NH_3 + NaCl + HOH$$

In this reaction, Na^+ and Cl^- ions are not involved in the proton transfer. The equation can be rewritten ionically as follows to show the acidity of the ammonium ion:

$$NH_4^+ + OH^- \rightarrow NH_3 + HOH$$

The ammonium ion donates a H^+ ion (proton) to the reaction. The H^+ combines with the hydroxide ion (OH^-), and this converts the former into ammonia gas and the latter into water.

Acids With Single Ionizable Hydrogen. Simple compounds such as hydrochloric acid (HCl) ionize into one cation and one anion:

$$HCl \rightarrow H^+ + Cl^-$$

Acids With Multiple Ionizable Hydrogens. The H^+ ions in an acid may become available in stages. The degree of ionization increases as an electrolyte solution becomes more dilute. Concentrated sulfuric acid ionizes only one of its two H^+ atoms per molecule, as follows:

$$H_2SO_4 \rightarrow H^+ + HSO_4^-$$

With further dilution, second-stage ionization occurs:

$$H_2SO_4 \rightarrow H^+ + H^+ + SO_4^-$$

Bases

A **base** is a compound that yields hydroxyl ions (OH^-) when placed into aqueous solution. A substance capable of inactivating acids is also considered a base. These compounds, called *hydroxides,* consist of a metal that is ionically bound to a OH^- ion or ions. The OH^- may also be bound to an ammonium cation (NH_4^+). An example of this type of base is sodium hydroxide (NaOH). The Brönsted-Lowry definition of a base is any compound that accepts a proton; bases are paired with acids that donate the proton, and these are called *conjugate pairs.* This definition includes substances other than hydroxides, such as ammonia, carbonates, and certain proteins.

Hydroxide Bases. In aqueous solution, the following are typical dissociations of hydroxide bases:

$$Na^+OH \rightarrow Na^+ + OH^-$$
$$K^+OH \rightarrow K^+ + OH^-$$
$$Ca^{++}(OH^-)2 \rightarrow Ca^{++} + 2(OH^-)$$

Inactivation of an acid is part of the definition of a base. This inactivation is accomplished by OH^- reacting with H^+ to form water:

$$NaOH + HCl \rightarrow NaCl + HOH$$

Nonhydroxide Bases. Ammonia and carbonates are examples of nonhydroxide bases. Proteins, with their amino groups, also can serve as nonhydroxide bases.

MINI CLINI

Methacholine Dilution

The dilution equation ($V_1C_1 = V_2C_2$) is commonly used to calculate volumes or concentrations of medications when a specific dosage needs to be administered to a patient. If three of the variables are known, the fourth can be determined.

PROBLEM: Methacholine is a drug used to induce airway constriction in patients suspected of having. In healthy subjects, only higher doses of methacholine cause bronchospasm. In asthmatics, very low doses can precipitate a 20% decrease in the forced expiratory volume in 1 second (FEV_1). The methacholine challenge test begins with a low dose and increases the concentration (either doubling or quadrupling) until the patient has a significant change in FEV_1 or the highest dose has been given. Methacholine is supplied in vials that contain 100 mg of the active substance to which 6.25 ml of diluent (saline) can be added to produce a concentration of 16 mg/ml. This is the highest dosage administered to the patient. How can you make serial dilutions of the drug so that five different dosages are available and each one is four times more concentrated than the previous dose?

SOLUTION: Starting with a 16 mg/ml stock solution of methacholine, how much diluent needs to be added to 3 ml of the stock to make a 4 mg/ml dose (one-fourth of the original concentration)?

Using the dilution equation:

$$C_1V_1 = C_2V_2$$
$$(16)(3.0) = (4)V_2$$
$$48/4 = V_2$$
$$12 = V_1$$

Because there was 3 ml of the stock solution to begin with, the amount of diluent to add is the difference between 12 (V_2) and 3, or 9 ml. Adding 9 ml of diluent to the original 3 ml of stock (16 mg/ml) provides 12 ml of methacholine with a concentration of 4 mg/ml, exactly one-fourth of the highest dose. Additional dilutions can be prepared using 3 ml of solution according to the following table:

Start With		To Make
3 ml of 4 mg/ml	9 ml	1 mg/ml
3 ml of 1 mg/ml	9 ml	0.25 mg/ml
3 ml of 0.25 mg/ml	9 ml	0.0625 mg/ml

Each of these dilutions uses the same proportions used in the first dilution as determined by the dilution equation. Methacholine is administered by nebulizer to the patient, starting with the lowest concentration (0.0625 mg/ml) and increasing until a change in FEV_1 is observed. (See Chapter 20 for additional information on pulmonary function testing.)

Ammonia. Ammonia qualifies as a base because it reacts with water to yield OH^-:

$$NH_3 + HOH \rightarrow NH_4^+ + OH^-$$

and neutralizes H^+ directly:

$$NH^3 + H^+ \rightarrow NH_4^+$$

In both instances, NH_3 accepts a proton to become NH_4^+. Ammonia plays an important role in renal excretion of acid (see Chapter 14).

Carbonates. The carbonate ion (CO_3^{2-}), can react with water in the following way to produce OH^-:

(1) $$Na_2CO_3 \rightleftharpoons 2Na^+ + CO_3^{2-}$$

(2) $$CO_3^{2-} + HOH \rightleftharpoons HCO_3^- + OH^-$$

In this reaction, CO_3^{2-} accepts a proton from water, becoming the HCO_3^- ion. It simultaneously produces a hydroxide ion. The CO_3^{2-} ion also can react directly with H^+ to inactivate it:

$$CO_3^{2-} + H^+ \rightleftharpoons HCO_3^-$$

Protein Bases. Proteins are composed of amino acids bound together by peptide links. Physiologic reactions in the body occur in a mildly alkaline environment. This environment allows proteins to act as H^+ receptors, or bases. Cellular and blood proteins acting as bases are transcribed as $prot^-$.

The imidazole group of the amino acid histidine is an example of an H^+ acceptor on a protein molecule (Figure 13-4). The ability of proteins to accept H^+ ions limits H^+ activity in solution, which is called **buffering.** The buffering effect of hemoglobin (Hb) is produced by imidazole groups in the protein. Each Hb molecule contains 38 histidine residues. Each O_2-carrying component (heme group) of Hb is attached to a histidine residue. The ability of Hb to accept (i.e., buffer) H^+ ions depends on its oxygenation state. Deoxygenated (reduced) Hb is a stronger base (i.e., a better H^+ acceptor) than oxygenated Hb. This difference partially accounts for the ability of reduced Hb to buffer more acid than oxygenated Hb can (see Chapter 14). Plasma proteins also act as buffers, although with less buffering power than Hb, which contains more histidine.

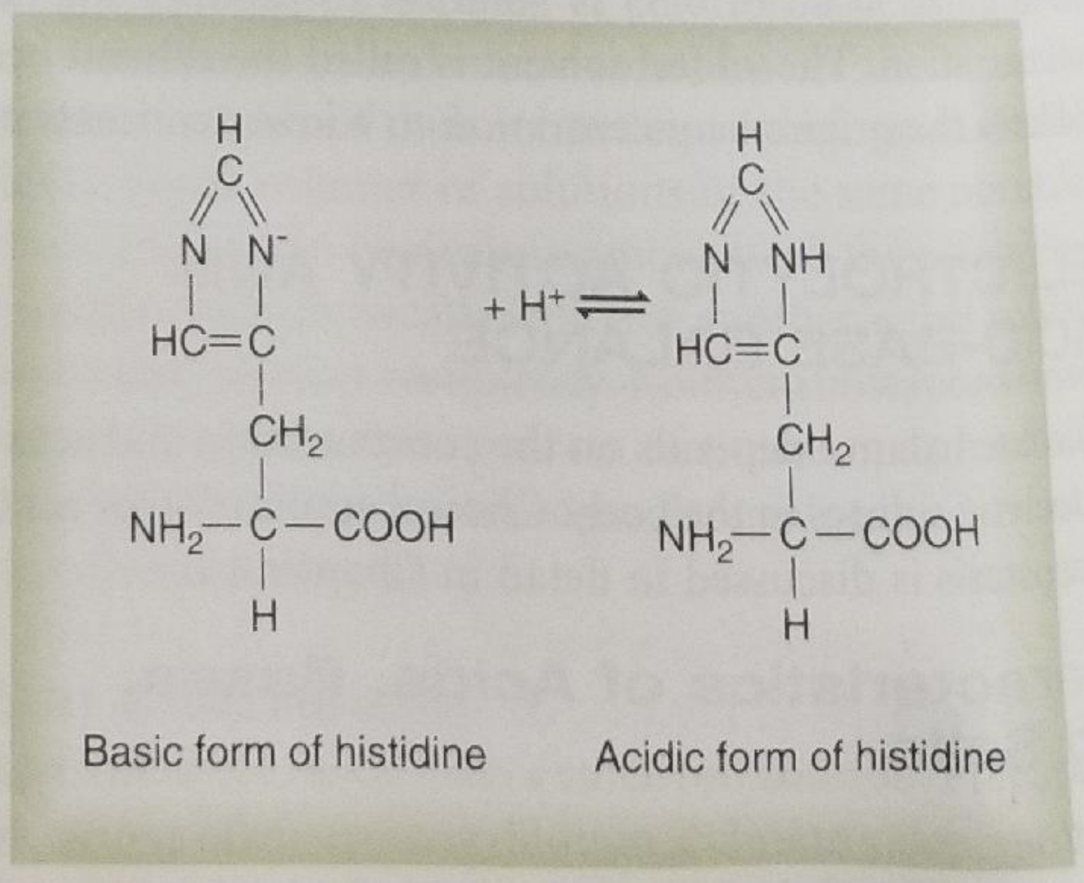

FIGURE 13-4 Histidine portion of a protein molecule (at *top*) serving as a proton acceptor (base).

Designation of Acidity and Alkalinity

Pure water can be used as a reference point for determining acidity or alkalinity. The concentration of both H^+ and OH^- in pure water is 10^{-7} mol/L. A solution that has a greater H^+ concentration or lower OH^- concentration than water acts as an acid. A solution that has a lower H^+ concentration or a greater OH^- concentration than water is alkaline, or basic.

The H^+ concentration $[H^+]$ of pure water has been adopted as the standard for comparing reactions of other solutions. Electrochemical techniques are used to measure the $[H^+]$ of unknown solutions. Acidity or alkalinity is determined by variation of the $[H^+]$ greater than or less than 1×10^{-7}. For example, a solution with a $[H^+]$ of 89.2×10^{-4} has a higher $[H^+]$ than water and is acidic. A solution with a $[H^+]$ of 3.6×10^{-8} has fewer H^+ ions than water and is by definition alkaline. Two related techniques are used for expressing the acidity or alkalinity of solutions using the $[H^+]$ of water (i.e., 10^{-7}) as a neutral factor: (1) the $[H^+]$ in nanomoles per liter and (2) the logarithmic pH scale.

Nanomolar Concentrations

The acidity or alkalinity of solutions may be reported using the molar concentration of H^+ compared with that of water. The $[H^+]$ of water is 1×10^{-7} mol/L, or 0.0000001 (one ten-millionth of a mole). The unit for one-billionth of a mole is a **nanomole** (nmol). The $[H^+]$ of water can be expressed as 100 nmol/L. A solution that has a $[H^+]$ of 100 nmol/L is neutral. A solution with an $[H^+]$ greater than 100 nmol/L is acidic; one with an $[H^+]$ less than 100 nmol/L is alkaline. This system is limited because of the wide range of possible $[H^+]$ but is applicable in clinical medicine because the physiologic range of $[H^+]$ is narrow. $[H^+]$ in healthy individuals is usually 30 to 50 nmol/L.

pH Scale

The pH scale is used to describe the concentration of H^+, ($[H^+]$), (i.e., Brönsted-Lowry acid) in a solution. Rather than expressing the $[H^+]$ in nanomoles, it is more convenient to describe it in terms of the negative logarithm of the nanomolar $[H^+]$. The equation for calculating pH is:

$$pH = -\log[H^+]$$

The pH of pure water is 7.0: The $[H^+]$ of water is 1×10^{-7} mol/L. The logarithm of 1×10^{-7} is -7, so the negative logarithm of 1×10^{-7} is 7.

Using this scheme, in a solution with a pH of 7.00, the $[H^+]$ is the same as would be seen in pure water, so by convention this is called "neutral." As the pH decreases below 7.00, the solution is termed *acidic*. When the pH increases above 7.00, the solution is considered to be *basic*. With a whole number change in pH (i.e., pH decreasing from 7.00 to 6.00), the $[H^+]$ is a factor of 10 less. With a pH increase from 7.00 to 8.00, the $[H^+]$ is 10 times greater (Figure 13-5). A pH of 7.00 is equivalent to a $[H^+]$ of 100 nmol. A pH of 8.00 is equivalent to a $[H^+]$ concentration of 10 nmol. Similarly, a change in pH of 0.3 units equals a twofold change in $[H^+]$.

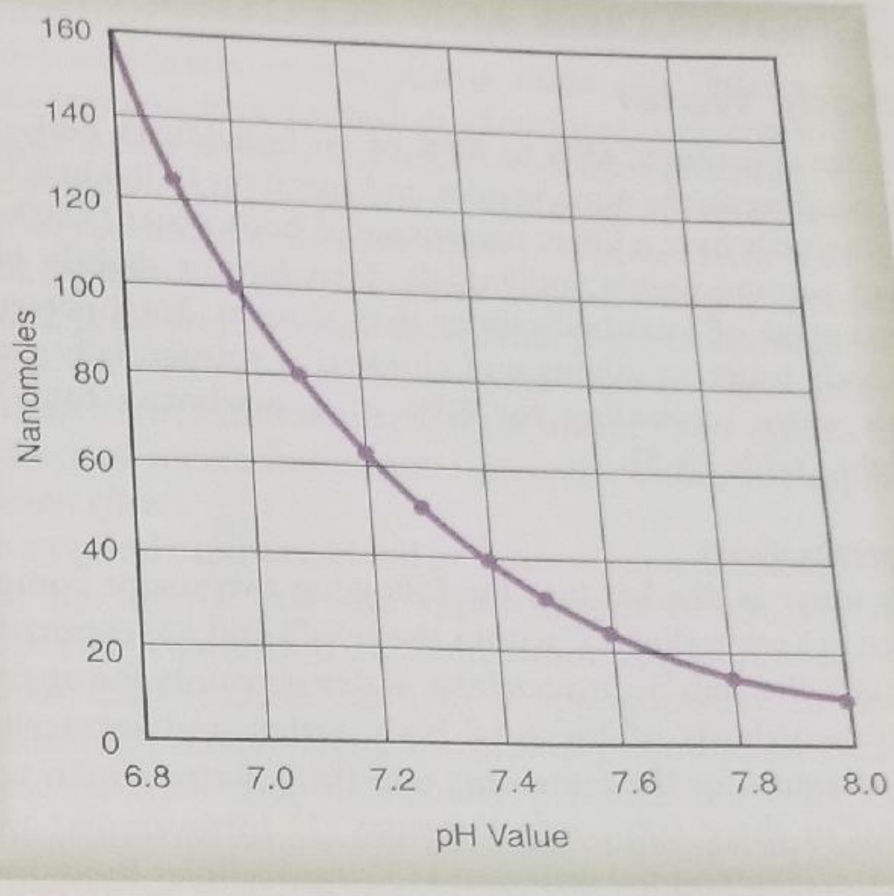

FIGURE 13-5 Relationship between pH scale and $[H^+]$ concentrations in nanomoles per liter (nmol/L). pH of 7.00 equals 100 nmol/L H^+, whereas the normal human pH (arterial blood) of 7.40 is equal to about 40 nmol/L.

Applying these concepts in an example pertinent to clinical medicine yields the following:

$$[H^+] \text{ in blood} = 4.0 \times 10^{-8} \text{ mol/L}$$
$$pH = -\log(4.0 \times 10^{-8})$$
$$= -\log 4.0 + -\log 10^{-8}$$
$$= -\log 4.0 + \log 10^{8}$$
$$= -0.602 + 8$$
$$= 7.40$$

In this example, the $[H^+]$ in arterial blood of a healthy adult is approximately 4.0×10^{-8} mol/L, or 40 nmol/L.

RULE OF THUMB

The pH scale is logarithmic. pH is a positive number representing the negative log of the hydrogen ion concentration $[H^+]$ of a solution. To visualize changes in acidity or alkalinity, the following two rules are helpful:

1. A pH change of 0.3 unit equals a 2-fold change in $[H^+]$.
2. A pH change of 1 unit equals a 10-fold change in $[H^+]$.

For example, if a patient's blood pH decreased from 7.40 (normal) to 7.10, the $[H^+]$ concentration would be twice as high. If a patient's urine pH decreased from 7.00 to 6.00, the $[H^+]$ would have increased by 10 times.

BODY FLUIDS AND ELECTROLYTES

Body Water

Water constitutes 45% to 80% of an individual's body mass, depending on the mass, gender, and age of the individual. Obese individuals have a lower percentage of body water (≤30% less) than normal-weight individuals. Men have a slightly higher percentage of total-body water than women. Total percentage of body water in infants and children is substantially greater, with water accounting for 80% of a newborn's total-body weight (Table 13-3).

Distribution

Body water is divided into the following two major compartments: (1) *intracellular* ("within the cells") and (2) *extracellular* ("outside the cells"). Intracellular water accounts for approximately two-thirds of the total-body water, and extracellular water accounts for the remaining one-third. Extracellular water is found in three sub-compartments: (1) intravascular water (plasma), (2) interstitial water, and (3) transcellular fluid. Intravascular water constitutes approximately 5% of the body weight. Interstitial water is water in the tissues between the cells. It constitutes approximately 15% of the body weight. The proportion of *transcellular fluid* is quite small in proportion to plasma and **interstitial fluid.** Interstitial fluid is a matrix—a collagen/gel substance that allows the interstitium to provide structural support during times of extracellular volume depletion.[10] Examples of transcellular fluid include cerebrospinal fluid, digestive juices, and mucus. Transcellular fluid can become an important third space in some pathologic conditions, such as *ascites* (excess fluid in the peritoneal cavity) or *pleural effusion* (fluid collection in the pleural space).

Composition

The concentration of ionic solutes in intracellular and extracellular fluids differs significantly. Sodium (Na^+), chloride (Cl^-), and bicarbonate (HCO_3^-) are predominantly extracellular electrolytes. Potassium (K^+), magnesium (Mg^{++}), phosphate (PO_4^{3-}), sulfate (SO_4^{2-}), and protein constitute the main intracellular electrolytes. Although protein does not dissociate ionically, it can create H^+ and other weak bonds and distribute net extra charge within its molecule. Intravascular and interstitial fluids have similar electrolyte compositions. Plasma contains substantially more protein than interstitial fluid. Proteins, chiefly albumin, account for the high osmotic pressure of plasma. Osmotic pressure is an important determinant of fluid distribution between vascular and interstitial compartments.

TABLE 13-3

Distribution of Body Fluids

Body Water	Man (% Body Weight)	Woman (% Body Weight)	Infant (% Body Weight)
Total body Water	60 ± 15	50 ± 15	80
Intracellular	45	40	50
Extracellular	15-20	15-20	30
Interstitial	11-15	11-15	24
Intravascular	4.5	4.5	5.0
Transcellular	<1	<1	<1

Regulation

As discussed, movement of certain ions and proteins between body compartments is restricted yet water diffuses freely. Control of total-body water occurs through regulation of water intake (thirst) and water excretion (urine production, insensible loss, and stool water). The kidneys are mainly responsible for water excretion. If water intake is low, the kidneys reduce urine volume. Solutes in the urine can be concentrated up to four times the concentration of solutes in the plasma. If water intake is high, the kidneys can excrete large volumes of dilute urine.

The kidneys maintain the volume and composition of body fluids via two related mechanisms. First, filtration and reabsorption of Na^+ adjust urinary Na^+ excretion to match changes in dietary intake. Second, water excretion is regulated by osmoreceptors that are located in the hypothalamus and modulate secretion of antidiuretic hormone (ADH, also known as *vasopressin*).[6,11,12] These receptors are exceptionally sensitive; in vivo studies have shown that a single neuron can respond to either an osmotic or a nonosmotic baroreceptor simulus.[12] These mechanisms allow the kidneys to maintain the volume and concentration of body fluid despite variations in salt and water intake. Analysis of the urine (urinalysis) often provides diagnostic clues in disorders of body fluid volume.

Water Losses. Water may be lost from the body through the skin, lungs, kidneys, and gastrointestinal (GI) tract. Water loss can be *insensible,* such as evaporation of water from the skin and lungs, or *sensible,* such as losses from urine and the GI tract (Table 13-4).[13] Fluid losses from the body also may occur during vomiting, diarrhea, or suctioning from the stomach. Fever, in conjunction with sweating, also can cause significant losses.

The GI tract manufactures 8 to 10 L of fluid per day. More than 98% of this volume is reclaimed in the large intestine. In

TABLE 13-4

Daily Water Exchange

Regulation	Average Daily Volume (ml)	Maximum Daily Volume
Water Losses		
Insensible		
Skin	700	1500 ml
Lung	200	
Sensible		
Urine	1000-1200	>2000 ml/hr
Intestinal	200	8000 ml
Sweat	0	>2000 ml/hr
Water Gain		
Ingestion		
Fluids	1500-2000	1500 ml/hr
Solids	500-600	1500 ml/hr
Body metabolism	250	1000 ml

patients who are vomiting or have diarrhea, water losses through the GI tract can be considerable. Individuals with severe burns or open wounds can lose large quantities of water.

Other causes of abnormal fluid loss include certain renal and respiratory disorders. Patients with renal disease may have to excrete larger quantities of urine to get rid of extra nitrogenous wastes. Patients with increased ventilation also have increased water losses through increased evaporation from the respiratory tract. Patients with artificial airways are prone to evaporative water loss if inspired air is not adequately humidified. Infants have a greater proportion of body water than adults, particularly in the extracellular compartments (see Table 13-3). Water loss in infants may be twice the water loss in adults. Infants also have a greater body surface area (in proportion to body volume) than adults, making their basal heat production twice as high. Higher metabolic rates in infants necessitate greater urinary excretion. Infants turn over approximately half of their extracellular fluid volume daily versus one-seventh for adults. Fluid loss or lack of intake can rapidly deplete an infant of water.

Water Replacement. Water is replenished in two major ways: ingestion and metabolism (see Table 13-4).

Ingestion. Water is replaced mainly by ingestion, through the consumption of liquids. An average adult drinks 1500 to 2000 ml of water per day. An additional 500 to 600 ml of water is ingested from solid food.

Metabolism. Water also is gained from the oxidation of fats, carbohydrates, and proteins in the body; the destruction of cells also releases some water. During total starvation, 2000 ml of water can be produced daily by the metabolism of 1 kg of fat. Recovery after surgery or trauma may be similar to starvation; under such conditions, approximately 500 mg of protein and a similar amount of fat are metabolized. This metabolism yields approximately 1 L of water per day.

Transport Between Compartments

Homeostasis depends largely on the total volume of body fluids and on fluid transport between body compartments. The first stage of homeostasis is fluid exchange between systemic capillaries and interstitial fluid via passive diffusion. Capillary walls are permeable to crystalline electrolytes. This allows equilibrium between the two extracellular compartments to occur quickly. Except for the large protein molecules, plasma also can move through capillary walls into the tissue spaces. Because water and small molecules can cross the capillary membranes, they produce little or no osmotic effect.

Movement of fluid and solutes from capillary blood to interstitial spaces is enhanced by the difference in **hydrostatic pressure** (pressure exerted by a liquid at rest with respect to adjacent bodies) between compartments. Hydrostatic pressure difference depends on blood pressure, blood volume, and the vertical distance of the capillary from the heart (i.e., the effects of gravity). Hydrostatic pressure tends to cause fluid to leak out of capillaries into the interstitial spaces.

Osmotic pressure differences between interstitial and intravascular compartments oppose hydrostatic pressure; that is, osmotic pressure tends to keep fluid in the capillaries. Proteins with molecular weights greater than approximately 70,000 in colloidal suspension in the plasma cause this difference in osmotic pressure. Proteins such as albumin are too large to pass through the pores of the capillary. Instead, these proteins remain in the intravascular compartment and exert osmotic pressure, which draws water and small solute molecules back into the capillaries; this is called **plasma colloid osmotic pressure (oncotic pressure).** Because these large proteins are negatively charged, they attract (but do not bind) an equivalent amount of cations to the intravascular compartment. These cations have the effect of increasing osmotic pressure within the capillary (*Donnan effect*).

In a typical capillary, blood pressure is approximately 30 mm Hg at the arterial end and approximately 20 mm Hg at the venous end (Figure 13-6). Colloid osmotic pressure of the intravascular fluid remains constant at approximately 25 mm Hg. Hydrostatic pressure along the capillary continually decreases. At the arterial end, hydrostatic pressure normally exceeds osmotic pressure, and water flows out of the vascular space into the interstitial space. At the venous end, colloidal osmotic pressure exceeds hydrostatic forces. Water is pulled back into the vascular compartment.

The outflow of water and electrolytes from the capillary at the arterial end is not completely balanced by the return on the venous end. Slightly more water diffuses out than is reabsorbed. This slight outward excess is balanced by fluid return through the lymphatic circulation (see Chapter 9). Fluid return via lymphatic channels also depends on pressure differences. The pressure in the interstitial space is determined by the volume of interstitial fluid and its electrolyte content. Interstitial fluid moves from a region of higher pressure (interstitial space) to a region of lower pressure (lymphatic channels). This lymph fluid moves into larger lymphatic spaces, where the pressure is continuously decreasing.

Three examples of the forces in Starling's equation are fluid return from gravity-dependent areas of the body, fluid exchange in the lung, and tissue edema.

Because of hydrostatic effects, capillary pressure in the feet can reach 100 mm Hg when an individual is standing. Reabsorption of tissue fluid can be accomplished, although hydrostatic pressure greatly exceeds colloidal osmotic pressure. Three factors favor reabsorption under these circumstances:

1. High intravascular hydrostatic pressure is balanced by a proportionally greater interstitial pressure.
2. The "pumping" action of the skeletal muscles surrounding leg veins reduces venous pressures.
3. Lymph flow back to the thorax is enhanced via a similar mechanism; this facilitates clearance of excess interstitial fluid.

However, when an imbalance results from changes in the basic pressures (e.g., arterial hypertension), edema tends to occur in the dependent limbs.

The lungs present a different situation. In systemic tissues, a constant exchange of interstitial fluid is essential. In the lungs, the alveoli must be kept relatively dry. Otherwise, interstitial

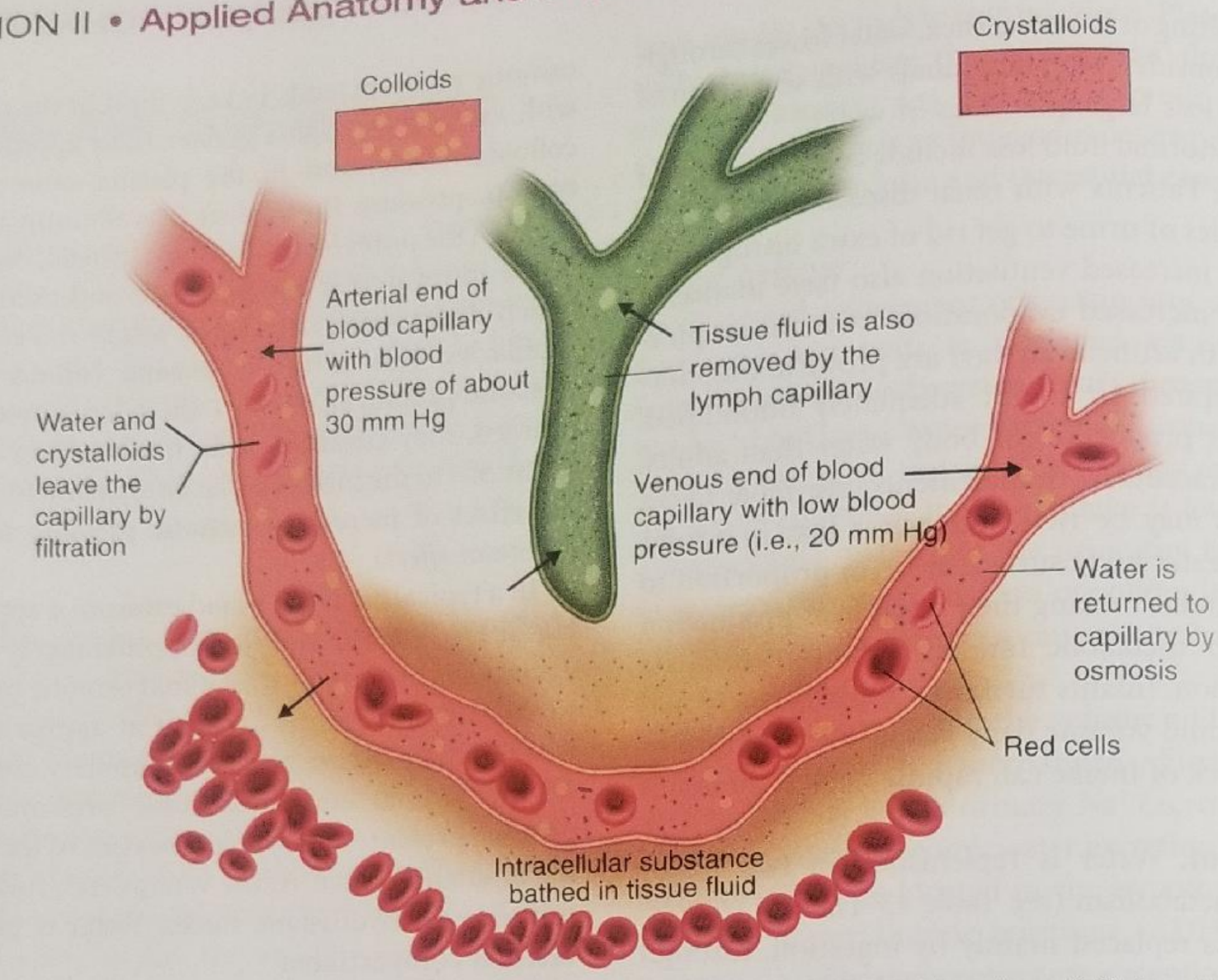

FIGURE 13-6 Tissue fluid is formed by a process of filtration at the arterial end of a systemic capillary *(left)*, in which blood pressure exceeds colloid osmotic pressure. The fluid is absorbed by the blood capillaries and lymphatic vessels. It returns to the venous end of the capillary *(right)* when colloid osmotic pressure exceeds blood pressure. Fluid is absorbed into the lymphatic capillary system when interstitial fluid pressure is greater than the pressure within the lymphatic capillary. Normally, little colloid escapes from the capillary. Colloid that does escape is returned to the blood circulation by the lymphatic vessels. (Modified from Burke SR: The composition and function of body fluids, ed 3, St Louis, 1980, Mosby.)

fluid in the alveolar-capillary spaces would impede the diffusion of gas. Colloid osmotic pressure in pulmonary blood vessels is the same as it is in the systemic circulation. To minimize interstitial fluid in the alveolar-capillary region, the hydrostatic pressure difference must be kept low. The pulmonary circulation is a low-pressure system. The mean pulmonary vascular pressures are approximately one-sixth of those in the systemic circulation. Colloid osmotic pressure exceeds hydrostatic forces across the entire length of the pulmonary capillaries in healthy individuals. The alveoli are relatively free of excess interstitial water.

If hydrostatic pressure increases in the pulmonary circulation, this balance can be upset. This causes fluid movement into the alveolar-capillary spaces. Excess fluid in the interstitial space is called *edema*. In the lungs, edema caused by increased hydrostatic pressure often is a result of backpressure from a failing left ventricle (e.g., in congestive heart failure).

Edema can be caused by other factors. The **Starling equilibrium** equation given earlier shows that edema can be caused by a decrease in colloid osmotic pressure or an increase in capillary permeability. If albumin is depleted in the blood, the balance of forces is upset, favoring increased movement of fluid into the interstitium. Likewise, an increase in capillary permeability results in more fluid leaving the capillaries. Increased capillary permeability is a major factor in certain types of acute lung injuries (see Chapter 29).[14]

Electrolytes

Electrolytes in the various body fluids are not passive solutes. Electrolytes maintain the internal environment while making possible essential chemical and physiologic events. There are seven major electrolytes: sodium, chloride, bicarbonate, potassium, calcium, magnesium, and phosphorus (phosphate).

Sodium (Na^+)

Na^+ is the major circulating cation within the body.[15] Regulation of Na^+ concentration in plasma and urine is related to regulation of total-body water. Of the total-body stores of Na^+, 50% is extracellular. The remaining Na^+ is found in bone (40%) and in cells (10%). The normal serum concentration of Na^+ is 136 to 145 mEq/L. In cells, the Na^+ concentration is much lower, averaging only 4.5 mEq/L.

The average adult ingests and excretes approximately 100 mEq of Na^+ every 24 hours. Children require approximately half this amount, and infants typically exchange 20 mEq of Na^+ per day. Most Na^+ is reabsorbed through the kidney. Approximately 80% of the Na^+ in the body is reclaimed passively in the proximal tubules. The remainder is actively reabsorbed in the distal tubules. Na^+ reabsorption in the kidneys is governed mainly by the level of aldosterone, which is secreted by the adrenal cortex. Na^+ reabsorption in the distal tubules of the

TABLE 13-5

Electrolyte Disorders and Clinical Findings

Electrolyte	Imbalance	Causes	Symptoms
Sodium (Na^+)	Hyponatremia	GI loss, sweating, fever, diuretics, ascites, congestive heart failure, kidney failure	Weakness, lassitude, apathy, headache, orthostatic hypotension, tachycardia
	Hypernatremia	Net sodium gain, net water loss, increased aldosterone, steroid therapy	Tremulousness, irritability, ataxia, confusion, seizures, coma
Chloride (Cl^-)	Hypochloremia	GI loss, diuretics	Metabolic alkalosis, muscle spasm, coma (severe cases)
	Hyperchloremia	Dehydration, metabolic acidosis, respiratory alkalosis	(Minimal)
Potassium (K^+)	Hypokalemia	Diuretics, steroid therapy, renal tubular disease, vomiting, diarrhea, malnutrition, trauma	Muscle weakness, paralysis, ECG abnormalities, supraventricular arrhythmias, circulatory failure, cardiac arrest
	Hyperkalemia	Chronic renal disease, hemorrhage, tissue necrosis, nonsteroidal antiinflammatory drugs, ACE inhibitors, cyclosporine, K^+-sparing diuretics	ECG changes, ventricular arrhythmias, cardiac arrest
Calcium (Ca^{++})	Hypocalcemia	Hyperparathyroidism, pancreatitis, renal failure, trauma	Hyperactive tendon reflexes, muscle twitching, spasm, abdominal cramps, ECG changes, seizures (rarely)
	Hypercalcemia	Hyperthyroidism, hyperparathyroidism, metastatic bone cancer, sarcoidosis	Fatigue, depression, muscle weakness, anorexia, nausea, vomiting, constipation
Magnesium (Mg^{++})	Hypomagnesemia	Inadequate intake/impaired absorption of Mg^{++}, pancreatitis, alcoholism	Muscle weakness, irritability, tetany, ECG changes, arrhythmias, delirium, seizures
	Hypermagnesemia	Dehydration, renal insufficiency, tissue trauma, lupus erythematosus	ECG changes (along with hyperkalemia, cardiac arrest, respiratory muscle paralysis)
Phosphate (HPO_4^{2-})	Hypophosphatemia	Starvation, malabsorption, hyperparathyroidism, hyperthyroidism, uncontrolled diabetes mellitus	Diaphragmatic weakness
	Hyperphosphatemia	Endocrine disorders, acromegaly, chronic renal insufficiency, acute renal failure, tissue trauma	(Minimal)

ACE, Angiotensin-converting enzyme; *ECG,* electrocardiogram.

kidney occurs in exchange for other cations. Na^+ balance is involved in acid-base homeostasis (i.e., H^+ exchange) and the regulation of K^+. Abnormal losses of Na^+ can lead to *hyponatremia* (low Na^+ concentration in the plasma) and may occur for numerous reasons, as shown in Table 13-5.

Hyponatremia, which is the most common electrolyte imbalance found in hospitalized patients, is defined as having serum Na^+ levels less than 135 mEq/L.[6] Previously considered to be benign, mild hyponatremia has been shown in more recent studies to have a significant impact on a patient's cognitive function and gait stability, and it is thought to be a contributing factor in falls.[16] Hyponatremia can lead to cerebral edema owing to a change in osmotic pressure; the two most common causes for acute hyponatremia are postoperative iatrogenic and self-induced secondary to water intoxication.[16] One type of normal-volume (euvolemic) hyponatremia is known as the *syndrome of inappropriate antidiuretic hormone secretion* (SIADH).[15-17]

Treatment of hypovolemic hyponatremia can have dire consequences as well. If fluid is administered too quickly, damage to the central nervous system occurs. With significant fluid shifts in Na^+ concentrations, rapid changes in cellular volume can lead to cell damage and cell death (apoptosis).[6] Osmotic demyelination syndrome occurs when serum Na^+ concentration changes more than 10 mEq/L in chronic hyponatremia or 18 mEq/L over 48 hours.[16]

Chloride (Cl^-)

Cl^- is the most prominent anion in the body. Two-thirds of the body's store of Cl^- is extracellular; the remainder is intracellular. Intracellular Cl^- is present in significant amounts in red and white blood cells. It also is present in cells that have excretory functions, such as the GI mucosa.

Normal serum levels of Cl^- are 98 to 106 mEq/L. The concentration of extracellular Cl^- is inversely proportional to the concentration of the other major anion, HCO_3^-. Cl^- is regulated by the kidney in much the same manner as Na^+ (80% reabsorbed in the proximal tubules and 20% reabsorbed in the distal tubules). Cl^- is usually excreted with K^+ in the form of KCl. An imbalance in one of these electrolytes usually affects both. Replacement therapy usually includes both K^+ and Cl^-. The stomach and the small bowel also affect the balance of Cl^-, and sweat contains hypotonic quantities of Cl^-. Abnormal Cl^- levels may occur for various reasons (see Table 13-5).

Bicarbonate (HCO_3^-)

After Cl^-, HCO_3^- is the most important body fluid anion. It plays an important role in acid-base homeostasis and is the strong base in the HCO_3–H_2CO_3 buffer pair (see Chapter 14). HCO_3^- is the primary means for transporting CO_2 from the tissues to the lungs. The ratio of HCO_3^- to H_2CO_3 in healthy individuals is maintained near 20:1; this results in a pH of close

to 7.40. HCO_3^- stores are evenly divided between intracellular and extracellular compartments. Normal serum HCO_3^- levels in arterial blood range from 22 to 26 mEq/L. HCO_3^- levels are slightly higher in venous blood as CO_2 is being transported to the lungs.

In acid-base disorders, the kidneys regulate HCO_3^- levels to maintain a near-normal pH. In healthy individuals, more than 80% of blood HCO_3^- is reabsorbed in the proximal tubules of the kidneys. The remainder is reclaimed in the distal tubules. In respiratory acidosis, the kidneys retain or produce HCO_3^- to buffer the additional acid caused by CO_2 retention. In respiratory alkalosis, the opposite occurs. A reciprocal relationship exists between Cl^- and HCO_3^- concentrations. HCO_3^- retention is associated with Cl^- excretion, and vice versa (Chapter 14).

MINI CLINI

Water, Salt, and Congestive Heart Failure

PROBLEM: Why do patients who have congestive heart failure (CHF) need to adhere to a low-salt diet?

SOLUTION: CHF occurs when the left ventricle cannot pump all of the blood presented to it. This situation leads to pooling of blood in the lungs and venous circulation and an increase in peripheral venous pressure. Normally, the ventricle pumps most of the blood entering it. This volume is the "preload" of the heart. The volume of extracellular water partially determines the preload of the ventricle.

The ventricle can fail as a pump either because of intrinsic heart disease, such as infarction or ischemia, or because of elevated distal pressures against which it must pump (hypertension). In addition to pooling of blood in the systemic venous circulation, blood can back up in the lungs, resulting in congestion and edema.

The most important determinant of the extracellular water volume is its Na^+ content. Changes in extracellular water are dictated by the net gain or loss of Na^+, with an accompanying gain or loss of water. To reduce the work of the heart, fluid volume must be carefully regulated. By restricting Na^+ intake, extracellular fluid volume can be reduced, allowing the heart to function more effectively as a pump. Treatment of CHF must address not only excess fluid volume but also the underlying cause.

Diuretics are often used to help reduce fluid volume. Many diuretics cause the kidney to excrete Na^+, causing water to follow and reducing the extracellular fluid load. Because some diuretics also cause K^+ to be excreted, care must be taken in the management of CHF not to cause electrolyte imbalances. K^+ supplements may be used so that diuresis does not result in hypokalemia. Because of the central role of extracellular water in CHF, weighing the patient is a simple yet sensitive means of detecting excess fluid volume.

Potassium (K^+)

K^+ is the main cation of the intracellular compartment. Most of the K^+ (98%) in the body is found in cells. **Active transport** of K^+ into the cells occurs through an ionic pump mechanism. An electrical differential across the cell membrane also facilitates K^+ movement into the cell. For every three K^+ ions that enter a cell, two Na^+ ions and one H^+ ion must leave. This transfer maintains electrical neutrality in the cell.

The difference in K^+ distribution is evident when comparing concentrations between fluid compartments. Intracellular K^+ concentration is approximately 150 mEq/L, whereas serum K^+ concentration normally ranges from 3.5 to 5.0 mEq/L. Serum K^+ is an indirect indicator only of the total-body K^+. Serum K^+ is usually analyzed by assessing both intake and excretion.

The average adult excretes 40 to 75 mEq of K^+ in the urine every 24 hours. An additional 10 mEq is excreted in the stool. The average dietary intake of K^+ ranges from 50 to 85 mEq/day. Patients who have undergone surgery, have sustained trauma, or have renal disease often have greater K^+ losses. Consequently, such patients may need K^+ replacement averaging 100 to 120 mEq/day.

Serum K^+ concentration is determined primarily by the pH of extracellular fluid and the size of the intracellular K^+ pool. In extracellular acidosis, excess H^+ ions are exchanged for intracellular K^+. Movement of K^+ from intracellular to extracellular spaces may produce dangerous levels of *hyperkalemia* (elevated K^+). Alkalosis has the opposite effect. When pH increases, K^+ moves into cells. In the absence of acid-base disturbances, serum K^+ reflects total-body K^+. With excessive loss of K^+ from the GI tract, serum K^+ decreases. A 10% loss of total-body K^+ causes the serum K^+ level to decrease approximately 1 mEq/L.

Renal excretion of K^+ is controlled by aldosterone levels.[18] Aldosterone inhibits the enzyme responsible for K^+ transport in the distal renal tubular cells of the kidney. Metabolic acidosis also inhibits the transport system. Na^+ and H^+ ions enter cells at the expense of increased K^+ excretion. Alkalosis has the reverse effect. It stimulates cellular retention of K^+. Kidney failure results in K^+ retention and hyperkalemia.

Hypokalemia (reduced serum K^+) disturbs cellular function in numerous organ systems, including the GI, neuromuscular, renal, and cardiovascular systems (see Table 13-5), and is one of the most common electrolyte abnormalities within the hospital environment.[18] Management of hypokalemia involves replacement of K^+ losses and treatment of the underlying disorder. To manage the associated Cl^- deficit, K^+ is given with Cl^-. Caution is required in the administration of intravenous K^+ because cardiac muscle is very sensitive to extracellular concentrations of this electrolyte.

Hyperkalemia (elevated serum K^+) is most common in patients with renal insufficiency (see Table 13-5). The primary treatment of hyperkalemia is restriction of K^+ intake. The processes that precipitated the hyperkalemia also must be controlled. Temporary measures for reducing serum K^+ levels include administration of insulin, calcium gluconate, Na^+ salts, or large volumes of hypertonic glucose. Cation exchange resins may be given orally or rectally. If these measures fail, peritoneal or renal dialysis can aid in K^+ removal.

Calcium (Ca^{++})

Ca^{++} is an important mediator of neuromuscular function and cell enzyme processes. Most of the Ca^{++} in the body is contained in the bones. The normal serum calcium is 8.7 to 10.4 mg/dl, or approximately 4.5 to 5.25 mEq/L. This concentration is maintained by the interaction of parathyroid hormone, vitamin D (calcitriol), and calcitonin.

Ca^{++} is present in the blood in the following three forms: ionized, protein bound, and complex. The proportion of Ca^{++} in each form is affected by blood pH, concentration of plasma proteins, and presence of Ca^{++}-combining anions (e.g., HCO_3^- and hydrogen phosphate [HPO_4^{2-}]). Approximately 50% of serum Ca is ionized (Ca^{++}) and is physiologically active. An additional 10% forms Ca-anion complexes. The remaining 40% is bound to plasma proteins, primarily albumen. Ionized Ca^{++} is physiologically active in processes such as enzyme activity, blood clotting, neuromuscular irritability, and bone calcification. Acidemia increases the concentration of Ca^{++} in the serum, and alkalemia decreases the concentration.

Abnormal levels of Ca^{++} can cause various serious symptoms (see Table 13-5). Treatment of *hypocalcemia* (low serum levels of Ca^{++}) consists of correcting the underlying cause and replacing Ca^{++} either orally or intravenously. *Hypercalcemia* (increased levels of Ca^{++}) can result from numerous disorders. The most common causes are hyperparathyroidism and malignancies (e.g., multiple myeloma, lung cancer). Acute hypercalcemia requires emergency treatment because death may occur quickly if serum Ca^{++} increases to more than 17 mg/L (8.5 mEq/L). In such cases, there is usually an associated deficit of extracellular fluid. Volume replacement reduces serum Ca^{++} by dilution.

Magnesium (Mg^{++})

Mg^{++} is the second most abundant intracellular cation after K^+. Mg^{++} plays an important role in cellular functions, including energy transfer; metabolism of protein, carbohydrate, and fat; and maintenance of normal cell membrane function (see Table 13-5). Systemically, Mg^{++} decreases blood pressure and alters peripheral vascular resistance. Abnormalities of Mg^{++} levels can result in disturbances in nearly every organ system and can cause potentially fatal complications (e.g., ventricular arrhythmia, coronary artery vasospasm, sudden death). Hypomagnesemia is also associated with multiple neuromuscular symptoms, such as muscular weakness, tetany, coma, and seizures. There is some evidence that intercellular Mg^{++} levels may be related to bronchial hyperresponsiveness.

Normal values for serum Mg^{++} range from 1.7 to 2.1 mg/dl (1.7 to 1.4 mEq/L) in healthy adults. Most (99%) of the Mg^{++} in the body is intracellular. Of the small portion in extracellular spaces, 80% is ionized or bound to other ions (e.g., phosphate) and the remaining 20% bound to proteins. Extracellular Mg^{++} is in equilibrium with Mg^{++} in the bone, kidneys, intestine, and other soft tissues. In contrast to most electrolytes, Mg^{++} excretion in urine is not regulated hormonally, and circulating Mg^{++} in the extracellular fluid does not exchange readily with its main repository—the bones. Serum levels of Mg^{++} may remain normal even if total-body stores are depleted by 20%. Conversely, when there is a negative Mg^{++} balance, most of the losses come from the extracellular spaces.

Phosphorus (P)

An average adult has approximately 1 kg (1000 g) of P, of which 80% to 90% is in bone and teeth in the form of apatite. The remaining P is mostly present in the viscera and skeletal muscle, with a very small amount (<0.1%) in the extracellular fluids.[19] Of this total, 10% to 17% is combined with proteins, carbohydrates, and lipids in muscle tissue and blood, and the remainder is incorporated into complex organic compounds. Only about 1% of the total-body P is available as free serum compounds, so the serum level (1.2 to 2.3 mEq/L) does not reflect total-body content. Serum P levels are influenced by several factors (see Table 13-5), including the serum Ca^{++} concentration and the pH of blood.

Organic phosphate (HPO_4^{2-}) is the main anion within cells, with 20% present in the mitochondria. Approximately 30% of cellular HPO_4^{2-} is stored in the endoplasmic reticulum and is used in the phosphorylation of various proteins.[19] Inorganic phosphate plays a primary role in the metabolism of cellular energy, being the source from which adenosine triphosphate is synthesized. In acid-base homeostasis, phosphate is the main urinary buffer for titratable acid excretion (see Chapter 14).

P homeostasis depends on balance between GI absorption and urinary excretion. The parathyroid hormone provides hormonal regulation. *Hyperphosphatemia* (elevated serum levels of P) can occur when the load (e.g., GI absorption, cellular release) exceeds renal excretion and tissue uptake. Hyperphosphatemia precipitates Ca^{++}, causing hypocalcemia, which can be life-threatening if severe. Central nervous system symptoms such as altered mental status, paresthesias, and seizures can result from hyperphosphatemia. Prolonged hyperphosphatemia can result in abnormal deposition of calcium phosphate in previously healthy connective tissues, such as cardiac valves, and in solid organs, such as muscles.

SUMMARY CHECKLIST

- The body is a water-based organism in which chemical substances and particles exist in solution or suspension.
- The concentration of solutes in a solution may be quantified (1) by actual weight (grams, milligrams, or micrograms) or (2) by chemical combining power (equivalents or milliequivalents). The weight of a solute does not give an indication of its chemical combining power, but gram equivalent weights do.
- Solutions commonly involve the action of osmotic pressure. Body cell membranes are semipermeable, and osmotic pressure maintains the distribution of water and solutes in physiologic ranges.
- Concentrations of solutions may be calculated using ratio, weight/volume, or percent methods.
- Physiologically active compounds in the body are mostly weak electrolytic covalent substances. In aqueous solutions, some molecules ionize, leaving the remainder