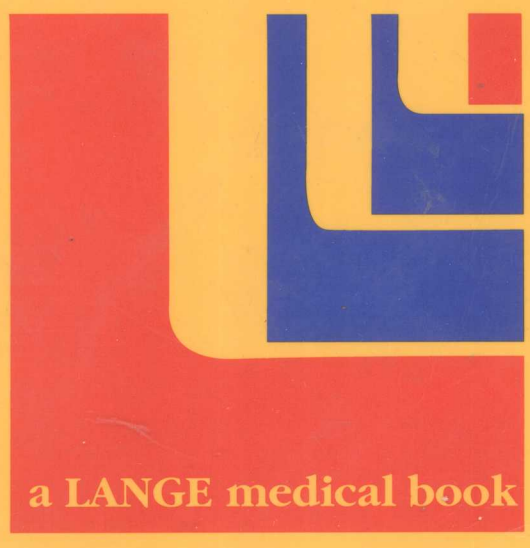
STUDY GUIDE INCLUDED

sixteenth edition

Review of Medical Physiology

William F. Ganong



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Review of Medical Physiology

sixteenth edition

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Preface

This book is designed to provide a concise summary of mammalian and, particularly, of human physiology, which medical students and others can use as a text by itself or 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.

A new feature in this edition is a Self-Study Section, which provides for each chapter a list of objectives, some general essay-type questions, and a selection of multiple-choice questions. Most of the multiple-choice questions are similar to the questions used in the National Board Examinations in the USA, although some K and other types are also included to provide breadth and variety. Answers are provided at the end of the section. The material in the section is a truncated, revised version of the material that was formerly published separately in my Study Guide. Students found *Physiology: A Study Guide*, the third edition of which was published by Appleton & Lange in 1989, to be helpful in organizing their thinking and preparing for board examinations. Publication of this material as part of *Review of Medical Physiology* should increase its value and availability.

Review of Medical Physiology also includes an appendix that contains, among other things, general references, a discussion of statistical methods, a glossary of abbreviations 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, it has not been possible to be complete and concise without also being dogmatic. I believe, however, that the conclusions presented without a 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 of the illustrations. Further discussions of particular subjects and information on subjects not considered in detail in this book 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 view of physiology presented here. This 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 sixteenth edition, as in previous editions, the entire book has been thoroughly revised, 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 have been continued advances in knowledge about intracellular signaling. To accommodate this new information and present it in the most effective way, Chapter 1 has been reorganized and now has expanded coverage of heterotrimeric and other types of G proteins, guanylate cyclases, the various families of protein kinases, and the interplay between phosphoryla-

tion and dephosphorylation of proteins in the regulation of cell function. The exploding field of growth factors, which now permeates all aspects of physiology, is covered in general terms in Chapter 1 and in terms of effects on specific systems in Chapters 19, 21, 22, and 27. The molecular motors responsible for cell movement and muscle contraction are now considered in more detail in Chapters 1 and 3. The section on the basal ganglia has been revised and updated, with emphasis on the role of the subthalamic nucleus, striasomes, and the abnormalities in Huntington's disease as well as Parkinson's disease. The section on learning and memory has been rewritten to emphasize both the growing knowledge about the molecular bases of the processes in simple neural systems and new ideas about the role of the hippocampus, limbic cortex, and neocortical association areas in short-term memory in humans. Chapter 31 has been expanded to give greater consideration to the cardiovascular and other functions of substances produced in the vascular endothelium, especially nitric oxide and the endothelins. The section on inflammation in Chapter 33 has been expanded to include wound healing and the role of integrins and other cell adhesion molecules in this process. The sixteenth edition also includes new information on many other topics, including immediate early genes and transcription factors, sex determination, olfactory discrimination, new multiple receptors for angiotensin II and the atrial natiuretic polypeptides, reperfusion-induced injury, autoimmune disease, and tubuloglomerular feedback and glomerulotubular balance in the kidneys.

I am greatly indebted to may individuals who helped with the preparation of this book. Those to whom I extend special thanks for their help with the sixteenth edition include Drs David Gardner, Otto Hansen, John Karam, and Ralph Kellogg. Katherine Cure provided invaluable secretarial assistance, and as always, my wife labored long hours typing and inserting corrections. Yvonne Strong did an excellent job of copyediting. 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 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 and are currently available: Portuguese (fourth edition), German (fourth edition), Italian (sixth edition), Spanish (twelfth edition), Japanese (twelfth edition), Indonesian (second edition), Greek (second edition), French, Chinese, and Hungarian. Translations have also been published in Czech, Polish, Serbo-Croatian, and Turkish but are no longer in print. New translations into Serbo-Croatian and Polish are under way, and the book is being translated into Malay. It has also appeared in various foreign English-language editions and has been recorded in English on tape for use by the blind. The tape recording is available from Recording for the Blind, Inc., 20 Roszel Road, Princeton, NJ 08540, USA. Finally, for computer users, the book is now available, along with several other Lange Medical Books, in STAT!-Ref, a searchable CD-ROM format, from Teton Data Systems.

San Francisco
March, 1993

William F. Ganong

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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 reviews fundamental aspects of cell physiology. Additional aspects of cellular and molecular biology are considered in the relevant chapters on the various organs.

BODY FLUID COMPARTMENTS

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 sea water, 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 2 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).**

Size of the Fluid Compartments

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 Fig 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 metabolized during the mixing period. The volume of distribution of the sucrose is

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

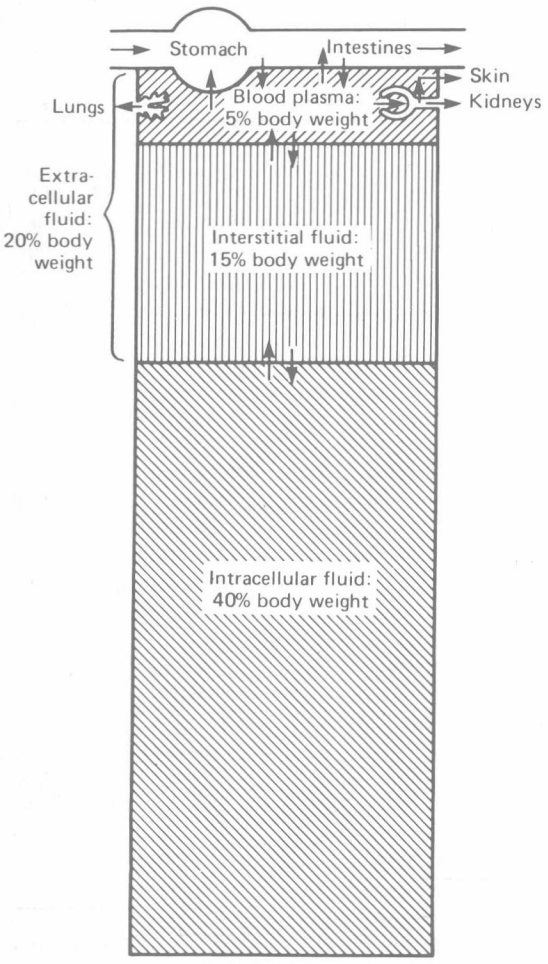

Figure 1–1. Body fluid compartments. Arrows represent fluid movement. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown. (Modified and reproduced, with permission, from Gamble JL: *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid,* 6th ed. Harvard Univ Press, 1954.)

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. Radioactive inulin has been prepared by substituting ^{14}C for one of the carbon atoms of the molecule; and when this material is used, inulin levels are easily determined by counting the samples with suitable radiation detectors. 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 total body water (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. In young men, water constitutes about 60% of body weight. The values for women are somewhat lower. 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. TBW (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).

It is worth noting that the molecular weight of a substance is the ratio of the mass of one molecule of the substance to the mass of 1/12 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 1/12 the mass of an atom of carbon-12, and 1000 Da = 1 kilodalton (kDa). The kilodalton, which is often expressed simply as K, is a useful unit for expressing the molecular mass of proteins. Thus, for example, one can speak of a 64K 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 64kDa.

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/1 = 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.

Osmoles

When one is dealing with concentrations of osmotically active particles, the amounts of these particles are usually expressed in osmoles. Osmosis is discussed in detail in a later section of this chapter. One osmole (osm) equals the molecular weight of the substance in grams divided by the number of freely moving particles each molecule liberates in solution. The milliosmole (mosm) is 1/1000 of 1 osm.

The **osmolal concentration** of a substance in a

fluid is measured by the degree to which it depresses the freezing point, 1 mol/L of ideal solute 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).

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 (Fig 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.

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: $H_2CO_3 \rightleftarrows H^+ + HCO_3^-$. 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 Chapters 35 and 39.

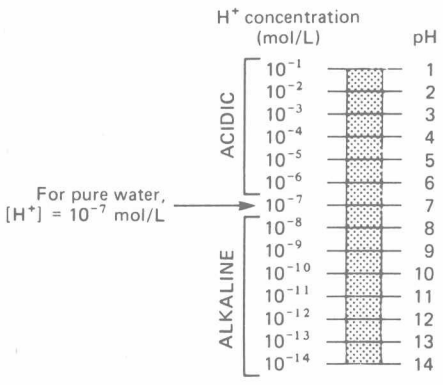

Figure 1–2. pH. (Reproduced, with permission, from Alberts B et al: *Molecular Biology of the Cell.* Garland, 1983.)

FUNCTIONAL MORPHOLOGY OF THE CELL

Revolutionary advances in the understanding of cell structure and function have been made through use of the techniques of modern cellular and molecular biology. There have also been major advances in the study of embryology and development at the cellular level. Developmental biology and the details of cell biology are beyond the scope of this book. However, a basic knowledge of cell biology is essential to an understanding of the organ systems in the body and the way they function.

The specialization of the cells in the various organs is very great, and no cell can be called "typical" of all cells in the body. However, a number of structures (**organelles**) are common to most cells. These structures are shown in Fig 1–3.

Cell Membrane

The membrane that surrounds the cell is a remarkable structure. Not only is it semipermeable, allowing some substances to pass through it and excluding others, but also its permeability can be varied. It is generally referred to as the **plasma membrane.** The nucleus is also surrounded by a membrane, and the organelles are surrounded by or made up of a membrane.

Although the chemical structure of membranes and their properties vary considerably from one location to another, they have certain common features. They are generally about 7.5 nm (75 Angstrom units) thick. They are made up primarily of protein and lipids. The chemistry of proteins and lipids is discussed in Chapter 17. The major lipids are phospholipids such as phosphatidylcholine and phosphatidylethanolamine. The shape of the phospholipid molecule is roughly that of a clothespin (Fig 1–4). The head end of the molecule contains the phosphate portion and is relatively soluble in water (polar, **hydrophilic**). The tails are relatively insoluble (nonpolar, **hydrophobic**). In the membrane, the hydrophilic ends of the molecules are exposed to the aqueous environment that bathes the exterior of the cells and the aqueous cytoplasm; the hydrophobic ends meet in the

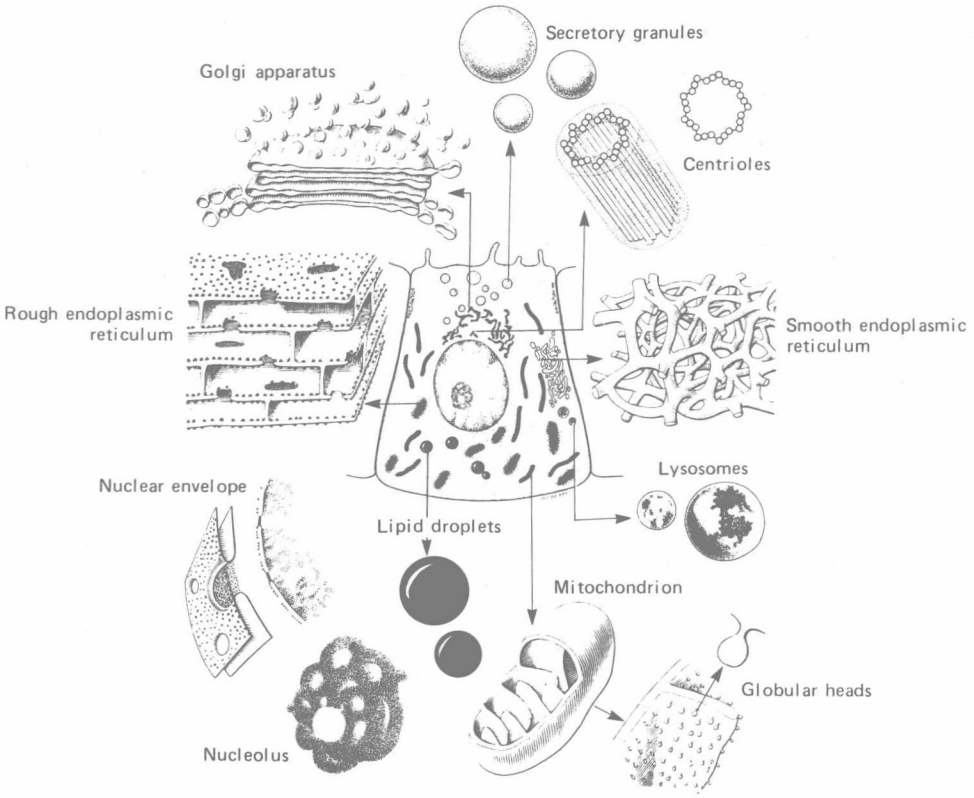

Figure 1–3. Diagram showing a hypothetical cell in the center as seen with the light microscope. It is surrounded by various organelles. (After Bloom and Fawcett. Reproduced, with permission, from Junqueira LC, Carneiro J, Kelley, RO: *Basic Histology,* 7th ed. Appleton & Lange, 1992.)

water-poor interior of the membrane. In **prokaryotes** (cells such as bacteria in which there is no nucleus), phospholipids are generally the only membrane lipids, but in **eukaryotes** (cells containing nuclei), cell membranes also contain cholesterol (in animals) or other steroids (in plants).

There are many different proteins embedded in the membrane. They exist as separate globular units and many pass through the membrane **(integral proteins),** whereas others **(peripheral proteins)** stud the inside and outside of the membrane (Fig 1–4). The amount of protein varies with the function of the membrane but makes up on average 50% of the mass of the membrane; ie, there is about one protein molecule per 50 of the much smaller phospholipid molecules. The uncharged, hydrophobic portions of the proteins are usually located in the interior of the membrane, whereas the charged, hydrophilic portions are located on the surfaces. Peripheral proteins are attached to the surfaces of the membrane in various ways. One common way is attachment to glycosylated forms of phosphatidylinositol. Proteins held by these **glycosyl-phosphatidylinositol anchors** include enzymes such as alkaline phosphatase, various antigens, and a number of cell adhesion molecules.

The proteins in the membranes carry out at least 7 functions. In addition to **structural proteins,** there are proteins that function as **pumps,** actively transporting ions across the membrane. Other proteins function as **carriers,** transporting substances down electrochemical gradients by facilitated diffusion. Still others are **ion channels,** which, when activated, permit the passage of ions into or out of the cell. The role of the pumps, carriers, and ion channels in transport across the cell membrane is discussed below. Proteins in a fifth group function as **receptors** that bind neurotransmitters and hormones, initiating physiologic changes inside the cell. Proteins in a sixth group function as **enzymes,** catalyzing reactions at the surfaces of the membrane. A seventh group is made up of glycoproteins that function in antibody processing and distinguishing self from nonself (see Chapter 27).

The protein structure—and particularly the enzyme content—of biologic membranes varies not only from cell to cell but also within the same cell. For example, there are different enzymes embedded