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医用生理学概要

Review of Medical Physiology

第 20 版

William F. Ganong

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- Comprehensive coverage—over730illustrations
- Includes self-study section—perfect for USMLE preparation

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Review of Medical Physiology

twentieth edition

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The editors were Janet Foltin, Isabel Nogueira, Jim Ransom, and Lester A. Sheinis.
The production supervisor was Phil Galea.
The production service was Rainbow Graphics.
The cover designer was Mary McKeon.
The art manager was Charissa Baker.
The art coordinator was Becky Hainz-Baxter.
The illustrators were Linda F. Harris, Shirley Bortoli, and Teshin Associates.
The indexer was Katherine Pitcoff.
R. R. Donnelley & Sons Company was printer and binder.

INTERNATIONAL EDITION ISBN 0-07-112064-5

图字：01－2001－3619

医用生理学概要（英文版）

主　　编： William F. Ganong, MD	**经　　销：** 新华书店
出版发行： 人民卫生出版社（中继线 67616688）	**开　　本：** 787×1092　1/16
地　　址：（100078）北京市丰台区方庄芳群园 3 区 3 号楼	**印　　张：** 55
	字　　数： 2058 千字
网　　址： http://www.pmph.com	**版　　次：** 2001 年 11 月第 20 版第 1 次印刷
E - mail: pmph@pmph.com	**标准书号：** ISBN 7-117-04560-4/R·4561
印　　刷： 北京人卫印刷厂	**定　　价：** 113.00 元

Preface

This book is designed to provide a concise summary of mammalian and, particularly, of human physiology that medical students and others can use by itself or can supplement with readings in current texts, monographs, and reviews. Pertinent aspects of general and comparative physiology are also included. Summaries of relevant anatomic considerations will be found in each section, but this book is written primarily for those who have some knowledge of anatomy, chemistry, and biochemistry. Examples from clinical medicine are given where pertinent to illustrate physiologic points. In many of the chapters, physicians desiring to use this book as a review will find short discussions of important symptoms produced by disordered function.

Review of Medical Physiology also includes a self-study section to help students review for Board and other examinations and an appendix that contains general references, a discussion of statistical methods, a glossary of abbreviations, acronyms, and symbols commonly used in physiology, and several useful tables. The index is comprehensive and specifically designed for ease in locating important terms, topics, and concepts.

In writing this book, the author has not been able to be complete and concise without also being dogmatic. I believe, however, that the conclusions presented without detailed discussion of the experimental data on which they are based are supported by the bulk of the currently available evidence. Much of this evidence can be found in the papers cited in the credit lines accompanying the illustrations. Further discussions of particular subjects and information on subjects not considered in detail can be found in the references listed at the end of each section. Information about serial review publications that provide up-to-date discussions of various physiologic subjects is included in the note on general references in the appendix. In the interest of brevity and clarity, I have in most instances omitted the names of the many investigators whose work made possible the views of physiology presented here. This omission is in no way intended to slight their contributions, but including their names and specific references to original papers would greatly increase the length of the book.

In this twentieth edition, as in previous editions, the entire book has been thoroughly revised, with a view to eliminating errors, incorporating suggestions of readers, updating concepts, and discarding material that is no longer relevant. In this way, the book has been kept as up-to-date and accurate as possible. Since the last edition, there has continued to be rapid expansion of knowledge about how extracellular signals initiate changes in gene expression and about the genetic basis of disease. Material on these topics has been updated. The section on immunology has been rewritten again for clarity and to expand consideration of the relation between innate and acquired immunity. The sections on the cerebral cortex in relation to vision, audition, and olfaction have been revised, and the chapter on sleep and waking states has been rewritten to emphasize the importance of thalamocortical oscillations. New information has been provided on many topics, including molecular motors, hormones of the heart, motilin and gastrointestinal motility, acute phase proteins, sleep apnea, and addiction.

The self-study section has been updated, and more emphasis has been placed on physiology in relation to disease, in keeping with the current trend in the United States Medical Licensing Examinations (USMLE).

I am greatly indebted to the many individuals who helped with the preparation of this book. Those to whom I express special thanks for their help with the twentieth edition include Dr. Walter Miller, Dr. Melvin Grumbach, Dr. Stephen McPhee, and Dr. Dolores Shoback. Jesse Loesberg provided invaluable secretarial assistance, and, as always, my wife made numerous contributions. Jim Ransom, who edited the first edition of this book 40 years ago, came back again and did an excellent job of editing this edition. Many associates and friends provided unpublished illustrative materials, and numerous authors and publishers generously granted permission to reproduce illustrations from other books and journals. I also thank all the students and others who took the time to write to me offering helpful criticisms and suggestions. Such comments are always welcome, and I solicit additional corrections and criticisms, which may be addressed to me at

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Since this book was first published in 1963, the following translations have been published: Bulgarian, Chinese (two independent translations), Czech (two editions), French, German (four editions), Greek (two editions), Hungarian, Indonesian (three editions), Italian (seven editions), Japanese (fifteen editions), Korean, Malaysian, Polish (two editions), Portuguese (seven editions), Serbo-Croatian, Spanish (sixteen editions), and Turkish (two editions). Various foreign English language editions have been published, and the book has been recorded in English on tape for use by the blind. The tape recording is available from Recording for the Blind, Inc., 20 Rozsel Road, Princeton, NJ 08540, USA. For computer users, the book is now available, along with several other titles in the Lange Medical Books series, in STAT!-Ref, a searchable CD-ROM, from Teton Data Systems, 211 East Broadway, Jackson, WY 83001, USA. More information about this and other Lange and McGraw-Hill books, including addresses of the publisher's international offices, is available on McGraw-Hill's Web site, *www.mghmedical.com.*

William F. Ganong

San Francisco
March 2001

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Section I. Introduction

The General & Cellular Basis of Medical Physiology

1

INTRODUCTION

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include a gastrointestinal system to digest and absorb food; a respiratory system to take up O_2 and eliminate CO_2; a urinary system to remove wastes; a cardiovascular system to distribute food, O_2, and the products of metabolism; a reproductive system to perpetuate the species; and nervous and endocrine systems to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

This chapter presents general concepts and principles that are basic to the function of all the systems. It also includes a short review of fundamental aspects of cell physiology. Additional aspects of cellular and molecular biology are considered in the relevant chapters on the various organs.

GENERAL PRINCIPLES

Organization of the Body

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea" of **extracellular fluid (ECF)** enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the ECF is divided into two components: the **interstitial fluid** and the circulating **blood plasma.** The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the **total blood volume.** The interstitial fluid is that part of the ECF that is outside the vascular system, bathing the cells. The special fluids lumped together as transcellular fluids are discussed below. About a third of the **total body water (TBW)** is extracellular; the remaining two-thirds are intracellular **(intracellular fluid).**

Body Composition

In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water. The distribution of this water is shown in Figure 1–1.

The intracellular component of the body water accounts for about 40% of body weight and the extracellular component for about 20%. Approximately 25% of the extracellular component is in the vascular system (plasma = 5% of body weight) and 75% outside the blood vessels (interstitial fluid = 15% of body weight). The total blood volume is about 8% of body weight.

Measurement of Body Fluid Volumes

It is theoretically possible to measure the size of each of the body fluid compartments by injecting substances that will stay in only one compartment and then calculating the volume of fluid in which the test substance is distributed (the **volume of distribution** of the injected material). The volume of distribution is equal to the amount injected (minus any that has been removed from the body by metabolism or excretion during the time allowed for mixing) divided by the concentration of the substance in the sample. *Example:* 150 mg of sucrose is injected into a 70 kg man. The plasma sucrose level after mixing is 0.01 mg/mL, and 10 mg has been excreted or me-

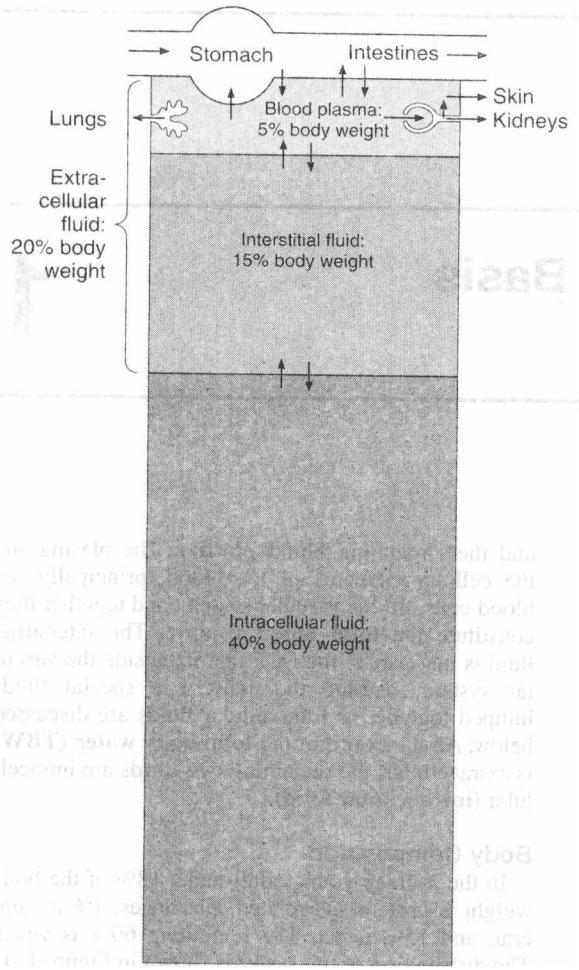

Figure 1–1. Body fluid compartments. Arrows represent fluid movement. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown.

tabolized during the mixing period. The volume of distribution of the sucrose is

$$\frac{150\text{ mg} - 10\text{ mg}}{0.01\text{ mg/mL}} = 14{,}000\text{ mL}$$

Since 14,000 mL is the space in which the sucrose was distributed, it is also called the **sucrose space.**

Volumes of distribution can be calculated for any substance that can be injected into the body provided the concentration in the body fluids and the amount removed by excretion and metabolism can be accurately measured.

Although the principle involved in such measurements is simple, a number of complicating factors must be considered. The material injected must be nontoxic, must mix evenly throughout the compartment being measured, and must have no effect of its own on the distribution of water or other substances in the body. In addition, either it must be unchanged by the body during the mixing period, or the amount changed must be known. The material also should be relatively easy to measure.

Plasma Volume, Total Blood Volume, & Red Cell Volume

Plasma volume has been measured by using dyes that become bound to plasma protein—particularly Evans blue (T-1824). Plasma volume can also be measured by injecting serum albumin labeled with radioactive iodine. Suitable aliquots of the injected solution and plasma samples obtained after injection are counted in a scintillation counter. An average value is 3500 mL (5% of the body weight of a 70 kg man, assuming unit density).

If one knows the plasma volume and the hematocrit (ie, the percentage of the blood volume that is made up of cells), the **total blood volume** can be calculated by multiplying the plasma volume by

$$\frac{100}{100 - \text{hematocrit}}$$

Example: The hematocrit is 38 and the plasma volume 3500 mL. The total blood volume is

$$3500 \times \frac{100}{100 - 38} = 5645\text{ mL}$$

The **red cell volume** (volume occupied by all the circulating red cells in the body) can be determined by subtracting the plasma volume from the total blood volume. It may also be measured independently by injecting tagged red blood cells and, after mixing has occurred, measuring the fraction of the red cells that is tagged. A commonly used tag is ^{51}Cr, a radioactive isotope of chromium that is attached to the cells by incubating them in a suitable chromium solution. Isotopes of iron and phosphorus (^{59}Fe and ^{32}P) and antigenic tagging have also been employed.

Extracellular Fluid Volume

The ECF volume is difficult to measure because the limits of this space are ill defined and because few substances mix rapidly in all parts of the space while remaining exclusively extracellular. The lymph cannot be separated from the ECF and is measured with it. Many substances enter the cerebrospinal fluid (CSF) slowly because of the blood-brain barrier (see Chapter 32). Equilibration is slow with joint fluid and aqueous humor and with the ECF in relatively avascular tissues such as dense connective tissue, cartilage, and some parts of bone. Substances that distribute in ECF appear in glandular secretions and in the contents of the gastrointestinal tract. Because they

are separated from the rest of the ECF, these fluids—as well as CSF, the fluids in the eye, and a few other special fluids—are called **transcellular fluids.** Their volume is relatively small.

Perhaps the most accurate measurement of ECF volume is that obtained by using inulin, a polysaccharide with a molecular weight of 5200. Mannitol and sucrose have also been used to measure ECF volume. A generally accepted value for ECF volume is 20% of the body weight, or about 14 L in a 70 kg man (3.5 L = plasma; 10.5 L = interstitial fluid).

Interstitial Fluid Volume

The interstitial fluid space cannot be measured directly, since it is difficult to sample interstitial fluid and since substances that equilibrate in interstitial fluid also equilibrate in plasma. The volume of the interstitial fluid can be calculated by subtracting the plasma volume from the ECF volume. The ECF volume/intracellular fluid volume ratio is larger in infants and children than it is in adults, but the absolute volume of ECF in children is, of course, smaller than in adults. Therefore, dehydration develops more rapidly and is frequently more severe in children than in adults.

Intracellular Fluid Volume

The intracellular fluid volume cannot be measured directly, but it can be calculated by subtracting the ECF volume from the TBW. TBW can be measured by the same dilution principle used to measure the other body spaces. Deuterium oxide (D_2O heavy water) is most frequently used. D_2O has slightly different properties from those of H_2O, but in equilibration experiments for measuring body water it gives accurate results. Tritium oxide and aminopyrine have also been used for this purpose.

The water content of lean body tissue is constant at 71–72 mL/100 g of tissue, but since fat is relatively free of water, the ratio of TBW to body weight varies with the amount of fat present. TBW is somewhat lower in women than men, and in both sexes, the values tend to decrease with age (Table 1–1).

Units for Measuring Concentration of Solutes

In considering the effects of various physiologically important substances and the interactions between them, the number of molecules, electrical charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, concentrations are frequently expressed in moles, equivalents, or osmoles.

Table 1–1. Total body water (as percentage of body weight) in relation to age and sex.

Age	Male	Female
10–18	59%	57%
18–40	61%	51%
40–60	55%	47%
Over 60	52%	46%

Moles

A mole is the gram-molecular weight of a substance, ie, the molecular weight of the substance in grams. Each mole (mol) consists of approximately 6×10^{23} molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 + 35.5 g = 58.5 g, and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system (see Appendix).

The molecular weight of a substance is the ratio of the mass of one molecule of the substance to the mass of one-twelfth the mass of an atom of carbon-12. Since molecular weight is a ratio, it is dimensionless. The dalton (Da) is a unit of mass equal to one-twelfth the mass of an atom of carbon-12, and 1000 Da = 1 kilodalton (kDa). The kilodalton, which is sometimes expressed simply as K, is a useful unit for expressing the molecular mass of proteins. Thus, for example, one can speak of a 64 K protein or state that the molecular mass of the protein is 64,000 Da. However, since molecular weight is a dimensionless ratio, it is incorrect to say that the molecular weight of the protein is 64 kDa.

Equivalents

The concept of electrical equivalence is important in physiology because many of the important solutes in the body are in the form of charged particles. One equivalent (eq) is 1 mol of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 eq of Na^+ and 1 eq of Cl^-. One equivalent of Na^+ = 23 g/L = 23 g; but 1 eq of Ca^{2+} = 40 g/2 = 20 g. The milliequivalent (meq) is 1/1000 of 1 eq.

Electrical equivalence is not necessarily the same as chemical equivalence. A gram equivalent is the weight of a substance that is chemically equivalent to 8.000 g of oxygen. The normality (N) of a solution is the number of gram equivalents in 1 liter. A 1 N solution of hydrochloric acid contains 1 + 35.5 g/L = 36.5 g/L.

pH

The maintenance of a stable hydrogen ion concentration in the body fluids is essential to life. The pH of a solution is the logarithm to the base 10 of the reciprocal of the H^+ concentration ($[H^+]$), ie, the negative logarithm of the $[H^+]$. The pH of water at 25 °C, in which H^+ and OH^- ions are present in equal numbers, is 7.0 (Figure 1–2). For each pH unit less than 7.0, the $[H^+]$ is increased tenfold; for each pH unit above 7.0, it is decreased tenfold.

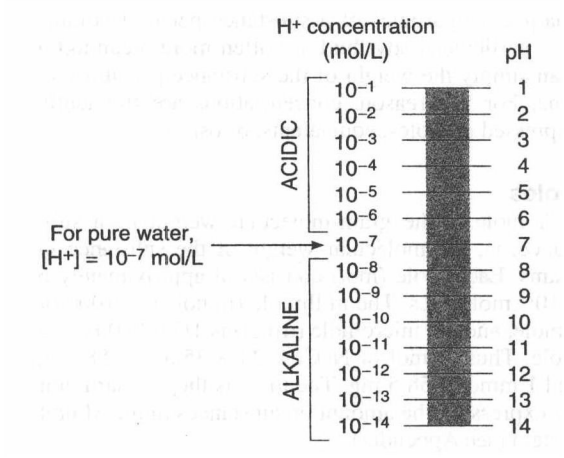

Figure 1–2. pH. (Reproduced, with permission, from Alberts B et al: *Molecular Biology of the Cell.* Garland, 1983.)

Buffers

Intracellular and extracellular pH are generally maintained at very constant levels. For example, the pH of the ECF is 7.40, and in health, this value usually varies less than ± 0.05 pH unit. Body pH is stabilized by the **buffering capacity** of the body fluids. A buffer is a substance that has the ability to bind or release H^+ in solution, thus keeping the pH of the solution relatively constant despite the addition of considerable quantities of acid or base. One buffer in the body is carbonic acid. This acid is only partly dissociated into H^+ and bicarbonate: $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. If H^+ is added to a solution of carbonic acid, the equilibrium shifts to the left and most of the added H^+ is removed from solution. If OH^- is added, H^+ and OH^- combine, taking H^+ out of solution. However, the decrease is countered by more dissociation of H_2CO_3, and the decline in H^+ concentration is minimized. Other buffers include the blood proteins and the proteins in cells. The quantitative aspects of buffering and the respiratory and renal adjustments that operate with buffers to maintain a stable ECF pH of 7.40 are discussed in Chapter 39.

Diffusion

Diffusion is the process by which a gas or a substance in solution expands, because of the motion of its particles, to fill all of the available volume. The particles (molecules or atoms) of a substance dissolved in a solvent are in continuous random movement. A given particle is equally likely to move into or out of an area in which it is present in high concentration. However, since there are more particles in the area of high concentration, the total number of particles moving to areas of lower concentration is greater; ie, there is a **net flux** of solute particles from areas of high to areas of low concentration. The time required for equilibrium by diffusion is proportionate to the square of the diffusion distance. The magnitude of the diffusing tendency from one region to another is directly proportionate to the cross-sectional area across which diffusion is taking place and the **concentration gradient,** or **chemical gradient,** which is the difference in concentration of the diffusing substance divided by the thickness of the boundary **(Fick's law of diffusion).** Thus,

$$J = -DA\frac{\Delta c}{\Delta x}$$

where J is the net rate of diffusion, D is the diffusion coefficient, A is the area, and $\Delta c/\Delta x$ is the concentration gradient. The minus sign indicates the direction of diffusion. When considering movement of molecules from a higher to a lower concentration, $\Delta c/\Delta x$ is negative, so multiplying by –DA gives a positive value. The permeabilities of the boundaries across which diffusion occurs in the body vary, but diffusion is still a major force affecting the distribution of water and solutes.

Osmosis

When a substance is dissolved in water, the concentration of water molecules in the solution is less than that in pure water, since the addition of solute to water results in a solution that occupies a greater volume than does the water alone. If the solution is placed on one side of a membrane that is permeable to water but not to the solute and an equal volume of water is placed on the other, water molecules diffuse down their concentration gradient into the solution (Figure 1–3). This process—the diffusion of **solvent** molecules into a region in which there is a higher concentration of a **solute** to which the membrane is impermeable—is called **osmosis.** It is an important factor in physiologic processes. The tendency for movement of solvent molecules to a region of greater solute concentration can be prevented by applying pressure to the more concentrated solution. The pressure necessary to prevent solvent migration is the **osmotic pressure** of the solution.

Osmotic pressure, like vapor pressure lowering, freezing-point depression, and boiling-point elevation, depends upon the number rather than the type of particles in a solution; ie, it is a fundamental colligative property of solutions. In an **ideal solution,** osmotic pressure (P) is related to temperature and volume in the same way as the pressure of a gas:

$$P = \frac{nRT}{V}$$

where n is the number of particles, R is the gas constant, T is the absolute temperature, and V is the volume. If T is held constant, it is clear that the osmotic pressure is proportionate to the number of particles in

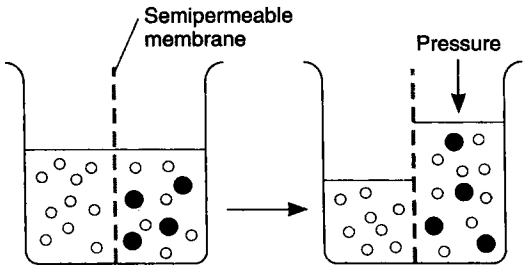

Figure 1–3. Diagrammatic representation of osmosis. Water molecules are represented by small open circles, solute molecules by large solid circles. In the diagram on the left, water is placed on one side of a membrane permeable to water but not to solute, and an equal volume of a solution of the solute is placed on the other. Water molecules move down their concentration gradient into the solution, and, as shown in the diagram on the right, the volume of the solution increases. As indicated by the arrow on the right, the osmotic pressure is the pressure that would have to be applied to prevent the movement of the water molecules.

solution per unit volume of solution. For this reason, the concentration of osmotically active particles is usually expressed in **osmoles.** One osmole (osm) equals the gram-molecular weight of a substance divided by the number of freely moving particles that each molecule liberates in solution. The milliosmole (mosm) is 1/1000 of 1 osm.

If a solute is a nonionizing compound such as glucose, the osmotic pressure is a function of the number of glucose molecules present. If the solute ionizes and forms an ideal solution, each ion is an osmotically active particle. For example, NaCl would dissociate into Na^+ and Cl^- ions, so that each mole in solution would supply 2 osm. One mole of Na_2SO_4 would dissociate into Na^+, Na^+, and SO_4^{2-}, supplying 3 osm. However, the body fluids are not ideal solutions, and although the dissociation of strong electrolytes is complete, the number of particles free to exert an osmotic effect is reduced owing to interactions between the ions. Thus, it is actually the effective concentration (**activity**) in the body fluids rather than the number of equivalents of an electrolyte in solution that determines its osmotic effect. This is why, for example, 1 mmol of NaCl per liter in the body fluids contributes somewhat less than 2 mosm of osmotically active particles per liter. The more concentrated the solution, the greater the deviation from an ideal solution.

The osmolal concentration of a substance in a fluid is measured by the degree to which it depresses the freezing point, with 1 mol of an ideal solution depressing the freezing point 1.86 Celsius degrees. The number of milliosmoles per liter in a solution equals the freezing point depression divided by 0.00186. The **osmolarity** is the number of osmoles per liter of solution—eg, plasma—whereas the **osmolality** is the number of osmoles per kilogram of solvent. Therefore, osmolarity is affected by the volume of the various solutes in the solution and the temperature, while the osmolality is not. Osmotically active substances in the body are dissolved in water, and the density of water is 1, so osmolal concentrations can be expressed as osmoles per liter (osm/L) of water. In this book, osmolal (rather than osmolar) concentrations are considered, and osmolality is expressed in milliosmoles per liter (of water).

Note that although a homogeneous solution contains osmotically active particles and can be said to have an osmotic pressure, it can exert an osmotic pressure only when it is in contact with another solution across a membrane permeable to the solvent but not to the solute.

Osmolal Concentration of Plasma: Tonicity

The freezing point of normal human plasma averages –0.54 °C, which corresponds to an osmolal concentration in plasma of 290 mosm/L. This is equivalent to an osmotic pressure against pure water of 7.3 atmospheres. The osmolality might be expected to be higher than this, because the sum of all the cation and anion equivalents in plasma is over 300. It is not this high because plasma is not an ideal solution and ionic interactions reduce the number of particles free to exert an osmotic effect. Except when there has been insufficient time after a sudden change in composition for equilibrium to occur, all fluid compartments of the body are in or nearly in osmotic equilibrium. The term **tonicity** is used to describe the osmolality of a solution relative to plasma. Solutions that have the same osmolality as plasma are said to be **isotonic;** those with greater osmolality are **hypertonic;** and those with lesser osmolality are **hypotonic.** All solutions that are initially isosmotic with plasma—ie, that have the same actual osmotic pressure or freezing-point depression as plasma—would remain isotonic if it were not for the fact that some solutes diffuse into cells and others are metabolized. Thus, a 0.9% saline solution remains isotonic because there is no net movement of the osmotically active particles in the solution into cells and the particles are not metabolized. On the other hand, a 5% glucose solution is isotonic when initially infused intravenously, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution.

It is important to note the relative contributions of the various plasma components to the total osmolal concentration of plasma. All but about 20 of the 290 mosm in each liter of normal plasma are contributed by Na^+ and its accompanying anions, principally Cl^- and HCO_3^-. Other cations and anions make a relatively small contribution. Although the concentration of the plasma proteins is large when expressed in

grams per liter, they normally contribute less than 2 mosm/L because of their very high molecular weights. The major nonelectrolytes of plasma are glucose and urea, which in the steady state are in equilibrium with cells. Their contributions to osmolality are normally about 5 mosm/L each but can become quite large in hyperglycemia or uremia. The total plasma osmolality is important in assessing dehydration, overhydration, and other fluid and electrolyte abnormalities. Hyperosmolality can cause coma (hyperosmolar coma; see Chapter 19). Because of the predominant role of the major solutes and the deviation of plasma from an ideal solution, one can ordinarily approximate the plasma osmolality within a few milliosmoles per liter by using the following formula, in which the constants convert the clinical units to millimoles of solute per liter:

$$\underset{\text{(mosm/L)}}{\text{Osmolality}} = \underset{\text{(meq/L)}}{2[Na^+]} + \underset{\text{(mg/dL)}}{0.055[\text{Glucose}]} + \underset{\text{(mg/dL)}}{0.36[\text{BUN}]}$$

BUN is the blood urea nitrogen. The formula is also useful in calling attention to abnormally high concentrations of other solutes. An observed plasma osmolality (measured by freezing-point depression) that greatly exceeds the value predicted by this formula probably indicates the presence of a foreign substance such as ethanol, mannitol (sometimes injected to shrink swollen cells osmotically), or poisons such as ethylene glycol or methanol (components of antifreeze).

Regulation of Cell Volume

Unlike plant cells, which have rigid walls, animal cell membranes are flexible. Therefore, animal cells swell when exposed to extracellular hypotonicity and shrink when exposed to extracellular hypertonicity. However, cell swelling activates channels in the cell membrane that permit increased efflux of K^+, Cl^-, organic anions, and small organic solutes referred to collectively as **organic osmolytes.** Water follows these osmotically active particles out of the cell, and the cell volume returns to normal. Ion channels and other membrane transport proteins are discussed in detail in a later section of this chapter.

Nonionic Diffusion

Some weak acids and bases are quite soluble in cell membranes in the undissociated form, whereas they cross membranes with difficulty in the ionic form. Consequently, if molecules of the undissociated substance diffuse from one side of the membrane to the other and then dissociate, there is appreciable net movement of the undissociated substance from one side of the membrane to another. This phenomenon, which occurs in the gastrointestinal tract (see Chapter 25) and kidneys (see Chapter 38), is called **nonionic diffusion.**

Donnan Effect

When there is an ion on one side of a membrane that cannot diffuse through the membrane, the distribution of other ions to which the membrane is permeable is affected in a predictable way. For example, the negative charge of a nondiffusible anion hinders diffusion of the diffusible cations and favors diffusion of the diffusible anions. Consider the following situation,

X	m	Y
K^+	|	K^+
Cl^-	|	Cl^-
$Prot^-$	|	

in which the membrane (m) between compartments X and Y is impermeable to $Prot^-$ but freely permeable to K^+ and Cl^-. Assume that the concentrations of the anions and of the cations on the two sides are initially equal. Cl^- diffuses down its concentration gradient from Y to X, and K^+ moves with the negatively charged Cl^-, maintaining electroneutrality on side Y. Therefore, at equilibrium,

$$[K^+_X] > [K^+_Y]$$

Furthermore,

$$[K^+_X] + [Cl^-_X] + [Prot^-_X] > [K^+_Y] + [Cl^-_Y]$$

ie, there are more osmotically active particles on side X than on side Y.

Donnan and Gibbs showed that in the presence of a nondiffusible ion, the diffusible ions distribute themselves so that at equilibrium, their concentration ratios are equal:

$$\frac{[K^+_X]}{[K^+_Y]} = \frac{[Cl^-_Y]}{[Cl^-_X]}$$

Cross-multiplying,

$$[K^+_X][Cl^-_X] = [K^+_Y][Cl^-_Y]$$

This is the **Gibbs-Donnan equation.** It holds for any pair of cations and anions of the same valence.

The Donnan effect on the distribution of ions has three effects in the body. First, because of proteins ($Prot^-$) in cells, there are more osmotically active particles in cells than in interstitial fluid, and since animal cells have flexible walls, osmosis would make them swell and eventually rupture if it were not for Na^+-K^+ ATPase pumping ions back out of cells (see below). Thus, normal cell volume and pressure depend on Na^+-K^+ ATPase. Second, because at equilibrium there is an asymmetric distribution of permeant ions across the membrane (m in the example used here), there will be an electrical difference across the membrane whose magnitude can be determined by the Nernst equation (see below). In the example used