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GUYTON AND HALL TEXTBOOK OF MEDICAL PHYSIOLOGY

THIRTEENTH EDITION

JOHN E. HALL

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13TH EDITION

Guyton and Hall Textbook of Medical Physiology

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To

My Family

For their abundant support, for their patience and understanding, and for their love

To

Arthur C. Guyton

For his imaginative and innovative research
For his dedication to education
For showing us the excitement and joy of physiology
And for serving as an inspirational role model

Preface

The first edition of the *Textbook of Medical Physiology* was written by Arthur C. Guyton almost 60 years ago. Unlike most major medical textbooks, which often have 20 or more authors, the first eight editions of the *Textbook of Medical Physiology* were written entirely by Dr. Guyton, with each new edition arriving on schedule for nearly 40 years. Dr. Guyton had a gift for communicating complex ideas in a clear and interesting manner that made studying physiology fun. He wrote the book to help students learn physiology, not to impress his professional colleagues.

I worked closely with Dr. Guyton for almost 30 years and had the privilege of writing parts of the ninth and tenth editions. After Dr. Guyton's tragic death in an automobile accident in 2003, I assumed responsibility for completing the subsequent editions.

For the thirteenth edition of the *Textbook of Medical Physiology*, I have the same goal as for previous editions—to explain, in language easily understood by students, how the different cells, tissues, and organs of the human body work together to maintain life.

This task has been challenging and fun because our rapidly increasing knowledge of physiology continues to unravel new mysteries of body functions. Advances in molecular and cellular physiology have made it possible to explain many physiology principles in the terminology of molecular and physical sciences rather than in merely a series of separate and unexplained biological phenomena.

The *Textbook of Medical Physiology*, however, is not a reference book that attempts to provide a compendium of the most recent advances in physiology. This is a book that continues the tradition of being written for students. It focuses on the basic principles of physiology needed to begin a career in the health care professions, such as medicine, dentistry, and nursing, as well as graduate studies in the biological and health sciences. It should also be useful to physicians and health care professionals who wish to review the basic principles needed for understanding the pathophysiology of human disease.

I have attempted to maintain the same unified organization of the text that has been useful to students in the past and to ensure that the book is comprehensive enough that students will continue to use it during their professional careers.

My hope is that this textbook conveys the majesty of the human body and its many functions and that it stimulates students to study physiology throughout their careers. Physiology is the link between the basic sciences and medicine. The great beauty of physiology is that it integrates the individual functions of all the body's different cells, tissues, and organs into a functional whole, the human body. Indeed, the human body is much more than the sum of its parts, and life relies upon this total function, not just on the function of individual body parts in isolation from the others.

This brings us to an important question: How are the separate organs and systems coordinated to maintain proper function of the entire body? Fortunately, our bodies are endowed with a vast network of feedback controls that achieve the necessary balances without which we would be unable to live. Physiologists call this high level of internal bodily control *homeostasis*. In disease states, functional balances are often seriously disturbed and homeostasis is impaired. When even a single disturbance reaches a limit, the whole body can no longer live. One of the goals of this text, therefore, is to emphasize the effectiveness and beauty of the body's homeostasis mechanisms as well as to present their abnormal functions in disease.

Another objective is to be as accurate as possible. Suggestions and critiques from many students, physiologists, and clinicians throughout the world have checked factual accuracy as well as balance in the text. Even so, because of the likelihood of error in sorting through many thousands of bits of information, I wish to issue a further request to all readers to send along notations of error or inaccuracy. Physiologists understand the importance of feedback for proper function of the human body; so, too, is feedback important for progressive improvement of a textbook of physiology. To the many persons who have already helped, I express sincere thanks. Your feedback has helped to improve the text.

A brief explanation is needed about several features of the thirteenth edition. Although many of the chapters have been revised to include new principles of physiology and new figures to illustrate these principles, the text length has been closely monitored to limit the book size so that it can be used effectively in physiology courses for medical students and health care professionals. Many of the figures have also been redrawn and are in full color. New references have been chosen primarily for their presentation of physiological principles, for the quality of their own references, and for their easy accessibility. The selected bibliography at the end of the chapters lists papers mainly from recently published scientific journals that can be freely accessed from the PubMed site at http://www.ncbi.nlm.nih.gov/pubmed/. Use of these references, as well as cross-references from them, can give the student almost complete coverage of the entire field of physiology.

The effort to be as concise as possible has, unfortunately, necessitated a more simplified and dogmatic presentation of many physiological principles than I normally would have desired. However, the bibliography can be used to learn more about the controversies and unanswered questions that remain in understanding the complex functions of the human body in health and disease.

Another feature is that the print is set in two sizes. The material in large print constitutes the fundamental physiological information that students will require in virtually all of their medical activities and studies. The material in small print and highlighted with a pale blue background is of several different kinds: (1) anatomic, chemical, and other information that is needed for immediate discussion but that most students will learn in more detail in other courses; (2) physiological information of special importance to certain fields of clinical medicine; and (3) information that will be of value to those students who may wish to study particular physiological mechanisms more deeply.

I wish to express sincere thanks to many persons who have helped to prepare this book, including my colleagues in the Department of Physiology and Biophysics at the University of Mississippi Medical Center who provided valuable suggestions. The members of our faculty and a brief description of the research and educational activities of the department can be found at http://physiology.umc.edu/. I am also grateful to Stephanie Lucas for excellent secretarial services and to James Perkins for excellent illustrations. Michael Schenk and Walter (Kyle) Cunningham also contributed to many of the illustrations. I also thank Elyse O'Grady, Rebecca Gruliow, Carrie Stetz, and the entire Elsevier team for continued editorial and production excellence.

Finally, I owe an enormous debt to Arthur Guyton for the great privilege of contributing to the *Textbook of Medical Physiology* for the past 25 years, for an exciting career in physiology, for his friendship, and for the inspiration that he provided to all who knew him.

John E. Hall

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13rd Edition

By John E. Hall, PhD, Arthur C. Guyton Professor and Chair, Department of Physiology and Biophysics, Director, Mississippi Center for Obesity Research, University of Mississippi Medical Center, Jackson, Mississippi

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MISSING

CHAPTER 1

Functional Organization of the Human Body and Control of the "Internal Environment"

Physiology is the science that seeks to explain the physical and chemical mechanisms that are responsible for the origin, development, and progression of life. Each type of life, from the simplest virus to the largest tree or the complicated human being, has its own functional characteristics. Therefore, the vast field of physiology can be divided into viral physiology, bacterial physiology, cellular physiology, plant physiology, invertebrate physiology, vertebrate physiology, mammalian physiology, human physiology, and many more subdivisions.

Human Physiology. The science of *human physiology* attempts to explain the specific characteristics and mechanisms of the human body that make it a living being. The fact that we remain alive is the result of complex control systems. Hunger makes us seek food, and fear makes us seek refuge. Sensations of cold make us look for warmth. Other forces cause us to seek fellowship and to reproduce. The fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exist under widely varying conditions, which otherwise would make life impossible.

CELLS ARE THE LIVING UNITS OF THE BODY

The basic living unit of the body is the cell. Each organ is an aggregate of many different cells held together by intercellular supporting structures.

Each type of cell is specially adapted to perform one or a few particular functions. For instance, the red blood cells, numbering about 25 trillion in each human being, transport oxygen from the lungs to the tissues. Although the red blood cells are the most abundant of any single type of cell in the body, about 75 trillion additional cells of other types perform functions different from those of the red blood cell. The entire body, then, contains about 100 trillion cells.

Although the many cells of the body often differ markedly from one another, all of them have certain basic characteristics that are alike. For instance, oxygen reacts with carbohydrate, fat, and protein to release the energy required for all cells to function. Further, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver products of their chemical reactions into the surrounding fluids.

Almost all cells also have the ability to reproduce additional cells of their own kind. Fortunately, when cells of a particular type are destroyed, the remaining cells of this type usually generate new cells until the supply is replenished.

EXTRACELLULAR FLUID—THE "INTERNAL ENVIRONMENT"

About 60 percent of the adult human body is fluid, mainly a water solution of ions and other substances. Although most of this fluid is inside the cells and is called *intracellular fluid,* about one third is in the spaces outside the cells and is called *extracellular fluid.* This extracellular fluid is in constant motion throughout the body. It is transported rapidly in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls.

In the extracellular fluid are the ions and nutrients needed by the cells to maintain life. Thus, all cells live in essentially the same environment—the extracellular fluid. For this reason, the extracellular fluid is also called the *internal environment* of the body, or the *milieu intérieur,* a term introduced more than 150 years ago by the great 19th-century French physiologist Claude Bernard (1813–1878).

Cells are capable of living and performing their special functions as long as the proper concentrations of oxygen, glucose, different ions, amino acids, fatty substances, and other constituents are available in this internal environment.

Differences Between Extracellular and Intracellular Fluids. The extracellular fluid contains large amounts of *sodium, chloride,* and *bicarbonate ions* plus nutrients for the cells, such as *oxygen, glucose, fatty acids,* and *amino acids.* It also contains *carbon dioxide* that is being transported from the cells to the lungs to be excreted, plus other cellular waste products that are being transported to the kidneys for excretion.

The intracellular fluid differs significantly from the extracellular fluid; for example, it contains large amounts of *potassium, magnesium,* and *phosphate ions* instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids. These transport processes are discussed in Chapter 4.

HOMEOSTASIS—MAINTENANCE OF A NEARLY CONSTANT INTERNAL ENVIRONMENT

In 1929 the American physiologist Walter Cannon (1871–1945) coined the term *homeostasis* to describe the *maintenance of nearly constant conditions in the internal environment*. Essentially all organs and tissues of the body perform functions that help maintain these relatively constant conditions. For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain constant ion concentrations, and the gastrointestinal system provides nutrients.

The various ions, nutrients, waste products, and other constituents of the body are normally regulated within a range of values, rather than at fixed values. For some of the body's constituents, this range is extremely small. Variations in blood hydrogen ion concentration, for example, are normally less than 5 *nanomoles* per liter (0.000000005 moles per liter). Blood sodium concentration is also tightly regulated, normally varying only a few *millimoles* per liter even with large changes in sodium intake, but these variations of sodium concentration are at least 1 million times greater than for hydrogen ions.

Powerful control systems exist for maintaining the concentrations of sodium and hydrogen ions, as well as for most of the other ions, nutrients, and substances in the body at levels that permit the cells, tissues, and organs to perform their normal functions despite wide environmental variations and challenges from injury and diseases.

A large segment of this text is concerned with how each organ or tissue contributes to homeostasis. Normal body functions require the integrated actions of cells, tissues, organs, and the multiple nervous, hormonal, and local control systems that together contribute to homeostasis and good health.

Disease is often considered to be a state of disrupted homeostasis. However, even in the presence of disease, homeostatic mechanisms continue to operate and maintain vital functions through multiple compensations. In some cases, these compensations may themselves lead to major deviations of the body's functions from the normal range, making it difficult to distinguish the primary cause of the disease from the compensatory responses. For example, diseases that impair the kidneys' ability to excrete salt and water may lead to high blood pressure, which initially helps return excretion to normal so that a balance between intake and renal excretion can be maintained. This balance is needed to maintain life, but over long periods of time the high blood pressure can damage various organs, including the kidneys, causing even greater increases in blood pressure and more renal damage. Thus, homeostatic compensations that ensue after injury, disease, or major environmental challenges to the body may represent a "trade-off" that is necessary to maintain vital body functions but may, in the long term, contribute to additional abnormalities of body function. The discipline of *pathophysiology* seeks to explain how the various physiological processes are altered in diseases or injury.

This chapter outlines the different functional systems of the body and their contributions to homeostasis; we then briefly discuss the basic theory of the body's control systems that allow the functional systems to operate in support of one another.

EXTRACELLULAR FLUID TRANSPORT AND MIXING SYSTEM—THE BLOOD CIRCULATORY SYSTEM

Extracellular fluid is transported through the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the *intercellular spaces* between the tissue cells.

Figure 1-1 shows the overall circulation of blood. All the blood in the circulation traverses the entire circulatory circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

As blood passes through the blood capillaries, continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. This process is shown in **Figure 1-2**. The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of plasma proteins, which are too large to readily pass through the capillaries. Therefore, large amounts of fluid and its dissolved constituents *diffuse* back and forth between the blood and the tissue spaces, as shown by the arrows. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions within the plasma and the fluid in the intercellular spaces, as well as through the capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body—both that of the

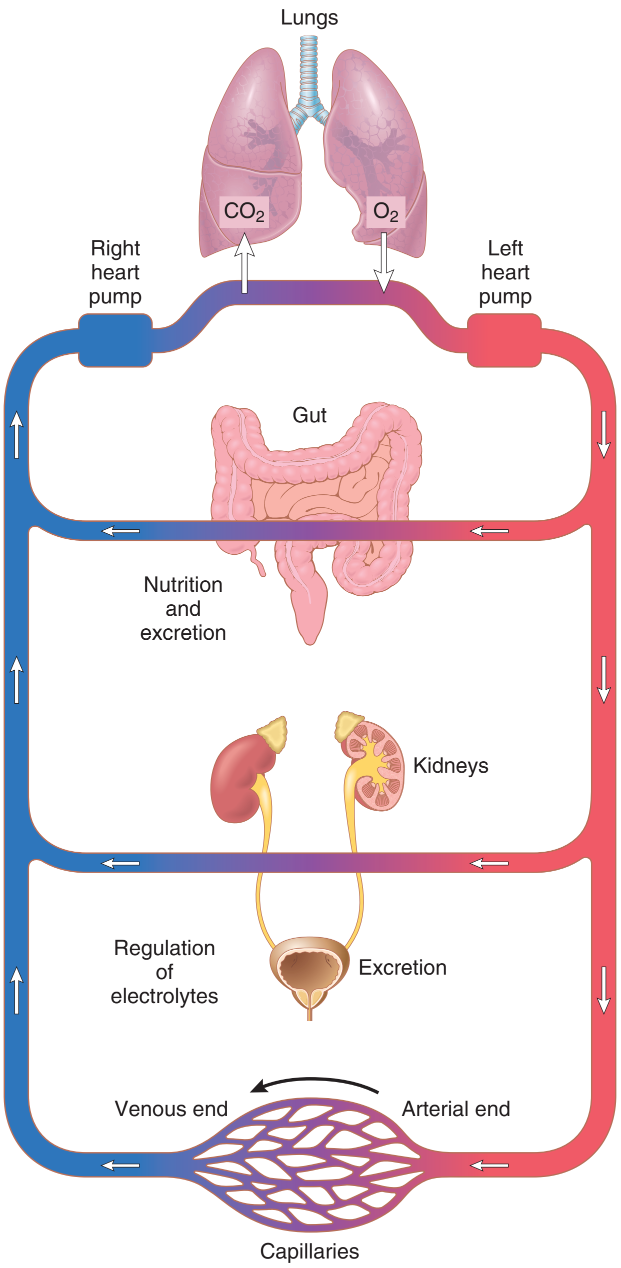

Figure 1-1. General organization of the circulatory system.

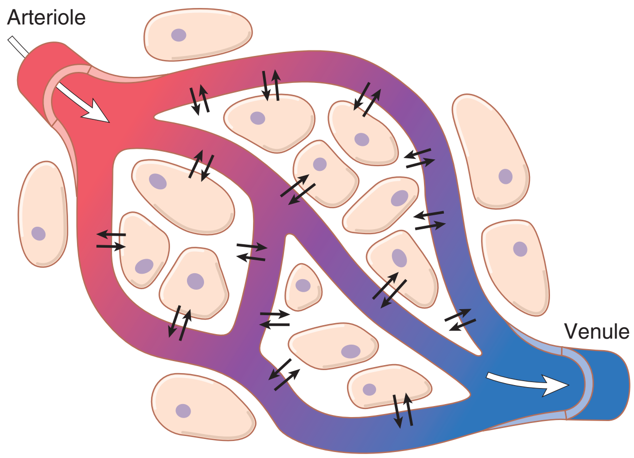

Figure 1-2. Diffusion of fluid and dissolved constituents through the capillary walls and through the interstitial spaces.

plasma and that of the interstitial fluid—is continually being mixed, thereby maintaining homogeneity of the extracellular fluid throughout the body.

ORIGIN OF NUTRIENTS IN THE EXTRACELLULAR FLUID

Respiratory System. Figure 1-1 shows that each time the blood passes through the body, it also flows through the lungs. The blood picks up *oxygen* in the alveoli, thus acquiring the oxygen needed by the cells. The membrane between the alveoli and the lumen of the pulmonary capillaries, the *alveolar membrane,* is only 0.4 to 2.0 micrometers thick, and oxygen rapidly diffuses by molecular motion through this membrane into the blood.

Gastrointestinal Tract. A large portion of the blood pumped by the heart also passes through the walls of the gastrointestinal tract. Here different dissolved nutrients, including *carbohydrates, fatty acids,* and *amino acids,* are absorbed from the ingested food into the extracellular fluid of the blood.

Liver and Other Organs That Perform Primarily Metabolic Functions. Not all substances absorbed from the gastrointestinal tract can be used in their absorbed form by the cells. The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body—fat cells, gastrointestinal mucosa, kidneys, and endocrine glands—help modify the absorbed substances or store them until they are needed. The liver also eliminates certain waste products produced in the body and toxic substances that are ingested.

Musculoskeletal System. How does the musculoskeletal system contribute to homeostasis? The answer is obvious and simple: Were it not for the muscles, the body could not move to obtain the foods required for nutrition. The musculoskeletal system also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed.

REMOVAL OF METABOLIC END PRODUCTS

Removal of Carbon Dioxide by the Lungs. At the same time that blood picks up oxygen in the lungs, *carbon dioxide* is released from the blood into the lung alveoli; the respiratory movement of air into and out of the lungs carries the carbon dioxide to the atmosphere. Carbon dioxide is the most abundant of all the metabolism products.

Kidneys. Passage of the blood through the kidneys removes from the plasma most of the other substances besides carbon dioxide that are not needed by the cells. These substances include different end products of cellular metabolism, such as urea and uric acid; they also include excesses of ions and water from the food that might have accumulated in the extracellular fluid.

The kidneys perform their function by first filtering large quantities of plasma through the glomerular capillaries into the tubules and then reabsorbing into the blood the substances needed by the body, such as glucose, amino acids, appropriate amounts of water, and many of the ions. Most of the other substances that are not needed by the body, especially metabolic waste products such as urea, are reabsorbed poorly and pass through the renal tubules into the urine.

Gastrointestinal Tract. Undigested material that enters the gastrointestinal tract and some waste products of metabolism are eliminated in the feces.

Liver. Among the functions of the liver is the detoxification or removal of many drugs and chemicals that are ingested. The liver secretes many of these wastes into the bile to be eventually eliminated in the feces.

REGULATION OF BODY FUNCTIONS

Nervous System. The nervous system is composed of three major parts: the *sensory input portion,* the *central nervous system* (or *integrative portion*), and the *motor output portion.* Sensory receptors detect the state of the body or the state of the surroundings. For instance, receptors in the skin alert us whenever an object touches the skin at any point. The eyes are sensory organs that give us a visual image of the surrounding area. The ears are also sensory organs. The central nervous system is composed of the brain and spinal cord. The brain can store information, generate thoughts, create ambition, and determine reactions that the body performs in response to the sensations. Appropriate signals are then transmitted through the motor output portion of the nervous system to carry out one's desires.

An important segment of the nervous system is called the *autonomic system.* It operates at a subconscious level and controls many functions of the internal organs, including the level of pumping activity by the heart, movements of the gastrointestinal tract, and secretion by many of the body's glands.

Hormone Systems. Located in the body are eight major *endocrine glands* and several organs and tissues that secrete chemical substances called *hormones.* Hormones are transported in the extracellular fluid to other parts of the body to help regulate cellular function. For instance, *thyroid hormone* increases the rates of most chemical reactions in all cells, thus helping to set the tempo of bodily activity. *Insulin* controls glucose metabolism; *adrenocortical hormones* control sodium and potassium ions and protein metabolism; and *parathyroid hormone* controls bone calcium and phosphate. Thus the hormones provide a system for regulation that complements the nervous system. The nervous system regulates many muscular and secretory activities of the body, whereas the hormonal system regulates many metabolic functions. The nervous and hormonal systems normally work together in a coordinated manner to control essentially all of the organ systems of the body.

PROTECTION OF THE BODY

Immune System. The immune system consists of the white blood cells, tissue cells derived from white blood cells, the thymus, lymph nodes, and lymph vessels that protect the body from pathogens such as bacteria, viruses, parasites, and fungi. The immune system provides a mechanism for the body to (1) distinguish its own cells from foreign cells and substances and (2) destroy the invader by *phagocytosis* or by producing *sensitized lymphocytes* or specialized proteins (e.g., *antibodies*) that either destroy or neutralize the invader.

Integumentary System. The skin and its various appendages (including the hair, nails, glands, and other structures) cover, cushion, and protect the deeper tissues and organs of the body and generally provide a boundary between the body's internal environment and the outside world. The integumentary system is also important for temperature regulation and excretion of wastes, and it provides a sensory interface between the body and the external environment. The skin generally comprises about 12 to 15 percent of body weight.

REPRODUCTION

Sometimes reproduction is not considered a homeostatic function. It does, however, help maintain homeostasis by generating new beings to take the place of those that are dying. This may sound like a permissive usage of the term *homeostasis,* but it illustrates that, in the final analysis, essentially all body structures are organized such that they help maintain the automaticity and continuity of life.

CONTROL SYSTEMS OF THE BODY

The human body has thousands of control systems. Some of the most intricate of these systems are the genetic control systems that operate in all cells to help control intracellular and extracellular functions. This subject is discussed in Chapter 3.

Many other control systems operate *within the organs* to control functions of the individual parts of the organs; others operate throughout the entire body *to control the interrelations between the organs.* For instance, the respiratory system, operating in association with the nervous system, regulates the concentration of carbon dioxide in the extracellular fluid. The liver and pancreas regulate the concentration of glucose in the extracellular fluid, and the kidneys regulate concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the extracellular fluid.

EXAMPLES OF CONTROL MECHANISMS

Regulation of Oxygen and Carbon Dioxide Concentrations in the Extracellular Fluid. Because oxygen is one of the major substances required for chemical reactions in the cells, the body has a special control mechanism to maintain an almost exact and constant oxygen concentration in the extracellular fluid. This mechanism depends principally on the chemical characteristics of *hemoglobin,* which is present in all red blood cells. Hemoglobin combines with oxygen as the blood passes through the lungs. Then, as the blood passes through the tissue capillaries, hemoglobin, because of its own strong chemical affinity for oxygen, does not release oxygen into the tissue fluid if too much oxygen is already there. However, if the oxygen concentration in the tissue fluid is too low, sufficient oxygen is released to re-establish an adequate concentration. Thus regulation of oxygen concentration in the tissues is vested principally in the chemical characteristics of hemoglobin. This regulation is called the *oxygen-buffering function of hemoglobin.*

Carbon dioxide concentration in the extracellular fluid is regulated in a much different way. Carbon dioxide is a major end product of the oxidative reactions in cells. If all the carbon dioxide formed in the cells continued to accumulate in the tissue fluids, all energy-giving reactions of the cells would cease. Fortunately, a higher than normal carbon dioxide concentration in the blood *excites the respiratory center,* causing a person to breathe rapidly and deeply. This deep, rapid breathing increases expiration of carbon dioxide and, therefore, removes excess carbon dioxide from the blood and tissue fluids. This process continues until the concentration returns to normal.

Regulation of Arterial Blood Pressure. Several systems contribute to the regulation of arterial blood pressure. One of these, the *baroreceptor system,* is a simple and excellent example of a rapidly acting control mechanism (**Figure 1-3**). In the walls of the bifurcation region of the carotid arteries in the neck, and also in the arch of the aorta in the thorax, are many nerve receptors called *baroreceptors* that are stimulated by stretch of the arterial wall. When the arterial pressure rises too high, the baroreceptors send barrages of nerve impulses to the medulla of the brain. Here these impulses inhibit the *vasomotor center,* which in turn decreases the number of impulses transmitted from the vasomotor center through the sympathetic nervous system to the heart and blood vessels. Lack of these impulses causes diminished pumping activity by the heart and also dilation of the peripheral blood vessels, allowing increased blood flow through the vessels. Both

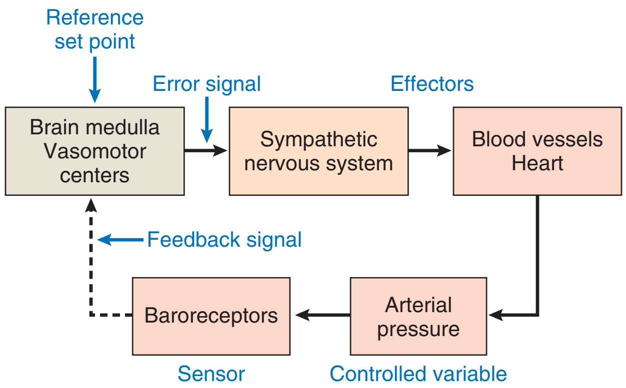

Figure 1-3. Negative feedback control of arterial pressure by the arterial baroreceptors. Signals from the sensor (baroreceptors) are sent to medulla of the brain, where they are compared with a reference set point. When arterial pressure increases above normal, this abnormal pressure increases nerve impulses from the baroreceptors to the medulla of the brain, where the input signals are compared with the set point, generating an error signal that leads to decreased sympathetic nervous system activity. Decreased sympathetic activity causes dilation of blood vessels and reduced pumping activity of the heart, which return arterial pressure toward normal.

of these effects decrease the arterial pressure, moving it back toward normal.

Conversely, a decrease in arterial pressure below normal relaxes the stretch receptors, allowing the vasomotor center to become more active than usual, thereby causing vasoconstriction and increased heart pumping. The decrease in arterial pressure also raises arterial pressure, moving it back toward normal.

Normal Ranges and Physical Characteristics of Important Extracellular Fluid Constituents

Table 1-1 lists some of the important constituents and physical characteristics of extracellular fluid, along with their normal values, normal ranges, and maximum limits without causing death. Note the narrowness of the normal range for each one. Values outside these ranges are often caused by illness, injury, or major environmental challenges.

Most important are the limits beyond which abnormalities can cause death. For example, an increase in the body temperature of only 11°F (7°C) above normal can lead to a vicious cycle of increasing cellular metabolism that destroys the cells. Note also the narrow range for acid-base balance in the body, with a normal pH value of 7.4 and lethal values only about 0.5 on either side of normal. Another important factor is the potassium ion concentration because whenever it decreases to less than one-third normal, a person is likely to be paralyzed as a result of the inability of the nerves to carry signals. Alternatively, if potassium ion concentration increases to two or more times normal, the heart muscle is likely to be severely depressed. Also, when calcium ion concentration falls below about one-half normal, a person is likely

Table 1-1 Important Constituents and Physical Characteristics of Extracellular Fluid

	Normal Value	Normal Range	Approximate Short-Term Nonlethal Limit	Unit
Oxygen (venous)	40	35-45	10-1000	mm Hg
Carbon dioxide (venous)	45	35-45	5-80	mm Hg
Sodium ion	142	138-146	115-175	mmol/L
Potassium ion	4.2	3.8-5.0	1.5-9.0	mmol/L
Calcium ion	1.2	1.0-1.4	0.5-2.0	mmol/L
Chloride ion	106	103-112	70-130	mmol/L
Bicarbonate ion	24	24-32	8-45	mmol/L
Glucose	90	75-95	20-1500	mg/dl
Body temperature	98.4 (37.0)	98-98.8 (37.0)	65-110 (18.3-43.3)	°F (°C)
Acid-base	7.4	7.3-7.5	6.9-8.0	pH

to experience tetanic contraction of muscles throughout the body because of the spontaneous generation of excess nerve impulses in the peripheral nerves. When glucose concentration falls below one-half normal, a person frequently exhibits extreme mental irritability and sometimes even has convulsions.

These examples should give one an appreciation for the extreme value and even the necessity of the vast numbers of control systems that keep the body operating in health; in the absence of any one of these controls, serious body malfunction or death can result.

CHARACTERISTICS OF CONTROL SYSTEMS

The aforementioned examples of homeostatic control mechanisms are only a few of the many thousands in the body, all of which have certain characteristics in common as explained in this section.

Negative Feedback Nature of Most Control Systems

Most control systems of the body act by *negative feedback,* which can best be explained by reviewing some of the homeostatic control systems mentioned previously. In the regulation of carbon dioxide concentration, a high concentration of carbon dioxide in the extracellular fluid increases pulmonary ventilation. This, in turn, decreases the extracellular fluid carbon dioxide concentration because the lungs expire greater amounts of carbon dioxide from the body. In other words, the high concentration of carbon dioxide initiates events that decrease the concentration toward normal, which is *negative* to the initiating stimulus. Conversely, a carbon dioxide concentration that falls too low results in feedback to increase the concentration. This response is also negative to the initiating stimulus.

In the arterial pressure–regulating mechanisms, a high pressure causes a series of reactions that promote a lowered pressure, or a low pressure causes a series of reactions that promote an elevated pressure. In both instances, these effects are negative with respect to the initiating stimulus.

Therefore, in general, if some factor becomes excessive or deficient, a control system initiates *negative feedback,* which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.

Gain of a Control System. The degree of effectiveness with which a control system maintains constant conditions is determined by the *gain* of the negative feedback. For instance, let us assume that a large volume of blood is transfused into a person whose baroreceptor pressure control system is not functioning, and the arterial pressure rises from the normal level of 100 mm Hg up to 175 mm Hg. Then, let us assume that the same volume of blood is injected into the same person when the baroreceptor system is functioning, and this time the pressure increases only 25 mm Hg. Thus the feedback control system has caused a "correction" of –50 mm Hg—that is, from 175 mm Hg to 125 mm Hg. There remains an increase in pressure of +25 mm Hg, called the "error," which means that the control system is not 100 percent effective in preventing change. The gain of the system is then calculated by using the following formula:

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}}$$

Thus, in the baroreceptor system example, the correction is –50 mm Hg and the error persisting is +25 mm Hg. Therefore, the gain of the person's baroreceptor system for control of arterial pressure is –50 divided by +25, or –2. That is, a disturbance that increases or decreases the arterial pressure does so only one third as much as would occur if this control system were not present.

The gains of some other physiologic control systems are much greater than that of the baroreceptor system. For instance, the gain of the system controlling internal body temperature when a person is exposed to moderately cold weather is about –33. Therefore, one can see

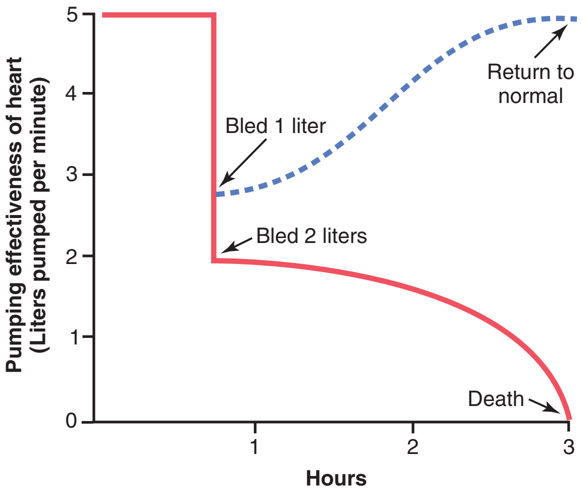

Figure 1-4. Recovery of heart pumping caused by *negative feedback* after 1 liter of blood is removed from the circulation. Death is caused by *positive feedback* when 2 liters of blood are removed.

that the temperature control system is much more effective than the baroreceptor pressure control system.

Positive Feedback Can Sometimes Cause Vicious Cycles and Death

Why do most control systems of the body operate by negative feedback rather than positive feedback? If one considers the nature of positive feedback, it is obvious that positive feedback leads to instability rather than stability and, in some cases, can cause death.

Figure 1-4 shows an example in which death can ensue from positive feedback. This figure depicts the pumping effectiveness of the heart, showing that the heart of a healthy human being pumps about 5 liters of blood per minute. If the person is suddenly bled 2 liters, the amount of blood in the body is decreased to such a low level that not enough blood is available for the heart to pump effectively. As a result, the arterial pressure falls and the flow of blood to the heart muscle through the coronary vessels diminishes. This scenario results in weakening of the heart, further diminished pumping, a further decrease in coronary blood flow, and still more weakness of the heart; the cycle repeats itself again and again until death occurs. Note that each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulus causes more of the same, which is *positive feedback.*

Positive feedback is better known as a "vicious cycle," but a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle then fails to develop. For instance, if the person in the aforementioned example is bled only 1 liter instead of 2 liters, the normal negative feedback mechanisms for controlling cardiac output and arterial pressure can counterbalance the positive feedback and the person can recover, as shown by the dashed curve of **Figure 1-4**.

Positive Feedback Can Sometimes Be Useful. In some instances, the body uses positive feedback to its advantage. Blood clotting is an example of a valuable use of positive feedback. When a blood vessel is ruptured and a clot begins to form, multiple enzymes called *clotting factors* are activated within the clot. Some of these enzymes act on other unactivated enzymes of the immediately adjacent blood, thus causing more blood clotting. This process continues until the hole in the vessel is plugged and bleeding no longer occurs. On occasion, this mechanism can get out of hand and cause formation of unwanted clots. In fact, this is what initiates most acute heart attacks, which can be caused by a clot beginning on the inside surface of an atherosclerotic plaque in a coronary artery and then growing until the artery is blocked.

Childbirth is another instance in which positive feedback is valuable. When uterine contractions become strong enough for the baby's head to begin pushing through the cervix, stretching of the cervix sends signals through the uterine muscle back to the body of the uterus, causing even more powerful contractions. Thus the uterine contractions stretch the cervix and the cervical stretch causes stronger contractions. When this process becomes powerful enough, the baby is born. If it is not powerful enough, the contractions usually die out and a few days pass before they begin again.

Another important use of positive feedback is for the generation of nerve signals. That is, stimulation of the membrane of a nerve fiber causes slight leakage of sodium ions through sodium channels in the nerve membrane to the fiber's interior. The sodium ions entering the fiber then change the membrane potential, which in turn causes more opening of channels, more change of potential, still more opening of channels, and so forth. Thus, a slight leak becomes an explosion of sodium entering the interior of the nerve fiber, which creates the nerve action potential. This action potential in turn causes electrical current to flow along both the outside and the inside of the fiber and initiates additional action potentials. This process continues again and again until the nerve signal goes all the way to the end of the fiber.

In each case in which positive feedback is useful, the positive feedback is part of an overall negative feedback process. For example, in the case of blood clotting, the positive feedback clotting process is a negative feedback process for maintenance of normal blood volume. Also, the positive feedback that causes nerve signals allows the nerves to participate in thousands of negative feedback nervous control systems.

More Complex Types of Control Systems—Adaptive Control

Later in this text, when we study the nervous system, we shall see that this system contains great numbers of interconnected control mechanisms. Some are simple feedback systems similar to those already discussed. Many are not. For instance, some movements of the body occur so rapidly that there is not enough time for nerve signals to travel from the peripheral parts of the body all the way to the brain and then back to the periphery again to control the movement. Therefore, the brain uses a principle called *feed-forward control* to cause required muscle contractions. That is, sensory nerve signals from the moving parts apprise the brain whether the movement is performed correctly. If not, the brain corrects the feed-forward signals that it sends to the muscles the *next* time the movement is required. Then, if still further correction is necessary, this process will be performed again for subsequent movements. This process is called *adaptive control.* Adaptive control, in a sense, is delayed negative feedback.

Thus, one can see how complex the feedback control systems of the body can be. A person's life depends on all of them. Therefore, a major share of this text is devoted to discussing these life-giving mechanisms.

SUMMARY—AUTOMATICITY OF THE BODY

The purpose of this chapter has been to point out, first, the overall organization of the body and, second, the means by which the different parts of the body operate in harmony. To summarize, the body is actually a *social order of about 100 trillion cells* organized into different functional structures, some of which are called *organs.* Each functional structure contributes its share to the maintenance of homeostatic conditions in the extracellular fluid, which is called the *internal environment.* As long as normal conditions are maintained in this internal environment, the cells of the body continue to live and function properly. Each cell benefits from homeostasis, and in turn, each cell contributes its share toward the maintenance of homeostasis. This reciprocal interplay provides continuous automaticity of the body until one or more functional systems lose their ability to contribute their share of function. When this happens, all the cells of the body suffer. Extreme dysfunction leads to death; moderate dysfunction leads to sickness.

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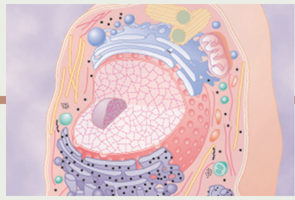

CHAPTER 2

The Cell and Its Functions

Each of the 100 trillion cells in a human being is a living structure that can survive for months or years, provided its surrounding fluids contain appropriate nutrients. Cells are the building blocks of the body, providing structure for the body's tissues and organs, ingesting nutrients and converting them to energy, and performing specialized functions. Cells also contain the body's hereditary code that controls the substances synthesized by the cells and permits them to make copies of themselves.

To understand the function of organs and other structures of the body, it is essential that we first understand the basic organization of the cell and the functions of its component parts.

ORGANIZATION OF THE CELL

A typical cell, as seen by the light microscope, is shown in **Figure 2-1**. Its two major parts are the *nucleus* and the *cytoplasm.* The nucleus is separated from the cytoplasm by a *nuclear membrane,* and the cytoplasm is separated from the surrounding fluids by a *cell membrane,* also called the *plasma membrane.*

The different substances that make up the cell are collectively called *protoplasm.* Protoplasm is composed mainly of five basic substances: water, electrolytes, proteins, lipids, and carbohydrates.

Water. The principal fluid medium of the cell is water, which is present in most cells, except for fat cells, in a concentration of 70 to 85 percent. Many cellular chemicals are dissolved in the water. Others are suspended in the water as solid particulates. Chemical reactions take place among the dissolved chemicals or at the surfaces of the suspended particles or membranes.

Ions. Important ions in the cell include *potassium, magnesium, phosphate, sulfate, bicarbonate,* and smaller quantities of *sodium, chloride,* and *calcium.* These ions are all discussed in more detail in Chapter 4, which considers the interrelations between the intracellular and extracellular fluids.

The ions provide inorganic chemicals for cellular reactions and also are necessary for operation of some of the cellular control mechanisms. For instance, ions acting at the cell membrane are required for transmission of electrochemical impulses in nerve and muscle fibers.

Proteins. After water, the most abundant substances in most cells are proteins, which normally constitute 10 to 20 percent of the cell mass. These proteins can be divided into two types: *structural proteins* and *functional proteins.*

Structural proteins are present in the cell mainly in the form of long filaments that are polymers of many individual protein molecules. A prominent use of such intracellular filaments is to form *microtubules* that provide the "cytoskeletons" of such cellular organelles as cilia, nerve axons, the mitotic spindles of cells undergoing mitosis, and a tangled mass of thin filamentous tubules that hold the parts of the cytoplasm and nucleoplasm together in their respective compartments. Fibrillar proteins are found outside the cell, especially in the collagen and elastin fibers of connective tissue and in blood vessel walls, tendons, ligaments, and so forth.

The *functional proteins* are an entirely different type of protein and are usually composed of combinations of a few molecules in tubular-globular form. These proteins are mainly the *enzymes* of the cell and, in contrast to the fibrillar proteins, are often mobile in the cell fluid. Also, many of them are adherent to membranous structures inside the cell. The enzymes come into direct contact with other substances in the cell fluid and catalyze specific intracellular chemical reactions. For instance, the chemical reactions that split glucose into its component parts and then combine these with oxygen to form carbon dioxide and water while simultaneously providing energy for cellular function are all catalyzed by a series of protein enzymes.

Lipids. Lipids are several types of substances that are grouped together because of their common property of being soluble in fat solvents. Especially important lipids are *phospholipids* and *cholesterol,* which together constitute only about 2 percent of the total cell mass. The significance of phospholipids and cholesterol is that they are mainly insoluble in water and therefore are used to form the cell membrane and intracellular membrane barriers that separate the different cell compartments.

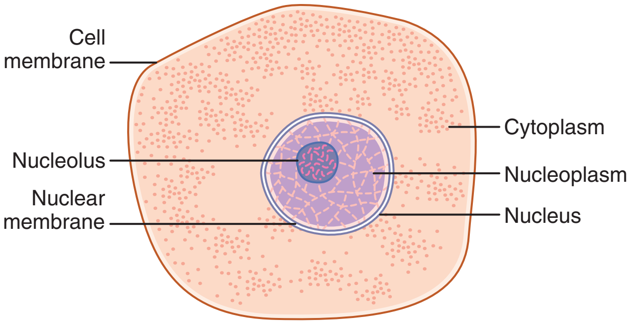

Figure 2-1. Structure of the cell as seen with the light microscope.

In addition to phospholipids and cholesterol, some cells contain large quantities of *triglycerides,* also called *neutral fat.* In the *fat cells,* triglycerides often account for as much as 95 percent of the cell mass. The fat stored in these cells represents the body's main storehouse of energy-giving nutrients that can later be used to provide energy wherever in the body it is needed.

Carbohydrates. Carbohydrates have little structural function in the cell except as parts of glycoprotein molecules, but they play a major role in nutrition of the cell. Most human cells do not maintain large stores of carbohydrates; the amount usually averages about 1 percent of their total mass but increases to as much as 3 percent in muscle cells and, occasionally, 6 percent in liver cells. However, carbohydrate in the form of dissolved glucose is always present in the surrounding extracellular fluid so that it is readily available to the cell. Also, a small amount of carbohydrate is stored in the cells in the form of *glycogen,* which is an insoluble polymer of glucose that can be depolymerized and used rapidly to supply the cells' energy needs.

PHYSICAL STRUCTURE OF THE CELL

The cell contains highly organized physical structures, called *intracellular organelles.* The physical nature of each organelle is as important as the cell's chemical constituents for cell function. For instance, without one of the organelles, the *mitochondria,* more than 95 percent of the cell's energy release from nutrients would cease immediately. The most important organelles and other structures of the cell are shown in **Figure 2-2**.

MEMBRANOUS STRUCTURES OF THE CELL

Most organelles of the cell are covered by membranes composed primarily of lipids and proteins. These membranes include the *cell membrane, nuclear membrane, membrane of the endoplasmic reticulum,* and *membranes of the mitochondria, lysosomes,* and *Golgi apparatus.*

The lipids in the membranes provide a barrier that impedes movement of water and water-soluble substances from one cell compartment to another because water is not soluble in lipids. However, protein molecules in the membrane often penetrate all the way through the membrane, thus providing specialized pathways, often organized into actual *pores,* for passage of specific substances through the membrane. Also, many other membrane proteins are *enzymes* that catalyze a multitude of different chemical reactions, discussed here and in subsequent chapters.

Cell Membrane

The cell membrane (also called the *plasma membrane*) envelops the cell and is a thin, pliable, elastic structure only 7.5 to 10 nanometers thick. It is composed almost entirely of proteins and lipids. The approximate composition is proteins, 55 percent; phospholipids, 25 percent; cholesterol, 13 percent; other lipids, 4 percent; and carbohydrates, 3 percent.

The Cell Membrane Lipid Barrier Impedes Penetration by Water-Soluble Substances. **Figure 2-3** shows the structure of the cell membrane. Its basic structure is a *lipid bilayer,* which is a thin, double-layered film of lipids—each layer only one molecule thick—that is continuous over the entire cell surface. Interspersed in this lipid film are large globular proteins.

The basic lipid bilayer is composed of three main types of lipids: *phospholipids, sphingolipids,* and *cholesterol.* Phospholipids are the most abundant of the cell membrane lipids. One end of each phospholipid molecule is soluble in water; that is, it is *hydrophilic.* The other end is soluble only in fats; that is, it is *hydrophobic.* The phosphate end of the phospholipid is hydrophilic, and the fatty acid portion is hydrophobic.

Because the hydrophobic portions of the phospholipid molecules are repelled by water but are mutually attracted to one another, they have a natural tendency to attach to one another in the middle of the membrane, as shown in **Figure 2-3**. The hydrophilic phosphate portions then constitute the two surfaces of the complete cell membrane, in contact with *intracellular* water on the inside of the membrane and *extracellular* water on the outside surface.

The lipid layer in the middle of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea. Conversely, fat-soluble substances, such as oxygen, carbon dioxide, and alcohol, can penetrate this portion of the membrane with ease.

Sphingolipids, derived from the amino alcohol *sphingosine,* also have hydrophobic and hydrophilic groups and are present in small amounts in the cell membranes, especially nerve cells. Complex sphingolipids in cell membranes are thought to serve several functions, including protection from harmful environmental factors, signal transmission, and as adhesion sites for extracellular proteins.

The cholesterol molecules in the membrane are also lipids because their steroid nuclei are highly fat soluble.

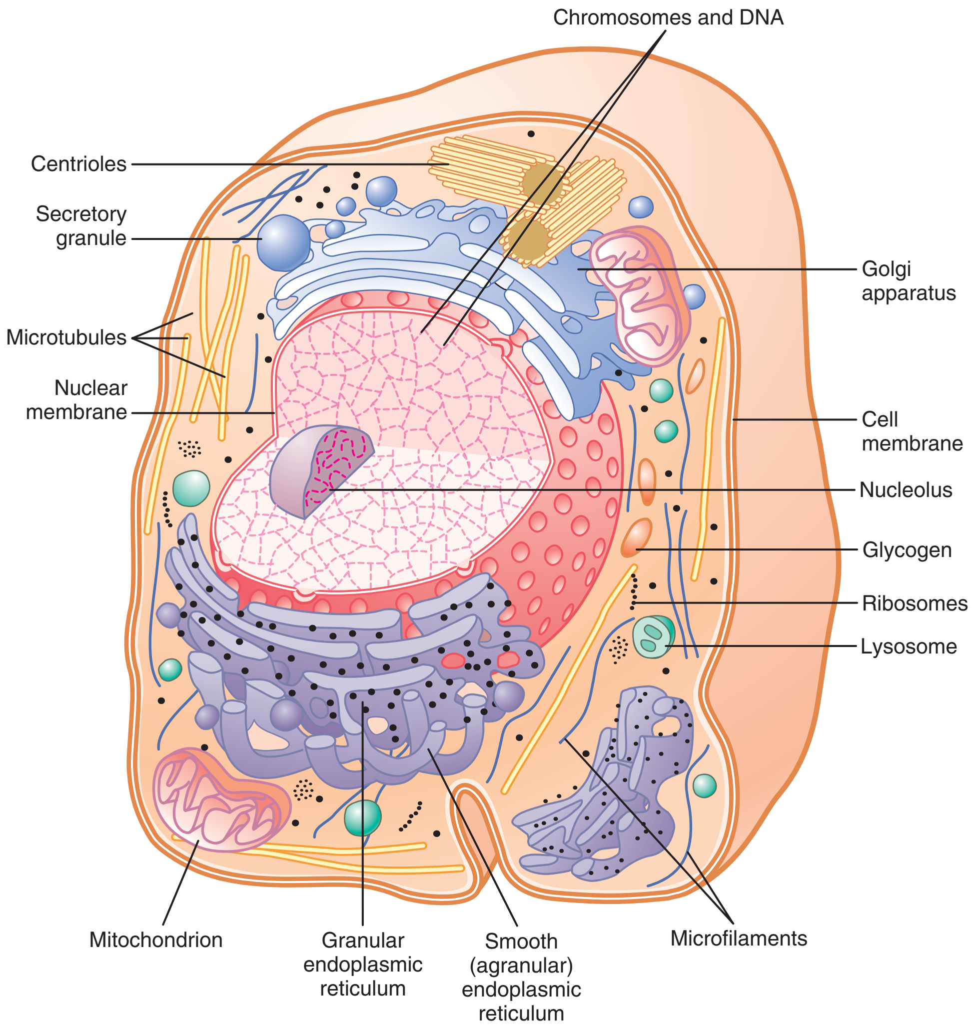

Figure 2-2. Reconstruction of a typical cell, showing the internal organelles in the cytoplasm and in the nucleus.

These molecules, in a sense, are dissolved in the bilayer of the membrane. They mainly help determine the degree of permeability (or impermeability) of the bilayer to water-soluble constituents of body fluids. Cholesterol controls much of the fluidity of the membrane as well.

Integral and Peripheral Cell Membrane Proteins. **Figure 2-3** also shows globular masses floating in the lipid bilayer. These membrane proteins are mainly *glycoproteins.* There are two types of cell membrane proteins: *integral proteins* that protrude all the way through the membrane and *peripheral proteins* that are attached only to one surface of the membrane and do not penetrate all the way through.

Many of the integral proteins provide structural *channels* (or *pores*) through which water molecules and water-soluble substances, especially ions, can diffuse between the extracellular and intracellular fluids. These protein channels also have selective properties that allow preferential diffusion of some substances over others.

Other integral proteins act as *carrier proteins* for transporting substances that otherwise could not penetrate the lipid bilayer. Sometimes these carrier proteins even transport substances in the direction opposite to their electrochemical gradients for diffusion, which is called "active transport." Still others act as *enzymes.*

Integral membrane proteins can also serve as *receptors* for water-soluble chemicals, such as peptide hormones, that do not easily penetrate the cell membrane. Interaction of cell membrane receptors with specific *ligands* that bind to the receptor causes conformational changes in the receptor protein. This process, in turn, enzymatically activates the intracellular part of the protein or induces interactions between the receptor and proteins in the cytoplasm that act as *second messengers,* relaying the signal from the extracellular part of the receptor to the interior of the cell. In this way, integral proteins spanning the cell membrane provide a means of conveying information about the environment to the cell interior.

Peripheral protein molecules are often attached to the integral proteins. These peripheral proteins function almost entirely as enzymes or as controllers of transport of substances through the cell membrane "pores."

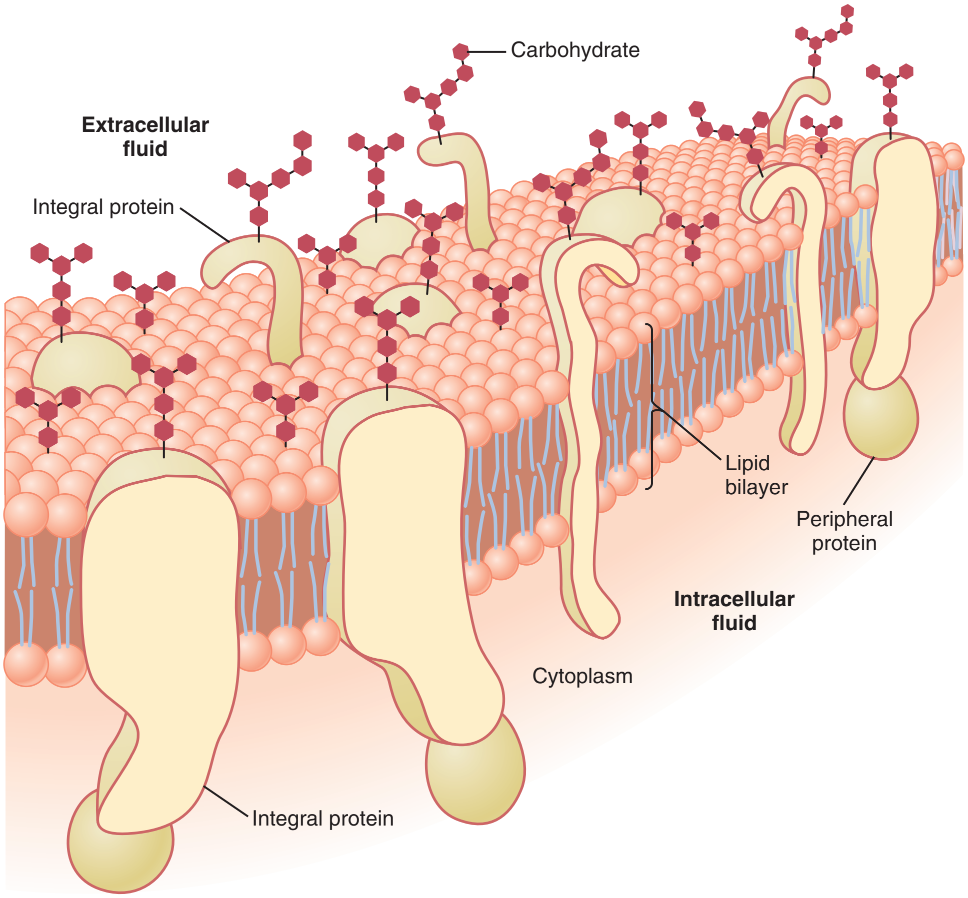

Figure 2-3. Structure of the cell membrane, showing that it is composed mainly of a lipid bilayer of phospholipid molecules, but with large numbers of protein molecules protruding through the layer. Also, carbohydrate moieties are attached to the protein molecules on the outside of the membrane and to additional protein molecules on the inside. *(Modified from Lodish HF, Rothman JE: The assembly of cell membranes. Sci Am 240:48, 1979. Copyright George V. Kevin.)*

Membrane Carbohydrates—The Cell "Glycocalyx." Membrane carbohydrates occur almost invariably in combination with proteins or lipids in the form of *glycoproteins* or *glycolipids.* In fact, most of the integral proteins are glycoproteins, and about one tenth of the membrane lipid molecules are glycolipids. The "glyco" portions of these molecules almost invariably protrude to the outside of the cell, dangling outward from the cell surface. Many other carbohydrate compounds, called *proteoglycans*—which are mainly carbohydrate substances bound to small protein cores—are loosely attached to the outer surface of the cell as well. Thus, the entire outside surface of the cell often has a loose carbohydrate coat called the *glycocalyx.*

The carbohydrate moieties attached to the outer surface of the cell have several important functions:

1. Many of them have a negative electrical charge, which gives most cells an overall negative surface charge that repels other negatively charged objects.
2. The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cells to one another.
3. Many of the carbohydrates act as *receptor substances* for binding hormones, such as insulin; when bound, this combination activates attached internal proteins that, in turn, activate a cascade of intracellular enzymes.
4. Some carbohydrate moieties enter into immune reactions, as discussed in Chapter 35.

CYTOPLASM AND ITS ORGANELLES

The cytoplasm is filled with both minute and large dispersed particles and organelles. The jelly-like fluid portion of the cytoplasm in which the particles are dispersed is called *cytosol* and contains mainly dissolved proteins, electrolytes, and glucose.

Dispersed in the cytoplasm are neutral fat globules, glycogen granules, ribosomes, secretory vesicles, and five especially important organelles: the *endoplasmic reticulum,* the *Golgi apparatus, mitochondria, lysosomes,* and *peroxisomes.*

Endoplasmic Reticulum

Figure 2-2 shows a network of tubular and flat vesicular structures in the cytoplasm, which is the *endoplasmic reticulum.* This organelle helps process molecules made by the cell and transports them to their specific