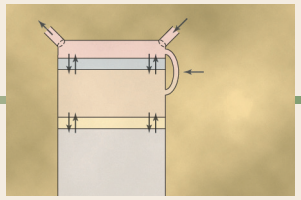

CHAPTER 25

UNIT V

The Body Fluid Compartments: Extracellular and Intracellular Fluids; Edema

The maintenance of a relatively constant volume and a stable composition of the body fluids is essential for homeostasis. Some of the most common and important problems in clinical medicine arise because of abnormalities in the control systems that maintain this relative constancy of the body fluids. In this chapter and in the following chapters on the kidneys, we discuss the overall regulation of body fluid volume, constituents of the extracellular fluid, acid-base balance, and control of fluid exchange between extracellular and intracellular compartments.

FLUID INTAKE AND OUTPUT ARE BALANCED DURING STEADY-STATE CONDITIONS

The relative constancy of the body fluids is remarkable because there is continuous exchange of fluid and solutes with the external environment, as well as within the different body compartments. For example, fluid intake is highly variable and must be carefully matched by equal output of water from the body to prevent body fluid volumes from increasing or decreasing.

DAILY INTAKE OF WATER

Water is added to the body by two major sources: (1) it is ingested in the form of liquids or water in food, which together normally add about 2100 ml/day to the body fluids, and (2) it is synthesized in the body by oxidation of carbohydrates, adding about 200 ml/day. These mechanisms provide a total water intake of about 2300 ml/day (**Table 25-1**). However, intake of water is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.

DAILY LOSS OF BODY WATER

Insensible Water Loss. Some water losses cannot be precisely regulated. For example, humans experience a continuous loss of water by evaporation from the respiratory tract and diffusion through the skin, which together account for about 700 ml/day of water loss under normal conditions. This loss is termed *insensible water loss* because we are not consciously aware of it, even though it occurs continually in all living humans.

Insensible water loss through the skin occurs independently of sweating and is present even in people who are born without sweat glands; the average water loss by diffusion through the skin is about 300 to 400 ml/day. This loss is minimized by the cholesterol-filled cornified layer of the skin, which provides a barrier against excessive loss by diffusion. When the cornified layer becomes denuded, as occurs with extensive burns, the rate of evaporation can increase as much as 10-fold, to 3 to 5 L/day. For this reason, persons with burns must be given large amounts of fluid, usually intravenously, to balance fluid loss.

Insensible water loss through the respiratory tract averages about 300 to 400 ml/day. As air enters the respiratory tract, it becomes saturated with moisture, to a vapor pressure of about 47 mm Hg, before it is expelled. Because the vapor pressure of the inspired air is usually less than 47 mm Hg, water is continuously lost through the lungs with respiration. In cold weather, the atmospheric vapor pressure decreases to nearly 0, causing an even greater loss of water from the lungs as the temperature decreases. This process explains the dry feeling in the respiratory passages in cold weather.

Fluid Loss in Sweat. The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise fluid loss in sweat occasionally increases to 1 to 2 L/hour. This fluid loss would rapidly deplete the body fluids if intake were not also increased by activating the thirst mechanism discussed in Chapter 29.

Water Loss in Feces. Only a small amount of water (100 ml/day) normally is lost in the feces. This loss can increase to several liters a day in people with severe diarrhea. For this reason, severe diarrhea can be life threatening if not corrected within a few days.

Water Loss by the Kidneys. The remaining water loss from the body occurs in the urine excreted by the kidneys.

Table 25-1 Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible: skin	350	350
Insensible: lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

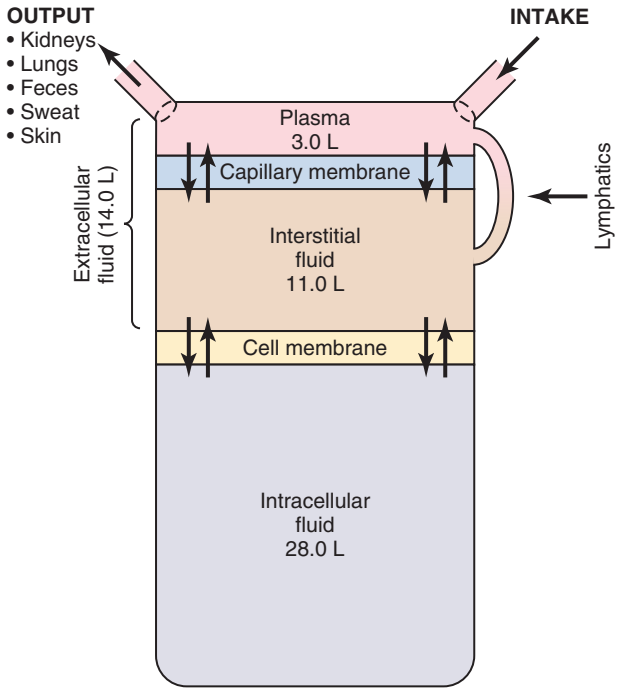

Figure 25-1. Summary of body fluid regulation, including the major body fluid compartments and the membranes that separate these compartments. The values shown are for an average 70-kilogram adult man.

Multiple mechanisms control the rate of urine excretion. In fact, the most important means by which the body maintains a balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rates at which the kidneys excrete these substances. For example, urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking tremendous amounts of water.

This variability of intake is also true for most of the electrolytes of the body, such as sodium, chloride, and potassium. In some people, sodium intake may be as low as 20 mEq/day, whereas in others, sodium intake may be as high as 300 to 500 mEq/day. The kidneys are faced with the task of adjusting the excretion rate of water and electrolytes to match precisely the intake of these substances, as well as compensating for excessive losses of fluids and electrolytes that occur in certain disease states. In Chapters 26 through 31, we discuss the mechanisms that allow the kidneys to perform these remarkable tasks.

BODY FLUID COMPARTMENTS

The total body fluid is distributed mainly between two compartments: the *extracellular fluid* and the *intracellular fluid* (**Figure 25-1**). The extracellular fluid is divided into the *interstitial fluid* and the blood *plasma.*

There is another small compartment of fluid that is referred to as *transcellular fluid.* This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid, although in some cases its composition may differ markedly from that of the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.

In a 70-kilogram adult man, the total body water is about 60 percent of the body weight, or about 42 liters. This percentage depends on age, gender, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This decrease is due in part to the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body.

Because women normally have a greater percentage of body fat compared with men, their total body water averages about 50 percent of the body weight. In premature and newborn babies, the total body water ranges from 70 to 75 percent of body weight. Therefore, when discussing "average" body fluid compartments, we should realize that variations exist, depending on age, gender, and percentage of body fat.

In many other countries, the average body weight (and fat mass) has increased rapidly during the past 30 years. Currently, the average body weight for men older than 20 years in the United States is estimated to be approximately 86.4 kg, and for women, it is 74.1 kg. Therefore the data discussed for an "average" 70 kg man in this chapter (as well as in other chapters) would need to be adjusted accordingly when considering body fluid compartments in most people.

INTRACELLULAR FLUID COMPARTMENT

About 28 of the 42 liters of fluid in the body are inside the 100 trillion cells and are collectively called the *intracellular fluid.* Thus, the intracellular fluid constitutes about 40 percent of the total body weight in an "average" person.

The fluid of each cell contains its individual mixture of different constituents, but the concentrations of these substances are similar from one cell to another. In fact, the composition of cell fluids is remarkably similar even in different animals, ranging from the most primitive microorganisms to humans. For this reason, the intracellular fluid of all the different cells together is considered to be one large fluid compartment.

EXTRACELLULAR FLUID COMPARTMENT

All the fluids outside the cells are collectively called the *extracellular fluid.* Together these fluids account for about 20 percent of the body weight, or about 14 liters in a 70-kilogram man. The two largest compartments of the extracellular fluid are the *interstitial fluid,* which makes up more than three fourths (11 liters) of the extracellular fluid, and the *plasma,* which makes up almost one fourth of the extracellular fluid, or about 3 liters. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so the plasma and interstitial fluids have about the same composition except for proteins, which have a higher concentration in the plasma.

BLOOD VOLUME

Blood contains both extracellular fluid (the fluid in plasma) and intracellular fluid (the fluid in the red blood cells). However, blood is considered to be a separate fluid compartment because it is contained in a chamber of its own, the circulatory system. The blood volume is especially important in the control of cardiovascular dynamics.

The average blood volume of adults is about 7 percent of body weight, or about 5 liters. About 60 percent of the blood is plasma and 40 percent is red blood cells, but these percentages can vary considerably in different people, depending on gender, weight, and other factors.

Hematocrit (Packed Red Blood Cell Volume). The hematocrit is the fraction of the blood composed of red blood cells, as determined by centrifuging blood in a "hematocrit tube" until the cells become tightly packed in the bottom of the tube. Because the centrifuge does not completely pack the red blood cells together, about 3 to 4 percent of the plasma remains entrapped among the cells, and the true hematocrit is only about 96 percent of the measured hematocrit.

In men, the measured hematocrit is normally about 0.40, and in women, it is about 0.36. In persons with severe *anemia,* the hematocrit may fall as low as 0.10, a value that is barely sufficient to sustain life. Conversely, in persons with some conditions excessive production of red blood cells occurs, resulting in *polycythemia.* In these persons, the hematocrit can rise to 0.65.

CONSTITUENTS OF EXTRACELLULAR AND INTRACELLULAR FLUIDS

Comparisons of the composition of the extracellular fluid, including the plasma and interstitial fluid, and the intracellular fluid are shown in **Figures 25-2** and **25-3** and in **Table 25-2**.

IONIC COMPOSITION OF PLASMA AND INTERSTITIAL FLUID IS SIMILAR

Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues.

Because of the *Donnan effect,* the concentration of positively charged ions (cations) is slightly greater (~2 percent) in the plasma than in the interstitial fluid. The plasma proteins have a net negative charge and therefore tend to bind cations such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions. For practical

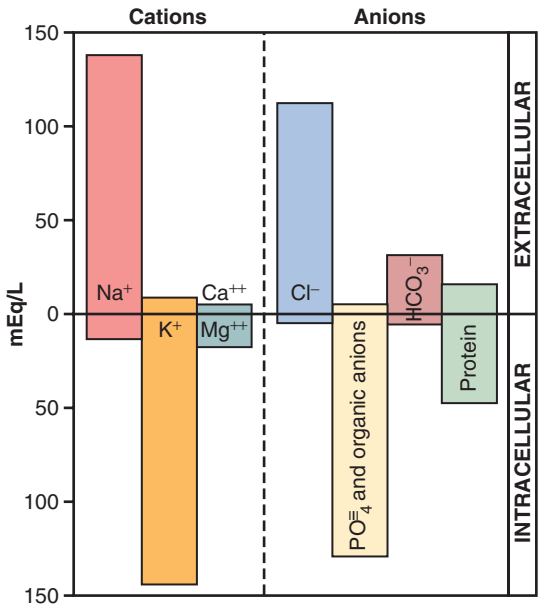

Figure 25-2. Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{++} and Mg^{++} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.

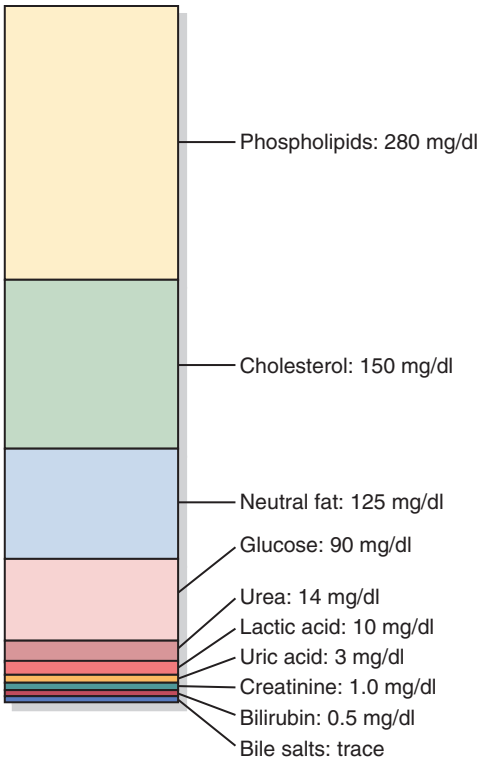

Figure 25-3. Nonelectrolytes of the plasma.

purposes, however, the concentration of ions in the interstitial fluid and in the plasma is considered to be about equal.

Referring again to **Figure 25-2,** one can see that the extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions.

The composition of extracellular fluid is carefully regulated by various mechanisms, but especially by the kidneys, as discussed later. This regulation allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

INTRACELLULAR FLUID CONSTITUENTS

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but is not permeable to most of the electrolytes in the body.

In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein—almost four times as much as in the plasma.

Table 25-2 Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{++}	1.3	1.2	0
Mg^{++}	0.8	0.7	20
Cl^-	106	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	299.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg)	5441	5423	5423

MEASUREMENT OF FLUID VOLUMES IN THE DIFFERENT BODY FLUID COMPARTMENTS—THE INDICATOR-DILUTION PRINCIPLE

The volume of a fluid compartment in the body can be measured by placing an indicator substance in the compartment, allowing it to disperse evenly throughout the compartment's fluid, and then analyzing the extent to which the substance becomes diluted. **Figure 25-4** shows this "indicator-dilution" method of measuring the volume of a fluid compartment. This method is based on the conservation of mass principle, which means that the total mass of a substance after dispersion in the fluid compartment will be the same as the total mass injected into the compartment.

In the example shown in **Figure 25-4**, a small amount of dye or other substance contained in the syringe is injected into a chamber and the substance is allowed to

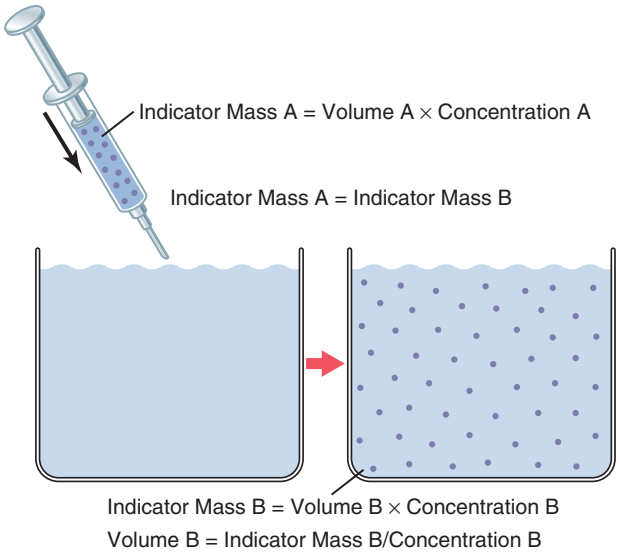

Figure 25-4. Indicator-dilution method for measuring fluid volumes.

disperse throughout the chamber until it becomes mixed in equal concentrations in all areas. Then a sample of fluid containing the dispersed substance is removed and the concentration is analyzed chemically, photoelectrically, or by other means. If none of the substance leaks out of the compartment, the total mass of substance in the compartment (Volume B × Concentration B) will equal the total mass of the substance injected (Volume A × Concentration A). By simple rearrangement of the equation, one can calculate the unknown volume of chamber B as

$$\text{Volume B} = \frac{\text{Volume A} \times \text{Concentration A}}{\text{Concentration B}}$$

Note that all one needs to know for this calculation is (1) the total amount of substance injected into the chamber (the numerator of the equation) and (2) the concentration of the fluid in the chamber after the substance has been dispersed (the denominator).

For example, if 1 milliliter of a solution containing 10 mg/ml of dye is dispersed into chamber B and the final concentration in the chamber is 0.01 milligram for each milliliter of fluid, the unknown volume of the chamber can be calculated as follows:

$$\text{Volume B} = \frac{1\,\text{ml} \times 10\,\text{mg/ml}}{0.01\,\text{mg/ml}} = 1000\,\text{ml}$$

This method can be used to measure the volume of virtually any compartment in the body as long as (1) the indicator disperses evenly throughout the compartment, (2) the indicator disperses only in the compartment that is being measured, and (3) the indicator is not metabolized or excreted. If the indicator is metabolized or excreted, correction must be made for loss of the indicator from the body. Several substances can be used to measure the volume of each of the different body fluids.

Table 25-3 Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	$^{3}H_2O$, $^{2}H_2O$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water – extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = plasma volume/(1 – hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume – plasma volume)

DETERMINATION OF VOLUMES OF SPECIFIC BODY FLUID COMPARTMENTS

Measurement of Total Body Water. Radioactive water (tritium, $^{3}H_2O$) or heavy water (deuterium, $^{2}H_2O$) can be used to measure total body water. These forms of water mix with the total body water within a few hours after being injected into the blood, and the dilution principle can be used to calculate total body water (Table 25-3). Another substance that has been used to measure total body water is *antipyrine,* which is very lipid soluble and can rapidly penetrate cell membranes and distribute itself uniformly throughout the intracellular and extracellular compartments.

Measurement of Extracellular Fluid Volume. The volume of extracellular fluid can be estimated using any of several substances that disperse in the plasma and interstitial fluid but do not readily permeate the cell membrane. They include radioactive sodium, radioactive chloride, radioactive iothalamate, thiosulfate ion, and inulin. When any one of these substances is injected into the blood, it usually disperses almost completely throughout the extracellular fluid within 30 to 60 minutes. Some of these substances, however, such as radioactive sodium, may diffuse into the cells in small amounts. Therefore, one frequently speaks of the *sodium space* or the *inulin space,* instead of calling the measurement the true extracellular fluid volume.

Calculation of Intracellular Volume. The intracellular volume cannot be measured directly. However, it can be calculated as

$$\text{Intracellular volume} = \text{Total body water} - \text{Extracellular volume}$$

Measurement of Plasma Volume. To measure plasma volume, a substance must be used that does not readily penetrate capillary membranes but remains in the vascular system after injection. One of the most commonly used substances for measuring plasma volume is serum

albumin labeled with radioactive iodine (^{125}I-albumin). Also, dyes that avidly bind to the plasma proteins, such as *Evans blue dye* (also called *T-1824*), can be used to measure plasma volume.

Calculation of Interstitial Fluid Volume. Interstitial fluid volume cannot be measured directly, but it can be calculated as

$$\text{Interstitial fluid volume} = \text{Extracellular fluid volume} - \text{Plasma volume}$$

Measurement of Blood Volume. If one measures plasma volume using the methods described earlier, blood volume can also be calculated if one knows the *hematocrit* (the fraction of the total blood volume composed of cells), using the following equation:

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

For example, if plasma volume is 3 liters and hematocrit is 0.40, total blood volume would be calculated as

$$\frac{3 \text{ liters}}{1 - 0.4} = 5 \text{ liters}$$

Another way to measure blood volume is to inject into the circulation red blood cells that have been labeled with radioactive material. After these mix in the circulation, the radioactivity of a mixed blood sample can be measured and the total blood volume can be calculated using the indicator-dilution principle. A substance frequently used to label the red blood cells is radioactive chromium (^{51}Cr), which binds tightly with the red blood cells.

REGULATION OF FLUID EXCHANGE AND OSMOTIC EQUILIBRIUM BETWEEN INTRACELLULAR AND EXTRACELLULAR FLUID

A frequent problem in treating seriously ill patients is maintaining adequate fluids in one or both of the intracellular and extracellular compartments. As discussed in Chapter 16 and later in this chapter, the relative amounts of extracellular fluid distributed between the plasma and interstitial spaces are determined mainly by the balance of hydrostatic and colloid osmotic forces across the capillary membranes.

The distribution of fluid between intracellular and extracellular compartments, in contrast, is determined mainly by the osmotic effect of the smaller solutes—especially sodium, chloride, and other electrolytes—acting across the cell membrane. The reason for this is that the cell membranes are highly permeable to water but relatively impermeable to even small ions such as sodium and chloride. Therefore, water moves across the cell membrane rapidly and the intracellular fluid remains isotonic with the extracellular fluid.

In the next section, we discuss the interrelations between intracellular and extracellular fluid volumes and the osmotic factors that can cause shifts of fluid between these two compartments.

BASIC PRINCIPLES OF OSMOSIS AND OSMOTIC PRESSURE

The basic principles of osmosis and osmotic pressure were presented in Chapter 4. Therefore, we review here only the most important aspects of these principles as they apply to volume regulation.

Because cell membranes are relatively impermeable to most solutes but are highly permeable to water (i.e., they are selectively permeable), whenever there is a higher concentration of solute on one side of the cell membrane, water diffuses across the membrane toward the region of higher solute concentration. Thus, if a solute such as sodium chloride is added to the extracellular fluid, water rapidly diffuses from the cells through the cell membranes into the extracellular fluid until the water concentration on both sides of the membrane becomes equal. Conversely, if a solute such as sodium chloride is removed from the extracellular fluid, water diffuses from the extracellular fluid through the cell membranes and into the cells. The rate of diffusion of water is called the *rate of osmosis.*

Osmolality and Osmolarity. The osmolal concentration of a solution is called *osmolality* when the concentration is expressed as *osmoles per kilogram of water;* it is called *osmolarity* when it is expressed as *osmoles per liter of solution.* In dilute solutions such as the body fluids, these two terms can be used almost synonymously because the differences are small. In most cases, it is easier to express body fluid quantities in liters of fluid rather than in kilograms of water. Therefore, most of the calculations used clinically and the calculations expressed in the next several chapters are based on osmolarities rather than osmolalities.

Calculation of the Osmolarity and Osmotic Pressure of a Solution. Using van't Hoff's law, one can calculate the potential osmotic pressure of a solution, assuming that the cell membrane is impermeable to the solute.

For example, the osmotic pressure of a 0.9 percent sodium chloride solution is calculated as follows: A 0.9 percent solution means that there is 0.9 gram of sodium chloride per 100 milliliters of solution, or 9 g/L. Because the molecular weight of sodium chloride is 58.5 g/mol, the molarity of the solution is 9 g/L divided by 58.5 g/mol, or about 0.154 mol/L. Because each molecule of sodium chloride is equal to 2 osmoles, the osmolarity of the solution is 0.154 × 2, or 0.308 osm/L. Therefore, the osmolarity of this solution is 308 mOsm/L. The potential osmotic pressure of this solution would therefore be 308 mOsm/L × 19.3 mm Hg/mOsm/L, or 5944 mm Hg.

This calculation is an approximation because sodium and chloride ions do not behave entirely independently in solution because of interionic attraction between them. One can correct for these deviations from the predictions of van't Hoff's law by using a correction factor called the *osmotic coefficient.* For sodium chloride, the osmotic coefficient is about 0.93. Therefore, the actual osmolarity of a 0.9 percent sodium chloride solution is 308 × 0.93, or about 286 mOsm/L. For practical reasons, the osmotic coefficients of different solutes are sometimes neglected in determining the osmolarity and osmotic pressures of physiologic solutions.

Osmolarity of the Body Fluids. Turning back to **Table 25-2**, note the approximate osmolarity of the various osmotically active substances in plasma, interstitial fluid, and intracellular fluid. Note that about 80 percent of the total osmolarity of the interstitial fluid and plasma is due to sodium and chloride ions, whereas for intracellular fluid, almost half the osmolarity is due to potassium ions and the remainder is divided among many other intracellular substances.

As shown in **Table 25-2**, the total osmolarity of each of the three compartments is about 300 mOsm/L, with the plasma being about 1 mOsm/L greater than that of the interstitial and intracellular fluids. The slight difference between plasma and interstitial fluid is caused by the osmotic effects of the plasma proteins, which maintain about 20 mm Hg greater pressure in the capillaries than in the surrounding interstitial spaces, as discussed in Chapter 16.

Corrected Osmolar Activity of the Body Fluids. At the bottom of **Table 25-2** are shown *corrected osmolar activities* of plasma, interstitial fluid, and intracellular fluid. The reason for these corrections is that cations and anions exert interionic attraction, which can cause a slight decrease in the osmotic "activity" of the dissolved substance.

OSMOTIC EQUILIBRIUM IS MAINTAINED BETWEEN INTRACELLULAR AND EXTRACELLULAR FLUIDS

Large osmotic pressures can develop across the cell membrane with relatively small changes in the concentrations of solutes in the extracellular fluid. As discussed earlier, for each milliosmole concentration gradient of an *impermeant solute* (one that will not permeate the cell membrane), about 19.3 mm Hg of osmotic pressure is exerted across the cell membrane. If the cell membrane is exposed to pure water and the osmolarity of intracellular fluid is 282 mOsm/L, the potential osmotic pressure that can develop across the cell membrane is more than 5400 mm Hg. This demonstrates the large force that can move water across the cell membrane when the intracellular and extracellular fluids are not in osmotic equilibrium. As a result of these forces, relatively small changes in the concentration of impermeant solutes in the extracellular fluid can cause large changes in cell volume.

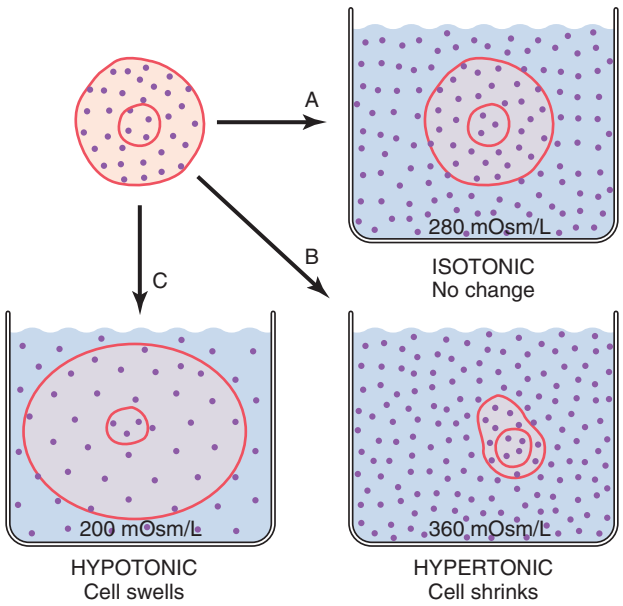

Figure 25-5. Effects of isotonic (*A*), hypertonic (*B*), and hypotonic (*C*) solutions on cell volume.

Isotonic, Hypotonic, and Hypertonic Fluids. The effects of different concentrations of impermeant solutes in the extracellular fluid on cell volume are shown in **Figure 25-5.** If a cell is placed in a solution of impermeant solutes having an osmolarity of 282 mOsm/L, the cells will not shrink or swell because the water concentration in the intracellular and extracellular fluids is equal and the solutes cannot enter or leave the cell. Such a solution is said to be *isotonic* because it neither shrinks nor swells the cells. Examples of isotonic solutions include a 0.9 percent solution of sodium chloride or a 5 percent glucose solution. These solutions are important in clinical medicine because they can be infused into the blood without the danger of upsetting osmotic equilibrium between the intracellular and extracellular fluids.

If a cell is placed into a *hypotonic* solution that has a lower concentration of impermeant solutes (<282 mOsm/L), water will diffuse into the cell, causing it to swell; water will continue to diffuse into the cell, diluting the intracellular fluid while also concentrating the extracellular fluid until both solutions have about the same osmolarity. Solutions of sodium chloride with a concentration of less than 0.9 percent are hypotonic and cause cells to swell.

If a cell is placed in a *hypertonic* solution having a higher concentration of impermeant solutes, water will flow out of the cell into the extracellular fluid, concentrating the intracellular fluid and diluting the extracellular fluid. In this case, the cell will shrink until the two

concentrations become equal. Sodium chloride solutions of greater than 0.9 percent are hypertonic.

Isosmotic, Hyperosmotic, and Hypo-Osmotic Fluids. The terms *isotonic, hypotonic,* and *hypertonic* refer to whether solutions will cause a change in cell volume. The tonicity of solutions depends on the concentration of impermeant solutes. Some solutes, however, can permeate the cell membrane. Solutions with an osmolarity the same as the cell are called *isosmotic,* regardless of whether the solute can penetrate the cell membrane.

The terms *hyperosmotic* and *hypo-osmotic* refer to solutions that have a higher or lower osmolarity, respectively, compared with the normal extracellular fluid, without regard for whether the solute permeates the cell membrane. Highly permeating substances, such as urea, can cause transient shifts in fluid volume between the intracellular and extracellular fluids, but given enough time, the concentrations of these substances eventually become equal in the two compartments and have little effect on intracellular volume under steady-state conditions.

Osmotic Equilibrium Between Intracellular and Extracellular Fluids Is Rapidly Attained. The transfer of fluid across the cell membrane occurs so rapidly that any differences in osmolarities between these two compartments are usually corrected within seconds or, at the most, minutes. This rapid movement of water across the cell membrane does not mean that complete equilibrium occurs between the intracellular and extracellular compartments throughout the whole body within the same short period. The reason for this is that fluid usually enters the body through the gut and must be transported by the blood to all tissues before complete osmotic equilibrium can occur. It usually takes about 30 minutes to achieve osmotic equilibrium everywhere in the body after drinking water.

VOLUME AND OSMOLALITY OF EXTRACELLULAR AND INTRACELLULAR FLUIDS IN ABNORMAL STATES

Some of the different factors that can cause extracellular and intracellular volumes to change markedly are excess ingestion or renal retention of water, dehydration, intravenous infusion of different types of solutions, loss of large amounts of fluid from the gastrointestinal tract, and loss of abnormal amounts of fluid by sweating or through the kidneys.

One can calculate both the changes in intracellular and extracellular fluid volumes and the types of therapy that should be instituted if the following basic principles are kept in mind:

1. *Water moves rapidly across cell membranes;* therefore, the osmolarities of intracellular and extracellular fluids remain almost exactly equal to each other except for a few minutes after a change in one of the compartments.
2. *Cell membranes are almost completely impermeable to many solutes,* such as sodium and chloride; therefore, the number of osmoles in the extracellular or intracellular fluid generally remains constant unless solutes are added to or lost from the extracellular compartment.

With these basic principles in mind, we can analyze the effects of different abnormal fluid conditions on extracellular and intracellular fluid volumes and osmolarities.

EFFECT OF ADDING SALINE SOLUTION TO THE EXTRACELLULAR FLUID

If *isotonic* saline is added to the extracellular fluid compartment, the osmolarity of the extracellular fluid does not change; therefore, no osmosis occurs through the cell membranes. The only effect is an increase in extracellular fluid volume (**Figure 25-6*A***). The sodium and chloride largely remain in the extracellular fluid because the cell membrane behaves as though it were virtually impermeable to the sodium chloride.

If a *hypertonic* solution is added to the extracellular fluid, the extracellular osmolarity increases and causes osmosis of water out of the cells into the extracellular compartment (see **Figure 25-6*B*).** Again, almost all the added sodium chloride remains in the extracellular compartment and fluid diffuses from the cells into the extracellular space to achieve osmotic equilibrium. The net effect is an increase in extracellular volume (greater than the volume of fluid added), a decrease in intracellular volume, and a rise in osmolarity in both compartments.

If a *hypotonic* solution is added to the extracellular fluid, the osmolarity of the extracellular fluid decreases and some of the extracellular water diffuses into the cells until the intracellular and extracellular compartments have the same osmolarity (see **Figure 25-6*C***). Both the intracellular and the extracellular volumes are increased by the addition of hypotonic fluid, although the intracellular volume increases to a greater extent.

Calculation of Fluid Shifts and Osmolarities After Infusion of Hypertonic Saline Solution. We can calculate the sequential effects of infusing different solutions on extracellular and intracellular fluid volumes and osmolarities. For example, if 2 liters of a hypertonic 3.0 percent sodium chloride solution are infused into the extracellular fluid compartment of a 70-kilogram patient whose initial plasma osmolarity is 280 mOsm/L, what would be the intracellular and extracellular fluid volumes and osmolarities after osmotic equilibrium?

The first step is to calculate the initial conditions, including the volume, concentration, and total milliosmoles in each compartment. Assuming that extracellular fluid volume is 20 percent of body weight and intracellular

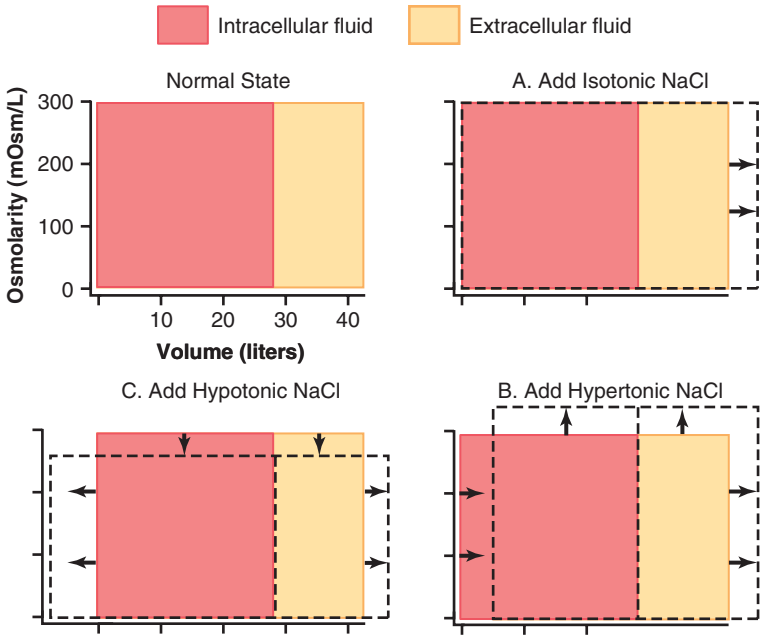

Figure 25-6. Effect of adding isotonic, hypertonic, and hypotonic solutions to the extracellular fluid after osmotic equilibrium. The normal state is indicated by the solid lines, and the shifts from normal are shown by the shaded areas. The volumes of intracellular and extracellular fluid compartments are shown in the abscissa of each diagram, and the osmolarities of these compartments are shown on the ordinates.

fluid volume is 40 percent of body weight, the following volumes and concentrations can be calculated.

Step 1. Initial Conditions

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	14	280	3920
Intracellular fluid	28	280	7840
Total body fluid	42	280	11,760

Next, we calculate the total milliosmoles added to the extracellular fluid in 2 liters of 3.0 percent sodium chloride. A 3.0 percent solution means that there are 3.0 g/100 ml, or 30 grams of sodium chloride per liter. Because the molecular weight of sodium chloride is about 58.5 g/mol, this means that there is about 0.5128 mole of sodium chloride per liter of solution. For 2 liters of solution, this would be 1.0256 mole of sodium chloride. Because 1 mole of sodium chloride is equal to approximately 2 osmoles (sodium chloride has two osmotically active particles per mole), the net effect of adding 2 liters of this solution is to add 2051 milliosmoles of sodium chloride to the extracellular fluid.

In Step 2, we calculate the instantaneous effect of adding 2051 milliosmoles of sodium chloride to the extracellular fluid along with 2 liters of volume. There would be no change in the *intracellular fluid* concentration or volume, and there would be no osmotic equilibrium. In the *extracellular fluid,* however, there would be an additional 2051 milliosmoles of total solute, yielding a total of 5971 milliosmoles. Because the extracellular compartment now has 16 liters of volume, the concentration can be calculated by dividing 5971 milliosmoles by 16 liters to yield a concentration of about 373 mOsm/L. Thus, the following values would occur instantly after adding the solution.

Step 2. Instantaneous Effect of Adding 2 Liters of 3.0 Percent Sodium Chloride

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	16	373	5971
Intracellular fluid	28	280	7840
Total body fluid	44	No equilibrium	13,811

In the third step, we calculate the volumes and concentrations that would occur within a few minutes after osmotic equilibrium develops. In this case, the concentrations in the intracellular and extracellular fluid compartments would be equal and can be calculated by dividing the total milliosmoles in the body, 13,811, by the total volume, which is now 44 liters. This calculation yields a concentration of 313.9 mOsm/L. Therefore, all the body fluid compartments will have this same concentration after osmotic equilibrium. Assuming that no solute or water has been lost from the body and that there is no movement of sodium chloride into or out of the cells, we then calculate the volumes of the intracellular and extracellular compartments. The intracellular fluid volume is calculated by dividing the total milliosmoles in the intracellular fluid (7840) by the concentration (313.9 mOsm/L), to yield a volume of 24.98 liters. Extracellular fluid volume is calculated by dividing the total milliosmoles in extracellular fluid (5971) by the concentration (313.9 mOsm/L),

to yield a volume of 19.02 liters. Again, these calculations are based on the assumption that the sodium chloride added to the extracellular fluid remains there and does not move into the cells.

Step 3. Effect of Adding 2 Liters of 3.0 Percent Sodium Chloride After Osmotic Equilibrium

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	19.02	313.9	5971
Intracellular fluid	24.98	313.9	7840
Total body fluid	44.0	313.9	13,811

Thus, one can see from this example that adding 2 liters of a hypertonic sodium chloride solution causes more than a 5-liter increase in extracellular fluid volume while *decreasing* intracellular fluid volume by almost 3 liters.

This method of calculating changes in intracellular and extracellular fluid volumes and osmolarities can be applied to virtually any clinical problem of fluid volume regulation. The reader should be familiar with such calculations because an understanding of the mathematical aspects of osmotic equilibrium between intracellular and extracellular fluid compartments is essential for understanding almost all fluid abnormalities of the body and their treatment.

GLUCOSE AND OTHER SOLUTIONS ADMINISTERED FOR NUTRITIVE PURPOSES

Many types of solutions are administered intravenously to provide nutrition to people who cannot otherwise ingest adequate amounts of nutrition. Glucose solutions are widely used, and amino acid and homogenized fat solutions are used to a lesser extent. When these solutions are administered, their concentrations of osmotically active substances are usually adjusted nearly to isotonicity, or they are given slowly enough that they do not upset the osmotic equilibrium of the body fluids.

After the glucose or other nutrients are metabolized, an excess of water often remains, especially if additional fluid is ingested. Ordinarily, the kidneys excrete this fluid in the form of dilute urine. The net result, therefore, is the addition of only nutrients to the body.

A 5 percent glucose solution, which is nearly isosmotic, is often used to treat dehydration. Because the solution is isosmotic, it can be infused intravenously without causing red blood cell swelling, as would occur with an infusion of pure water. Because glucose in the solution is rapidly transported into the cells and metabolized, infusion of a 5 percent glucose solution reduces extracellular fluid osmolarity and therefore helps correct the increase in extracellular fluid osmolarity associated with dehydration.

CLINICAL ABNORMALITIES OF FLUID VOLUME REGULATION: HYPONATREMIA AND HYPERNATREMIA

A measurement that is readily available to the clinician for evaluating a patient's fluid status is the plasma sodium concentration. Plasma osmolarity is not routinely measured, but because sodium and its associated anions (mainly chloride) account for more than 90 percent of the solute in the extracellular fluid, plasma sodium concentration is a reasonable indicator of plasma osmolarity under many conditions. When plasma sodium concentration is reduced more than a few milliequivalents below normal (about 142 mEq/L), a person is said to have *hyponatremia.* When plasma sodium concentration is elevated above normal, a person is said to have *hypernatremia.*

CAUSES OF HYPONATREMIA: EXCESS WATER OR LOSS OF SODIUM

Decreased plasma sodium concentration can result from loss of sodium chloride from the extracellular fluid or addition of excess water to the extracellular fluid (**Table 25-4**). A primary loss of sodium chloride usually results in *hyponatremia and dehydration* and is associated with decreased extracellular fluid volume. Conditions that can cause hyponatremia as a result of loss of sodium chloride include *diarrhea* and *vomiting. Overuse of diuretics* that inhibit the ability of the kidneys to conserve sodium and certain types of sodium-wasting kidney diseases can also cause modest degrees of hyponatremia. Finally, *Addison's disease,* which results from decreased secretion of the hormone aldosterone, impairs the ability of the kidneys

Table 25-4 Abnormalities of Body Fluid Volume Regulation: Hyponatremia and Hypernatremia

Abnormality	Cause	Plasma Na^+ Concentration	Extracellular Fluid Volume	Intracellular Fluid Volume
Hyponatremia—dehydration	Adrenal insufficiency; overuse of diuretics	↓	↓	↑
Hyponatremia—overhydration	Excess ADH (SIADH); bronchogenic tumors	↓	↑	↑
Hypernatremia—dehydration	Diabetes insipidus; excessive sweating	↑	↓	↓
Hypernatremia—overhydration	Cushing's disease; primary aldosteronism	↑	↑	↓

ADH, antidiuretic hormone; SIADH, syndrome of inappropriate ADH.

to reabsorb sodium and can cause a modest degree of hyponatremia.

Hyponatremia can also be associated with excess water retention, which dilutes the sodium in the extracellular fluid, a condition that is referred to as *hyponatremia—overhydration.* For example, *excessive secretion of antidiuretic hormone,* which causes the kidney tubules to reabsorb more water, can lead to hyponatremia and overhydration.

CONSEQUENCES OF HYPONATREMIA: CELL SWELLING

Rapid changes in cell volume as a result of hyponatremia can have profound effects on tissue and organ function, especially the brain. A rapid reduction in plasma sodium concentration, for example, can cause brain cell edema and neurological symptoms, including headache, nausea, lethargy, and disorientation. If plasma sodium concentration rapidly falls below 115 to 120 mmol/L, brain swelling may lead to seizures, coma, permanent brain damage, and death. Because the skull is rigid, the brain cannot increase its volume by more than about 10 percent without it being forced down the neck *(herniation),* which can lead to permanent brain injury and death.

When hyponatremia evolves more slowly over several days, the brain and other tissues respond by transporting sodium, chloride, potassium, and organic solutes, such as glutamate, from the cells into the extracellular compartment. This response attenuates osmotic flow of water into the cells and swelling of the tissues (**Figure 25-7**).

Transport of solutes from the cells during slowly developing hyponatremia, however, can make the brain vulnerable to injury if the hyponatremia is corrected too rapidly. When hypertonic solutions are added too rapidly to correct hyponatremia, this intervention can outpace the brain's ability to recapture the solutes lost from the cells and may lead to osmotic injury of the neurons that is associated with *demyelination,* a loss of the myelin sheath from nerves. This osmotic-mediated demyelination of neurons can be avoided by limiting the correction of chronic hyponatremia to less than 10 to 12 mmol/L in 24 hours and to less than 18 mmol/L in 48 hours. This slow rate of correction permits the brain to recover the lost osmoles that have occurred as a result of adaptation to chronic hyponatremia.

Hyponatremia is the most common electrolyte disorder encountered in clinical practice and may occur in up to 15% to 25% of hospitalized patients.

CAUSES OF HYPERNATREMIA: WATER LOSS OR EXCESS SODIUM

Increased plasma sodium concentration, which also causes increased osmolarity, can be due to either loss of water from the extracellular fluid, which concentrates the sodium ions, or excess sodium in the extracellular fluid.

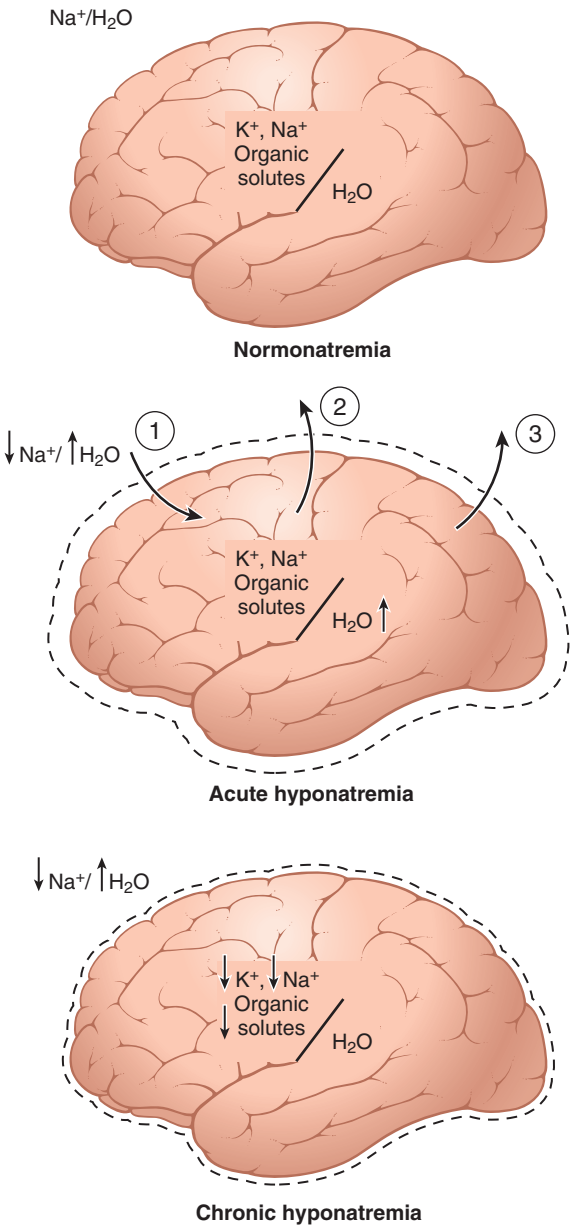

Figure 25-7. Brain cell volume regulation during hyponatremia. During acute hyponatremia, caused by loss of Na^+ or excess H_2O, there is diffusion of H_2O into the cells (*1*) and swelling of the brain tissue (indicated by the *dashed lines*). This process stimulates transport of Na^+, K^+, and organic solutes out of the cells (*2*), which then causes water diffusion out of the cells (*3*). With chronic hyponatremia, the brain swelling is attenuated by the transport of solutes from the cells.

Primary loss of water from the extracellular fluid results in *hypernatremia and dehydration.* This condition can occur from an inability to secrete antidiuretic hormone, which is needed for the kidneys to conserve water. As a result of lack of antidiuretic hormone, the kidneys excrete large amounts of dilute urine (a disorder referred to as *"central" diabetes insipidus*), causing dehydration and increased concentration of sodium chloride in the extracellular fluid. In certain types of renal diseases, the kidneys cannot respond to antidiuretic hormone, causing a type

of *"nephrogenic" diabetes insipidus.* A more common cause of hypernatremia associated with decreased extracellular fluid volume is simple *dehydration* caused by water intake that is less than water loss, as can occur with sweating during prolonged, heavy exercise.

Hypernatremia can also occur when excessive sodium chloride is added to the extracellular fluid. This often results in *hypernatremia—overhydration* because excess extracellular sodium chloride is usually associated with at least some degree of water retention by the kidneys as well. For example, *excessive secretion of the sodium-retaining hormone aldosterone* can cause a mild degree of hypernatremia and overhydration. The reason that the hypernatremia is not more severe is that the sodium retention caused by increased aldosterone secretion also stimulates secretion of antidiuretic hormone and causes the kidneys to also reabsorb greater amounts of water.

Thus, in analyzing abnormalities of plasma sodium concentration and deciding on proper therapy, one should first determine whether the abnormality is caused by a primary loss or gain of sodium or a primary loss or gain of water.

CONSEQUENCES OF HYPERNATREMIA: CELL SHRINKAGE

Hypernatremia is much less common than hyponatremia, and severe symptoms usually occur only with rapid and large increases in the plasma sodium concentration above 158 to 160 mmol/L. One reason for this phenomenon is that hypernatremia promotes intense thirst and stimulates secretion of antidiuretic hormone, which both protect against a large increase in plasma and extracellular fluid sodium, as discussed in Chapter 29. However, severe hypernatremia can occur in patients with hypothalamic lesions that impair their sense of thirst, in infants who may not have ready access to water, in elderly patients with altered mental status, or in persons with diabetes insipidus.

Correction of hypernatremia can be achieved by administering hypo-osmotic sodium chloride or dextrose solutions. However, it is prudent to correct the hypernatremia slowly in patients who have had chronic increases in plasma sodium concentration because hypernatremia also activates defense mechanisms that protect the cell from changes in volume. These defense mechanisms are opposite to those that occur for hyponatremia and consist of mechanisms that increase the intracellular concentration of sodium and other solutes.

EDEMA: EXCESS FLUID IN THE TISSUES

Edema refers to the presence of excess fluid in the body tissues. In most instances, edema occurs mainly in the extracellular fluid compartment, but it can involve intracellular fluid as well.

INTRACELLULAR EDEMA

Three conditions are especially prone to cause intracellular swelling: (1) hyponatremia, as discussed earlier; (2) depression of the metabolic systems of the tissues; and (3) lack of adequate nutrition to the cells. For example, when blood flow to a tissue is decreased, the delivery of oxygen and nutrients is reduced. If the blood flow becomes too low to maintain normal tissue metabolism, the cell membrane ionic pumps become depressed. When the pumps become depressed, sodium ions that normally leak into the interior of the cell can no longer be pumped out of the cells and the excess intracellular sodium ions cause osmosis of water into the cells. Sometimes this process can increase intracellular volume of a tissue area—even of an entire ischemic leg, for example—to two to three times normal. When such an increase in intracellular volume occurs, it is usually a prelude to death of the tissue.

Intracellular edema can also occur in inflamed tissues. Inflammation usually increases cell membrane permeability, allowing sodium and other ions to diffuse into the interior of the cell, with subsequent osmosis of water into the cells.

EXTRACELLULAR EDEMA

Extracellular fluid edema occurs when excess fluid accumulates in the extracellular spaces. There are two general causes of extracellular edema: (1) abnormal leakage of fluid from the plasma to the interstitial spaces across the capillaries, and (2) failure of the lymphatics to return fluid from the interstitium back into the blood, often called *lymphedema.* The most common clinical cause of interstitial fluid accumulation is excessive capillary fluid filtration.

Factors That Can Increase Capillary Filtration

To understand the causes of excessive capillary filtration, it is useful to review the determinants of capillary filtration discussed in Chapter 16. Mathematically, capillary filtration rate can be expressed as

$$\text{Filtration} = K_f \times (P_c - P_{if} - \pi_c + \pi_{if})$$

where K_f is the capillary filtration coefficient (the product of the permeability and surface area of the capillaries), P_c is the capillary hydrostatic pressure, P_{if} is the interstitial fluid hydrostatic pressure, π_c is the capillary plasma colloid osmotic pressure, and π_{if} is the interstitial fluid colloid osmotic pressure. From this equation, one can see *that any one of the following changes can increase the capillary filtration rate:*

- Increased capillary filtration coefficient
- Increased capillary hydrostatic pressure
- Decreased plasma colloid osmotic pressure

Lymphedema—Failure of the Lymph Vessels to Return Fluid and Protein to the Blood

When lymphatic function is greatly impaired as a result of blockage or loss of the lymph vessels, edema can become especially severe because plasma proteins that leak into the interstitium have no other way to be removed. The rise in protein concentration raises the colloid osmotic pressure of the interstitial fluid, which draws even more fluid out of the capillaries.

Blockage of lymph flow can be especially severe with infections of the lymph nodes, such as occurs with infection by *filaria nematodes (Wuchereria bancrofti),* which are microscopic, threadlike worms. The adult worms live in the human lymph system and are spread from person to person by mosquitoes. People with filarial infections can have severe lymphedema and *elephantiasis* and men can have swelling of the scrotum, called *hydrocele*. Lymphatic filariasis affects more than 120 million people in 80 countries throughout the tropics and subtropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America.

Lymphedema can also occur in persons who have certain types of cancer or after surgery in which lymph vessels are removed or obstructed. For example, large numbers of lymph vessels are removed during radical mastectomy, impairing removal of fluid from the breast and arm areas and causing edema and swelling of the tissue spaces. A few lymph vessels eventually regrow after this type of surgery, and thus the interstitial edema is usually temporary.

SUMMARY OF CAUSES OF EXTRACELLULAR EDEMA

A large number of conditions can cause fluid accumulation in the interstitial spaces by abnormal leaking of fluid from the capillaries or by preventing the lymphatics from returning fluid from the interstitium back to the circulation. The following is a partial list of conditions that can cause extracellular edema by these two types of abnormalities:

I. Increased capillary pressure
   A. Excessive kidney retention of salt and water
      1. Acute or chronic kidney failure
      2. Mineralocorticoid excess
   B. High venous pressure and venous constriction
      1. Heart failure
      2. Venous obstruction
      3. Failure of venous pumps
         (a) Paralysis of muscles
         (b) Immobilization of parts of the body
         (c) Failure of venous valves
   C. Decreased arteriolar resistance
      1. Excessive body heat
      2. Insufficiency of sympathetic nervous system
      3. Vasodilator drugs

II. Decreased plasma proteins
   A. Loss of proteins in urine (nephrotic syndrome)
   B. Loss of protein from denuded skin areas
      1. Burns
      2. Wounds
   C. Failure to produce proteins
      1. Liver disease (e.g., cirrhosis)
      2. Serious protein or caloric malnutrition

III. Increased capillary permeability
   A. Immune reactions that cause release of histamine and other immune products
   B. Toxins
   C. Bacterial infections
   D. Vitamin deficiency, especially vitamin C
   E. Prolonged ischemia
   F. Burns

IV. Blockage of lymph return
   A. Cancer
   B. Infections (e.g., filaria nematodes)
   C. Surgery
   D. Congenital absence or abnormality of lymphatic vessels

Edema Caused by Heart Failure. One of the most serious and common causes of edema is heart failure. In heart failure, the heart fails to pump blood normally from the veins into the arteries, which raises venous pressure and capillary pressure, causing increased capillary filtration. In addition, the arterial pressure tends to fall, causing decreased excretion of salt and water by the kidneys, which causes still more edema. Also, blood flow to the kidneys is reduced in persons with heart failure, and this reduced blood flow stimulates secretion of renin, causing increased formation of angiotensin II and increased secretion of aldosterone, both of which cause additional salt and water retention by the kidneys. Thus, in persons with untreated heart failure, all these factors acting together cause serious generalized extracellular edema.

In patients with left-sided heart failure but without significant failure of the right side of the heart, blood is pumped into the lungs normally by the right side of the heart but cannot escape easily from the pulmonary veins to the left side of the heart because this part of the heart has been greatly weakened. Consequently, all the pulmonary vascular pressures, including pulmonary capillary pressure, rise far above normal, causing serious and life-threatening pulmonary edema. When untreated, fluid accumulation in the lungs can rapidly progress, causing death within a few hours.

Edema Caused by Decreased Kidney Excretion of Salt and Water. Most sodium chloride added to the blood remains in the extracellular compartment, and only small amounts enter the cells. Therefore, in kidney diseases that compromise urinary excretion of salt and water, large amounts of sodium chloride and water are added to the extracellular fluid. Most of this salt and water leaks from

the blood into the interstitial spaces, but some remains in the blood. The main effects of this are (1) widespread increases in interstitial fluid volume (extracellular edema) and (2) hypertension because of the increase in blood volume, as explained in Chapter 19. As an example, in children who have acute glomerulonephritis, in which the renal glomeruli are injured by inflammation and therefore fail to filter adequate amounts of fluid, serious extracellular fluid edema also develops; along with the edema, severe hypertension usually develops.

Edema Caused by Decreased Plasma Proteins. Failure to produce normal amounts of proteins or leakage of proteins from the plasma causes the plasma colloid osmotic pressure to fall. This leads to increased capillary filtration throughout the body and extracellular edema.

One of the most important causes of decreased plasma protein concentration is loss of proteins in the urine in certain kidney diseases, a condition referred to as *nephrotic syndrome.* Multiple types of renal diseases can damage the membranes of the renal glomeruli, causing the membranes to become leaky to the plasma proteins and often allowing large quantities of these proteins to pass into the urine. When this loss exceeds the ability of the body to synthesize proteins, a reduction in plasma protein concentration occurs. Serious generalized edema occurs when the plasma protein concentration falls below 2.5 g/100 ml.

Cirrhosis of the liver is another condition that causes a reduction in plasma protein concentration. Cirrhosis means development of large amounts of fibrous tissue among the liver parenchymal cells. One result is failure of these cells to produce sufficient plasma proteins, leading to decreased plasma colloid osmotic pressure and the generalized edema that goes with this condition.

Another way liver cirrhosis causes edema is that the liver fibrosis sometimes compresses the abdominal portal venous drainage vessels as they pass through the liver before emptying back into the general circulation. Blockage of this portal venous outflow raises capillary hydrostatic pressure throughout the gastrointestinal area and further increases filtration of fluid out of the plasma into the intra-abdominal areas. When this occurs, the combined effects of decreased plasma protein concentration and high portal capillary pressures cause transudation of large amounts of fluid and protein into the abdominal cavity, a condition referred to as *ascites.*

SAFETY FACTORS THAT NORMALLY PREVENT EDEMA

Even though many disturbances can cause edema, usually the abnormality must be severe before serious edema develops. The reason the abnormality must be severe is that three major safety factors prevent excessive fluid accumulation in the interstitial spaces: (1) low compliance of the interstitium when interstitial fluid pressure is in the negative pressure range, (2) the ability of lymph flow to increase 10- to 50-fold, and (3) "washdown" of interstitial fluid protein concentration, which reduces interstitial fluid colloid osmotic pressure as capillary filtration increases.

Safety Factor Caused by Low Compliance of the Interstitium in the Negative Pressure Range

In Chapter 16, we noted that interstitial fluid hydrostatic pressure in most loose subcutaneous tissues of the body is slightly less than atmospheric pressure, averaging about –3 mm Hg. This slight suction in the tissues helps hold the tissues together. **Figure 25-8** shows the approximate relations between different levels of interstitial fluid pressure and interstitial fluid volume, as extrapolated to the human being from animal studies. Note in **Figure 25-8** that as long as the interstitial fluid pressure is in the negative range, small changes in interstitial fluid volume are associated with relatively large changes in interstitial fluid hydrostatic pressure. Therefore, in the negative pressure range, the *compliance* of the tissues, defined as the change in volume per millimeter of mercury pressure change, is low.

How does the low compliance of the tissues in the negative pressure range act as a safety factor against edema? To answer this question, recall the determinants

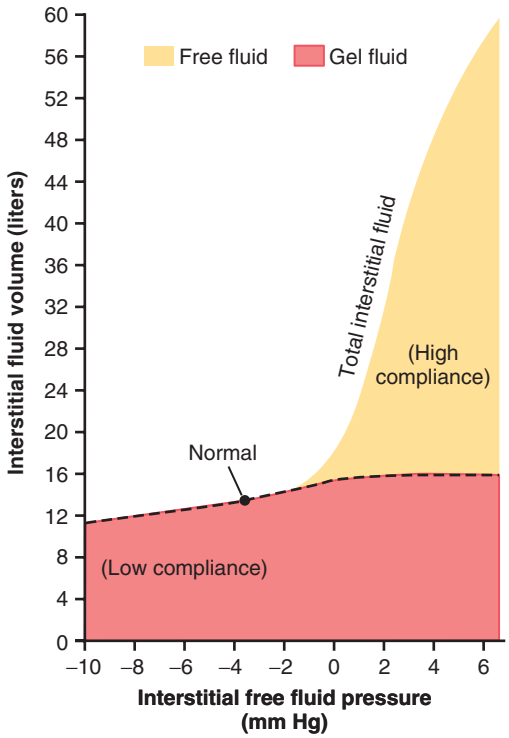

Figure 25-8. Relation between interstitial fluid hydrostatic pressure and interstitial fluid volumes, including total volume, free fluid volume, and gel fluid volume, for loose tissues such as skin. Note that significant amounts of free fluid occur only when the interstitial fluid pressure becomes positive. *(Modified from Guyton AC, Granger HJ, Taylor AE: Interstitial fluid pressure. Physiol Rev 51:527, 1971.)*

of capillary filtration discussed previously. When interstitial fluid hydrostatic pressure increases, this increased pressure tends to oppose further capillary filtration. Therefore, as long as the interstitial fluid hydrostatic pressure is in the negative pressure range, small increases in interstitial fluid volume cause relatively large increases in interstitial fluid hydrostatic pressure, opposing further filtration of fluid into the tissues.

Because the normal interstitial fluid hydrostatic pressure is –3 mm Hg, the interstitial fluid hydrostatic pressure must increase by about 3 mm Hg before large amounts of fluid will begin to accumulate in the tissues. Therefore, the safety factor against edema is a change of interstitial fluid pressure of about 3 mm Hg.

Once interstitial fluid pressure rises above 0 mm Hg, the compliance of the tissues increases markedly, allowing large amounts of fluid to accumulate in the tissues with relatively small additional increases in interstitial fluid hydrostatic pressure. Thus, in the positive tissue pressure range, this safety factor against edema is lost because of the large increase in compliance of the tissues.

Importance of Interstitial Gel in Preventing Fluid Accumulation in the Interstitium. Note in **Figure 25-8** that in normal tissues with negative interstitial fluid pressure, virtually all the fluid in the interstitium is in gel form. That is, the fluid is bound in a proteoglycan meshwork so that there are virtually no "free" fluid spaces larger than a few hundredths of a micrometer in diameter. The importance of the gel is that it prevents fluid from *flowing* easily through the tissues because of impediment from the "brush pile" of trillions of proteoglycan filaments. Also, when the interstitial fluid pressure falls to very negative values, the gel does not contract greatly because the meshwork of proteoglycan filaments offers an elastic resistance to compression. In the negative fluid pressure range, the interstitial fluid volume does not change greatly, regardless of whether the degree of suction is only a few millimeters of mercury negative pressure or 10 to 20 mm Hg negative pressure. In other words, the compliance of the tissues is very low in the negative pressure range.

By contrast, when interstitial fluid pressure rises to the positive pressure range, there is a tremendous accumulation of *free fluid* in the tissues. In this pressure range, the tissues are compliant, allowing large amounts of fluid to accumulate with relatively small additional increases in interstitial fluid hydrostatic pressure. Most of the extra fluid that accumulates is "free fluid" because it pushes the brush pile of proteoglycan filaments apart. Therefore, the fluid can flow freely through the tissue spaces because it is not in gel form. When this free flow of fluid occurs, the edema is said to be *pitting edema* because one can press the thumb against the tissue area and push the fluid out of the area. When the thumb is removed, a pit is left in the skin for a few seconds until the fluid flows back from the surrounding tissues. This type of edema is distinguished from *nonpitting edema,* which occurs when the tissue cells swell instead of the interstitium or when the fluid in the interstitium becomes clotted with fibrinogen so that it cannot move freely within the tissue spaces.

Importance of the Proteoglycan Filaments as a "Spacer" for the Cells and in Preventing Rapid Flow of Fluid in the Tissues. The proteoglycan filaments, along with much larger collagen fibrils in the interstitial spaces, act as a "spacer" between the cells. Nutrients and ions do not diffuse readily through cell membranes; therefore, without adequate spacing between the cells, these nutrients, electrolytes, and cell waste products could not be rapidly exchanged between the blood capillaries and cells located at a distance from one another.

The proteoglycan filaments also prevent fluid from flowing too easily through the tissue spaces. If it were not for the proteoglycan filaments, the simple act of a person standing up would cause large amounts of interstitial fluid to flow from the upper body to the lower body. When too much fluid accumulates in the interstitium, as occurs in edema, this extra fluid creates large channels that allow the fluid to flow readily through the interstitium. Therefore, when severe edema occurs in the legs, the edema fluid often can be decreased by simply elevating the legs.

Even though fluid does not *flow* easily through the tissues in the presence of the compacted proteoglycan filaments, different substances within the fluid can *diffuse* through the tissues at least 95 percent as easily as they normally diffuse. Therefore, the usual diffusion of nutrients to the cells and the removal of waste products from the cells are not compromised by the proteoglycan filaments of the interstitium.

Increased Lymph Flow as a Safety Factor Against Edema

A major function of the lymphatic system is to return to the circulation the fluid and proteins filtered from the capillaries into the interstitium. Without this continuous return of the filtered proteins and fluid to the blood, the plasma volume would be rapidly depleted, and interstitial edema would occur.

The lymphatics act as a safety factor against edema because lymph flow can increase 10- to 50-fold when fluid begins to accumulate in the tissues. This increased lymph flow allows the lymphatics to carry away large amounts of fluid and proteins in response to increased capillary filtration, preventing the interstitial pressure from rising into the positive pressure range. The safety factor caused by increased lymph flow has been calculated to be about 7 mm Hg.

"Washdown" of the Interstitial Fluid Protein as a Safety Factor Against Edema

As increased amounts of fluid are filtered into the interstitium, the interstitial fluid pressure increases, causing

increased lymph flow. In most tissues the protein concentration of the interstitium decreases as lymph flow is increased, because larger amounts of protein are carried away than can be filtered out of the capillaries; the reason for this phenomenon is that the capillaries are relatively impermeable to proteins compared with the lymph vessels. Therefore, the proteins are "washed out" of the interstitial fluid as lymph flow increases.

Because the interstitial fluid colloid osmotic pressure caused by the proteins tends to draw fluid out of the capillaries, decreasing the interstitial fluid proteins lowers the net filtration force across the capillaries and tends to prevent further accumulation of fluid. The safety factor from this effect has been calculated to be about 7 mm Hg.

SUMMARY OF SAFETY FACTORS THAT PREVENT EDEMA

Putting together all the safety factors against edema, we find the following:

1. The safety factor caused by low tissue compliance in the negative pressure range is about 3 mm Hg.
2. The safety factor caused by increased lymph flow is about 7 mm Hg.
3. The safety factor caused by washdown of proteins from the interstitial spaces is about 7 mm Hg.

Therefore, the total safety factor against edema is about 17 mm Hg. This means that the capillary pressure in a peripheral tissue could theoretically rise by 17 mm Hg, or approximately double the normal value, before marked edema would occur.

FLUIDS IN THE "POTENTIAL SPACES" OF THE BODY

Some examples of "potential spaces" are the pleural cavity, pericardial cavity, peritoneal cavity, and synovial cavities, including both the joint cavities and the bursae. Virtually all these potential spaces have surfaces that almost touch each other, with only a thin layer of fluid in between, and the surfaces slide over each other. To facilitate the sliding, a viscous proteinaceous fluid lubricates the surfaces.

Fluid Is Exchanged Between the Capillaries and the Potential Spaces. The surface membrane of a potential space usually does not offer significant resistance to the passage of fluids, electrolytes, or even proteins, which all move back and forth between the space and the interstitial fluid in the surrounding tissue with relative ease. Therefore, each potential space is in reality a large tissue space. Consequently, fluid in the capillaries adjacent to the potential space diffuses not only into the interstitial fluid but also into the potential space.

Lymphatic Vessels Drain Protein from the Potential Spaces. Proteins collect in the potential spaces because of leakage out of the capillaries, similar to the collection of protein in the interstitial spaces throughout the body. The protein must be removed through lymphatics or other channels and returned to the circulation. Each potential space is either directly or indirectly connected with lymph vessels. In some cases, such as the pleural cavity and peritoneal cavity, large lymph vessels arise directly from the cavity itself.

Edema Fluid in the Potential Spaces Is Called *Effusion.* When edema occurs in the subcutaneous tissues adjacent to the potential space, edema fluid usually collects in the potential space as well; this fluid is called *effusion.* Thus, lymph blockage or any of the multiple abnormalities that can cause excessive capillary filtration can cause effusion in the same way that interstitial edema is caused. The abdominal cavity is especially prone to collect effusion fluid, and in this instance, the effusion is called *ascites.* In serious cases, 20 liters or more of ascitic fluid can accumulate.

The other potential spaces, such as the pleural cavity, pericardial cavity, and joint spaces, can become seriously swollen when generalized edema is present. Also, injury or local infection in any one of the cavities often blocks the lymph drainage, causing isolated swelling in the cavity.

The dynamics of fluid exchange in the pleural cavity are discussed in detail in Chapter 39. These dynamics are mainly representative of all the other potential spaces as well. The normal fluid pressure in most or all of the potential spaces in the nonedematous state is *negative* in the same way that this pressure is negative (subatmospheric) in loose subcutaneous tissue. For instance, the interstitial fluid hydrostatic pressure is normally about –7 to –8 mm Hg in the pleural cavity, –3 to –5 mm Hg in the joint spaces, and –5 to –6 mm Hg in the pericardial cavity.

Bibliography

Adrogué HJ, Madias NE: The challenge of hyponatremia. J Am Soc Nephrol 23:1140, 2012.

Aukland K: Why don't our feet swell in the upright position? News Physiol Sci 9:214, 1994.

Berl T: An elderly patient with chronic hyponatremia. Clin J Am Soc Nephrol 8:469, 2013.

Bhave G, Neilson EG: Body fluid dynamics: back to the future. J Am Soc Nephrol 22:2166, 2011.

Centers for Disease Control and Prevention: Parasites: lymphatic filariasis. Available at www.cdc.gov/parasites/lymphaticfilariasis/index.html/.

Damkier HH, Brown PD, Praetorius J: Cerebrospinal fluid secretion by the choroid plexus. Physiol Rev 93:1847, 2013.

Guyton AC, Granger HJ, Taylor AE: Interstitial fluid pressure. Physiol Rev 51:527, 1971.

Jovanovich AJ, Berl T: Where vaptans do and do not fit in the treatment of hyponatremia. Kidney Int 83:563, 2013.

Jussila L, Alitalo K: Vascular growth factors and lymphangiogenesis. Physiol Rev 82:673, 2002.

Lindner G, Funk GC: Hypernatremia in critically ill patients. J Crit Care 28:216.e11, 2013.

Murdaca G, Cagnati P, Gulli R, et al: Current views on diagnostic approach and treatment of lymphedema. Am J Med 125:134, 2012.

Oliver G, Srinivasan RS: Lymphatic vasculature development: current concepts. Ann N Y Acad Sci 1131:75, 2008.

Parker JC: Hydraulic conductance of lung endothelial phenotypes and Starling safety factors against edema. Am J Physiol Lung Cell Mol Physiol 292:L378, 2007.

Planas-Paz L, Lammert E: Mechanical forces in lymphatic vascular development and disease. Cell Mol Life Sci 70:4341, 2013.

Sam R, Feizi I: Understanding hypernatremia. Am J Nephrol 36:97, 2012.

Schrier RW, Sharma S, Shchekochikhin D: Hyponatraemia: more than just a marker of disease severity? Nat Rev Nephrol 9:37, 2013.

Sterns RH, Hix JK, Silver SM: Management of hyponatremia in the ICU. Chest 144:672, 2013.

Trayes KP, Studdiford JS, Pickle S, Tully AS: Edema: diagnosis and management. Am Fam Physician 88:102, 2013.

Verbalis JG, Goldsmith SR, Greenberg A, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 126(10 Suppl 1):S1, 2013.