Study smart with Student Consult

GUYTON AND HALL TEXTBOOK OF MEDICAL PHYSIOLOGY

THIRTEENTH EDITION

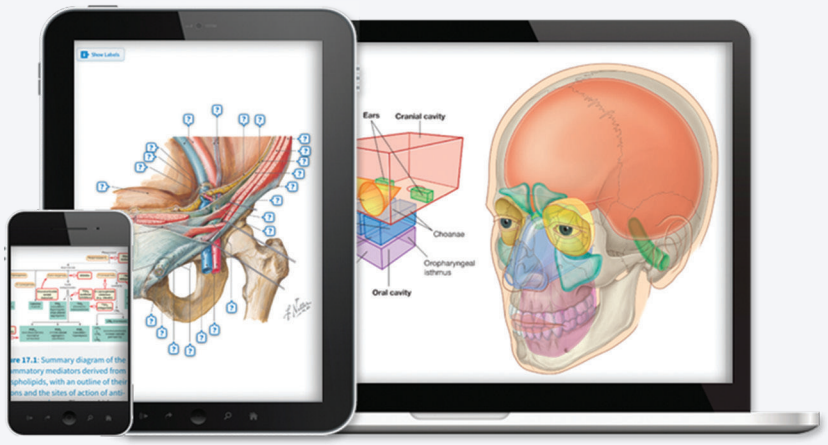
JOHN E. HALL

ELSEVIER

Student CONSULT Built with inkling | Ebooks

Any screen. Any time. Anywhere.

Activate the eBook version of this title at no additional charge.



Student Consult eBooks give you the power to browse and find content, view enhanced images, share notes and highlights—both online and offline.

Unlock your eBook today.

1. Visit **studentconsult.inkling.com/redeem**
2. Scratch off your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign Up
6. Go to "My Library"

It's that easy!

Scan this QR code to redeem your eBook through your mobile device:

FPO:
Peel Off Sticker

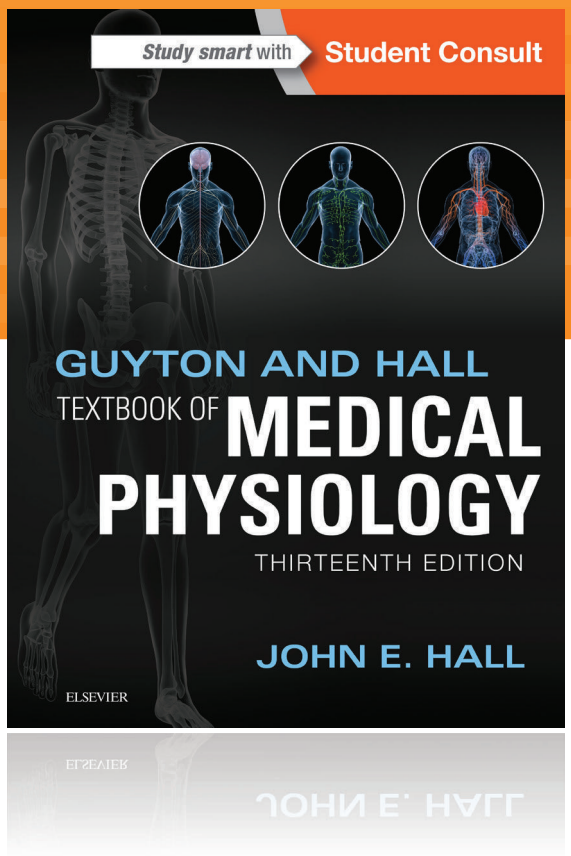
For technical assistance:
email studentconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8200 (outside the US)

ELSEVIER

ELSEVIER

GUYTON AND HALL

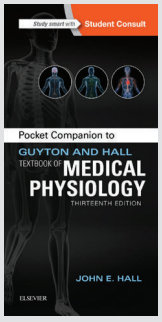
The world's foremost medical physiology resources



Guyton and Hall Textbook of Medical Physiology, 13th Edition

John E. Hall, PhD
978-1-4557-7005-2

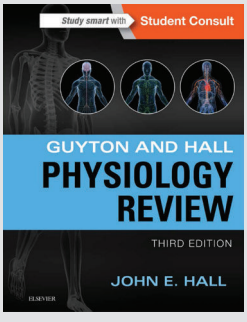
Unlike other physiology textbooks, this **clear and comprehensive guide** has a consistent, single-author voice and focuses on the content most relevant to clinical and pre-clinical students. The detailed but lucid text is complemented by **didactic illustrations** that summarize key concepts in physiology and pathophysiology.



Pocket Companion to Guyton and Hall Textbook of Medical Physiology, 13th Edition

John E. Hall, PhD
978-1-4557-7006-9

All of the essential information you need from the world's foremost medical physiology textbook – right in your pocket! Reflecting the structure and content of the larger text, it helps you **recall and easily review the most essential, need-to-know concepts in physiology.**



Guyton and Hall Physiology Review, 3rd Edition

John E. Hall, PhD
978-1-4557-7007-6

Prepare for class exams as well as the physiology portion of the USMLE Step 1. This review book features more than 1,000 **board-style questions and answers,** allowing you to test your knowledge of the most essential, need-to-know concepts in physiology!

ORDER TODAY! elsevierhealth.com

NOTE TO INSTRUCTORS:

Contact your Elsevier Sales Representative for teaching resources, including slides and image banks, for *Guyton and Hall Textbook of Medical Physiology*, 13e, or request these supporting materials at:
http://evolve.elsevier.com/Hall13

13TH EDITION

Guyton and Hall Textbook of Medical Physiology

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

ELSEVIER

ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

GUYTON AND HALL TEXTBOOK OF MEDICAL PHYSIOLOGY, THIRTEENTH EDITION ISBN: 978-1-4557-7005-2

INTERNATIONAL EDITION ISBN: 978-1-4557-7016-8

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Previous editions copyrighted 2011, 2006, 2000, 1996, 1991, 1986, 1981, 1976, 1971, 1966, 1961, 1956 by Saunders, an imprint of Elsevier, Inc.

Library of Congress Cataloging-in-Publication Data

Hall, John E. (John Edward), 1946-, author.
Guyton and Hall textbook of medical physiology / John E. Hall.—Thirteenth edition.
p. ; cm.
Textbook of medical physiology
Includes bibliographical references and index.
ISBN 978-1-4557-7005-2 (hardcover : alk. paper)
I. Title. II. Title: Textbook of medical physiology.
[DNLM: 1. Physiological Phenomena. QT 104]
QP34.5
612—dc23

2015002552

Senior Content Strategist: Elyse O'Grady
Senior Content Development Manager: Rebecca Gruliow
Publishing Services Manager: Patricia Tannian
Senior Project Manager: Carrie Stetz
Design Direction: Julia Dummitt

Printed in The United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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

This page intentionally left blank

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

Contents

UNIT VI

Blood Cells, Immunity, and Blood Coagulation

UNIT VII

Respiration

UNIT X

The Nervous System: B. The Special Senses

UNIT XI

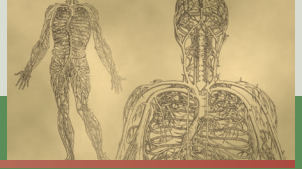
The Nervous System: C. Motor and Integrative Neurophysiology

UNIT XV
Sports Physiology

This page intentionally left blank

Guyton and Hall
Textbook of Medical Physiology

This page intentionally left blank



UNIT I

Introduction to Physiology: The Cell and General Physiology

	UNIT OUTLINE
1	Functional Organization of the Human Body and Control of the "Internal Environment"
2	The Cell and Its Functions
3	Genetic Control of Protein Synthesis, Cell Function, and Cell Reproduction

This page intentionally left blank

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

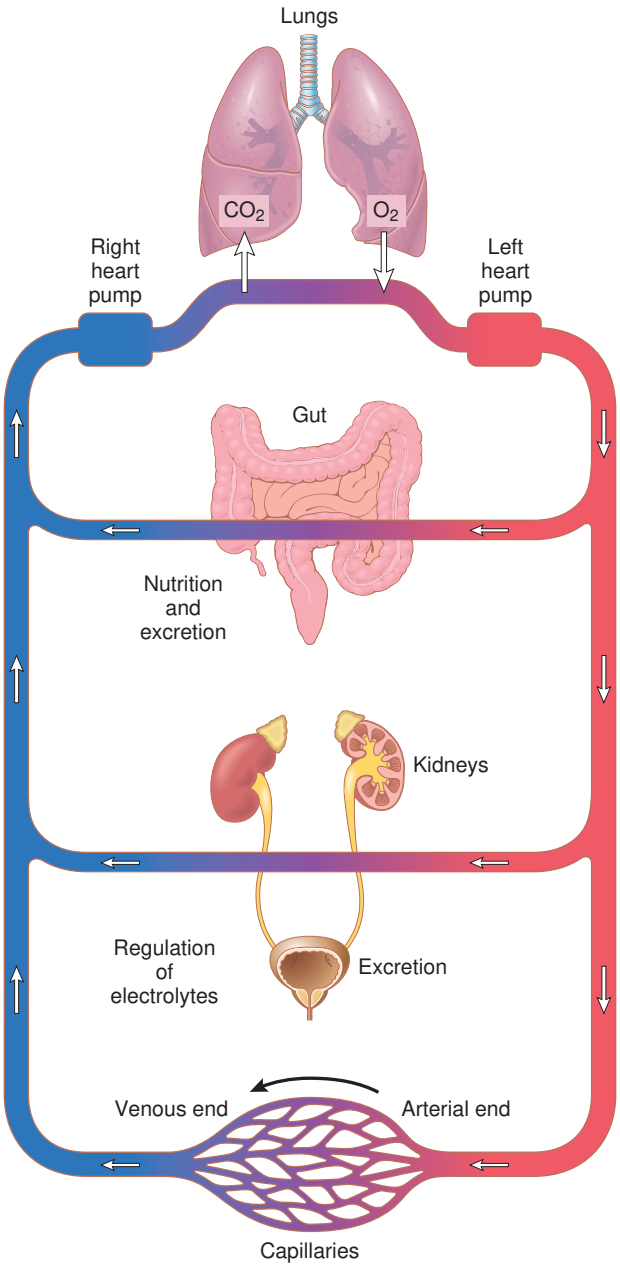


Figure 1-1. General organization of the circulatory system.

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.

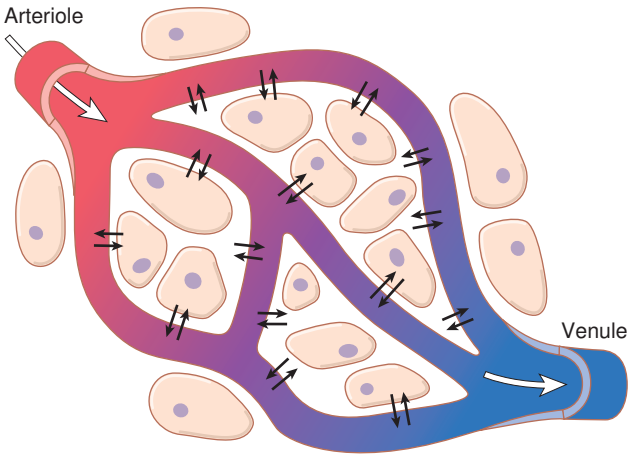


Figure 1-2. Diffusion of fluid and dissolved constituents through the capillary walls and through the interstitial spaces.

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

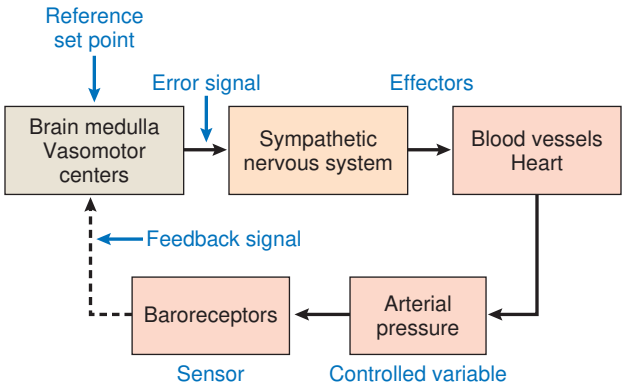


Figure 1-3. Negative feedback control of arterial pressure by the arterial baroreceptors. Signals from the sensor (baroreceptors) are sent to medulla of the brain, where they are compared with a reference set point. When arterial pressure increases above normal, this abnormal pressure increases nerve 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.

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

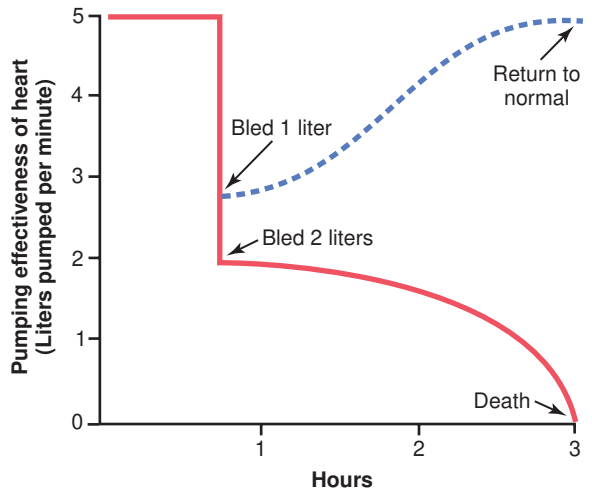


Figure 1-4. Recovery of heart pumping caused by *negative feedback* after 1 liter of blood is removed from the circulation. Death is caused by *positive feedback* when 2 liters of blood are removed.

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.

Bibliography

Adolph EF: Physiological adaptations: hypertrophies and superfunctions. Am Sci 60:608, 1972.

Bernard C: Lectures on the Phenomena of Life Common to Animals and Plants. Springfield, IL: Charles C Thomas, 1974.

Cannon WB: Organization for physiological homeostasis. Physiol Rev 9(3):399, 1929.

Chien S: Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell. Am J Physiol Heart Circ Physiol 292:H1209, 2007.

Csete ME, Doyle JC: Reverse engineering of biological complexity. Science 295:1664, 2002.

DiBona GF: Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 289:R633, 2005.

Dickinson MH, Farley CT, Full RJ, et al: How animals move: an integrative view. Science 288:100, 2000.

Eckel-Mahan K, Sassone-Corsi P: Metabolism and the circadian clock converge. Physiol Rev 93:107, 2013.

Gao Q, Horvath TL: Neuronal control of energy homeostasis. FEBS Lett 582:132, 2008.

Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.

Herman MA, Kahn BB: Glucose transport and sensing in the maintenance of glucose homeostasis and metabolic harmony. J Clin Invest 116:1767, 2006.

Krahe R, Gabbiani F: Burst firing in sensory systems. Nat Rev Neurosci 5:13, 2004.

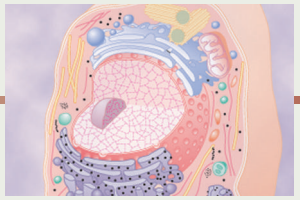
Orgel LE: The origin of life on the earth. Sci Am 271:76,1994.

Sekirov I, Russell SL, Antunes LC, Finlay BB: Gut microbiota in health and disease. Physiol Rev 90:859, 2010.

Smith HW: From Fish to Philosopher. New York: Doubleday, 1961.

Srinivasan MV: Honeybees as a model for the study of visually guided flight, navigation, and biologically inspired robotics. Physiol Rev 91:413, 2011.

Tjian R: Molecular machines that control genes. Sci Am 272:54, 1995.



CHAPTER 2

UNIT I

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.

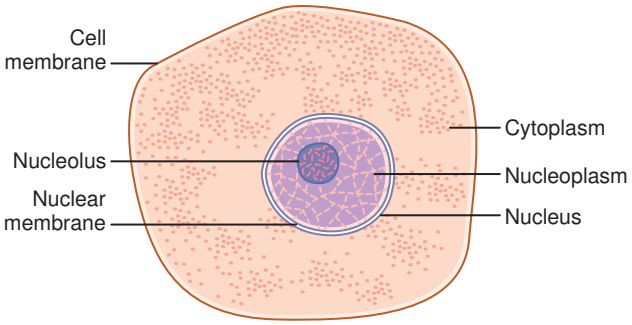


Figure 2-1. Structure of the cell as seen with the light microscope.

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.

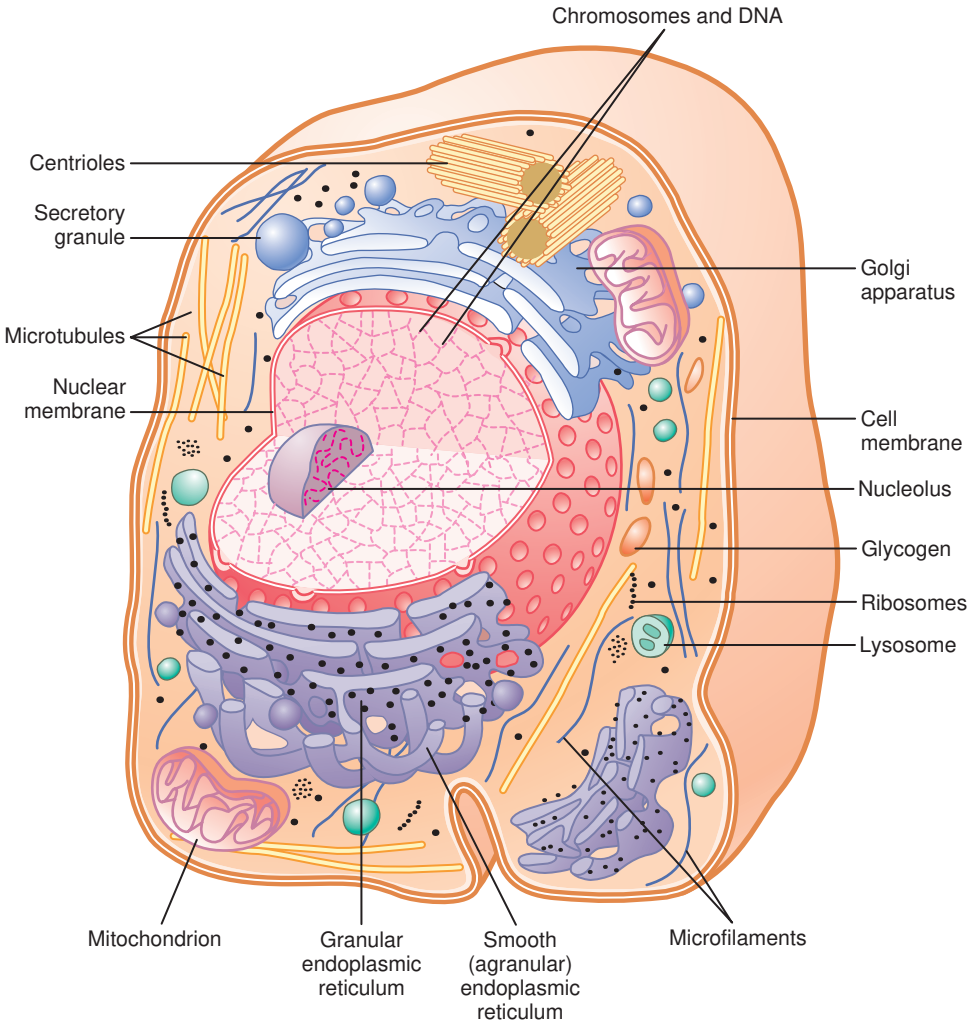


Figure 2-2. Reconstruction of a typical cell, showing the internal organelles in the cytoplasm and in the nucleus.

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."

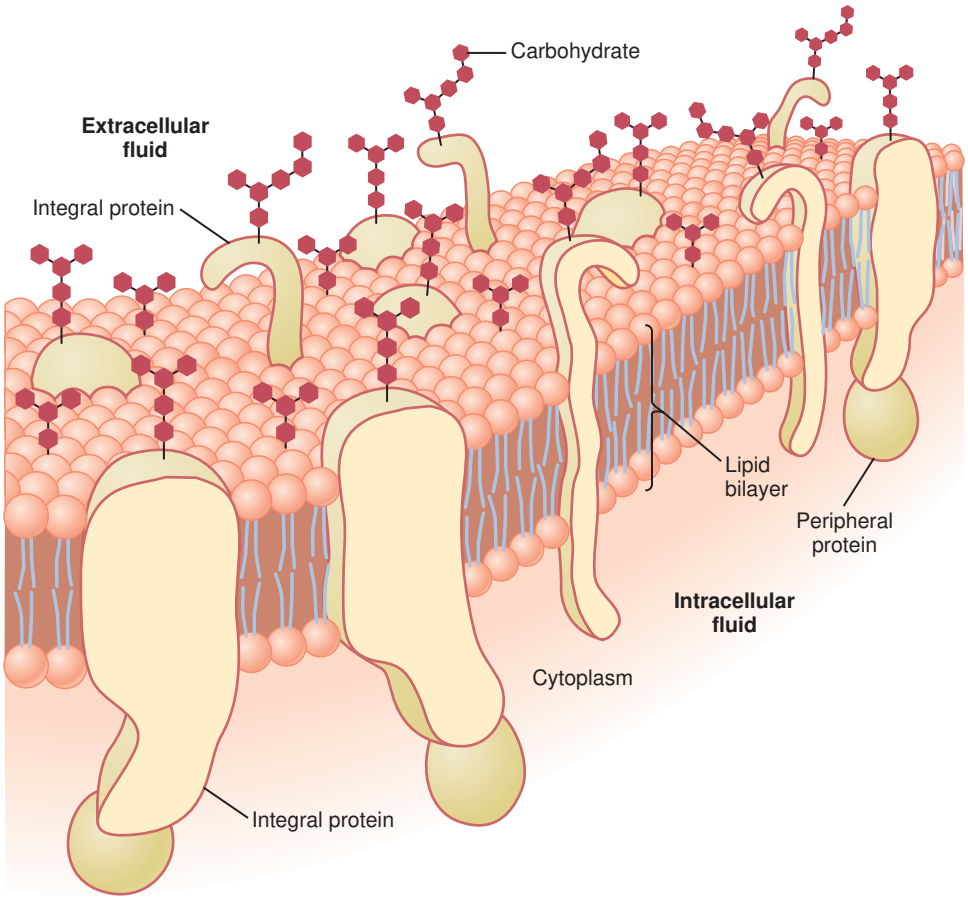


Figure 2-3. Structure of the cell membrane, showing that it is composed mainly of a lipid bilayer of phospholipid molecules, but with large numbers of protein molecules protruding through the layer. Also, carbohydrate moieties are attached to the protein molecules on the outside of the membrane and to 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

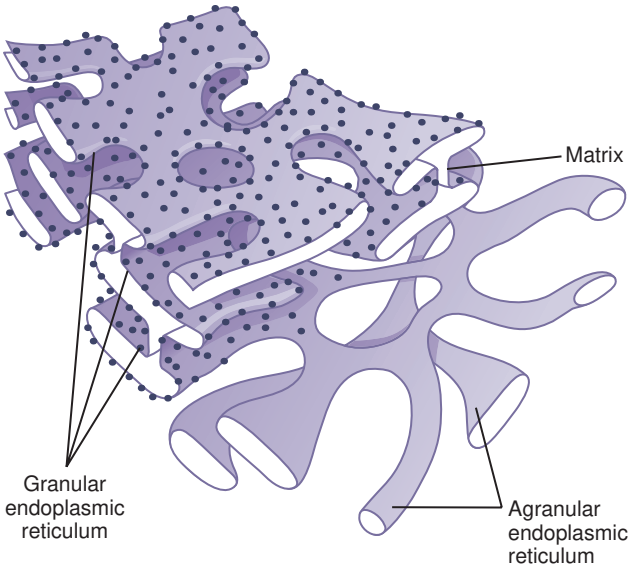


Figure 2-4. Structure of the endoplasmic reticulum. *(Modified from DeRobertis EDP, Saez FA, DeRobertis EMF: Cell Biology, 6th ed. Philadelphia: WB Saunders, 1975.)*

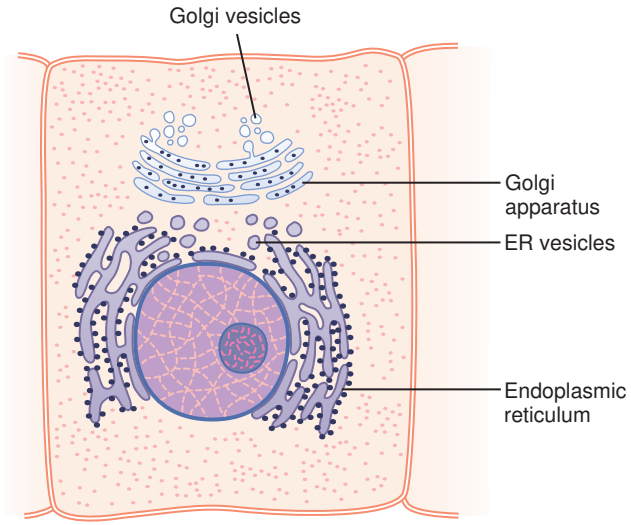


Figure 2-5. A typical Golgi apparatus and its relationship to the endoplasmic reticulum *(ER)* and the nucleus.

destinations inside or outside the cell. The tubules and vesicles interconnect. Also, their walls are constructed of lipid bilayer membranes that contain large amounts of proteins, similar to the cell membrane. The total surface area of this structure in some cells—the liver cells, for instance—can be as much as 30 to 40 times the cell membrane area.

The detailed structure of a small portion of endoplasmic reticulum is shown in **Figure 2-4**. The space inside the tubules and vesicles is filled with *endoplasmic matrix,* a watery medium that is different from the fluid in the cytosol outside the endoplasmic reticulum. Electron micrographs show that the space inside the endoplasmic reticulum is connected with the space between the two membrane surfaces of the nuclear membrane.

Substances formed in some parts of the cell enter the space of the endoplasmic reticulum and are then directed to other parts of the cell. Also, the vast surface area of this reticulum and the multiple enzyme systems attached to its membranes provide machinery for a major share of the metabolic functions of the cell.

Ribosomes and the Granular Endoplasmic Reticulum. Attached to the outer surfaces of many parts of the endoplasmic reticulum are large numbers of minute granular particles called *ribosomes.* Where these particles are present, the reticulum is called the *granular endoplasmic reticulum.* The ribosomes are composed of a mixture of RNA and proteins, and they function to synthesize new protein molecules in the cell, as discussed later in this chapter and in Chapter 3.

Agranular Endoplasmic Reticulum. Part of the endoplasmic reticulum has no attached ribosomes. This part is called the *agranular* or *smooth, endoplasmic reticulum.* The agranular reticulum functions for the synthesis of lipid substances and for other processes of the cells promoted by intrareticular enzymes.

Golgi Apparatus

The Golgi apparatus, shown in **Figure 2-5**, is closely related to the endoplasmic reticulum. It has membranes similar to those of the agranular endoplasmic reticulum. The Golgi apparatus is usually composed of four or more stacked layers of thin, flat, enclosed vesicles lying near one side of the nucleus. This apparatus is prominent in secretory cells, where it is located on the side of the cell from which the secretory substances are extruded.

The Golgi apparatus functions in association with the endoplasmic reticulum. As shown in **Figure 2-5**, small "transport vesicles" (also called endoplasmic reticulum vesicles, or *ER vesicles*) continually pinch off from the endoplasmic reticulum and shortly thereafter fuse with the Golgi apparatus. In this way, substances entrapped in the ER vesicles are transported from the endoplasmic reticulum to the Golgi apparatus. The transported substances are then processed in the Golgi apparatus to form lysosomes, secretory vesicles, and other cytoplasmic components that are discussed later in this chapter.

Lysosomes

Lysosomes, shown in **Figure 2-2**, are vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasm. The lysosomes provide an *intracellular digestive system* that allows the cell to digest (1) damaged cellular structures, (2) food particles that have been ingested by the cell, and (3) unwanted matter such as bacteria. The lysosome is quite different in various cell types, but it is usually 250 to 750 nanometers in diameter. It is surrounded by a typical lipid

bilayer membrane and is filled with large numbers of small granules 5 to 8 nanometers in diameter, which are protein aggregates of as many as 40 different *hydrolase (digestive) enzymes.* A hydrolytic enzyme is capable of splitting an organic compound into two or more parts by combining hydrogen from a water molecule with one part of the compound and combining the hydroxyl portion of the water molecule with the other part of the compound. For instance, protein is hydrolyzed to form amino acids, glycogen is hydrolyzed to form glucose, and lipids are hydrolyzed to form fatty acids and glycerol.

Hydrolytic enzymes are highly concentrated in lysosomes. Ordinarily, the membrane surrounding the lysosome prevents the enclosed hydrolytic enzymes from coming in contact with other substances in the cell and therefore prevents their digestive actions. However, some conditions of the cell break the membranes of some of the lysosomes, allowing release of the digestive enzymes. These enzymes then split the organic substances with which they come in contact into small, highly diffusible substances such as amino acids and glucose. Some of the specific functions of lysosomes are discussed later in this chapter.

Peroxisomes

Peroxisomes are similar physically to lysosomes, but they are different in two important ways. First, they are believed to be formed by self-replication (or perhaps by budding off from the smooth endoplasmic reticulum) rather than from the Golgi apparatus. Second, they contain oxidases rather than hydrolases. Several of the oxidases are capable of combining oxygen with hydrogen ions derived from different intracellular chemicals to form hydrogen peroxide (H_2O_2). Hydrogen peroxide is a highly oxidizing substance and is used in association with *catalase,* another oxidase enzyme present in large quantities in peroxisomes, to oxidize many substances that might otherwise be poisonous to the cell. For instance, about half the alcohol a person drinks is detoxified into acetaldehyde by the peroxisomes of the liver cells in this manner. A major function of peroxisomes is to catabolize long chain fatty acids.

Secretory Vesicles

One of the important functions of many cells is secretion of special chemical substances. Almost all such secretory substances are formed by the endoplasmic reticulum–Golgi apparatus system and are then released from the Golgi apparatus into the cytoplasm in the form of storage vesicles called *secretory vesicles* or *secretory granules.* **Figure 2-6** shows typical secretory vesicles inside pancreatic acinar cells; these vesicles store protein proenzymes (enzymes that are not yet activated). The proenzymes are secreted later through the outer cell membrane into the pancreatic duct and thence into the duodenum, where they become activated and perform digestive functions on the food in the intestinal tract.

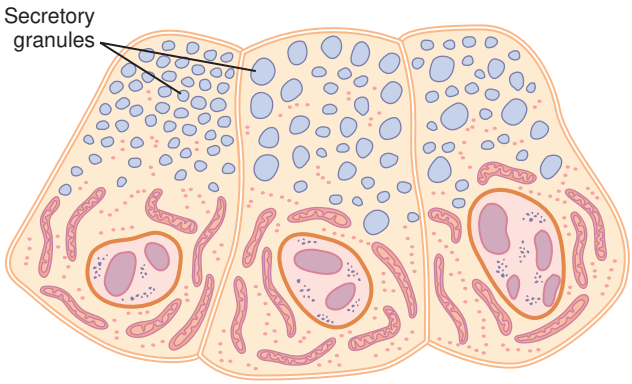


Figure 2-6. Secretory granules (secretory vesicles) in acinar cells of the pancreas.

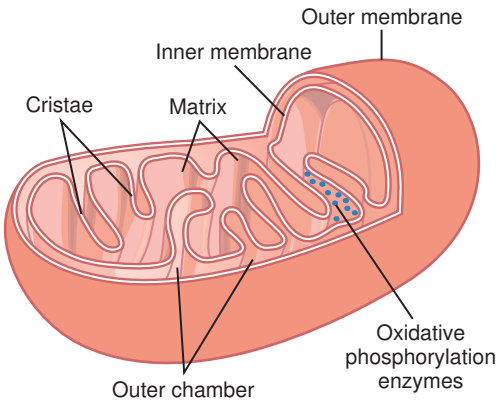


Figure 2-7. Structure of a mitochondrion. *(Modified from DeRobertis EDP, Saez FA, DeRobertis EMF: Cell Biology, 6th ed. Philadelphia: WB Saunders, 1975.)*

Mitochondria

The mitochondria, shown in **Figures 2-2** and **2-7**, are called the "powerhouses" of the cell. Without them, cells would be unable to extract enough energy from the nutrients, and essentially all cellular functions would cease.

Mitochondria are present in all areas of each cell's cytoplasm, but the total number per cell varies from less than a hundred up to several thousand, depending on the amount of energy required by the cell. The cardiac muscle cells (cardiomyocytes), for example, use large amounts of energy and have far more mitochondria than do fat cells (adipocytes), which are much less active and use less energy. Further, the mitochondria are concentrated in those portions of the cell that are responsible for the major share of its energy metabolism. They are also variable in size and shape. Some mitochondria are only a few hundred nanometers in diameter and are globular in shape, whereas others are elongated and are as large as 1 micrometer in diameter and 7 micrometers long; still others are branching and filamentous.

The basic structure of the mitochondrion, shown in **Figure 2-7**, is composed mainly of two lipid bilayer–protein membranes: an *outer membrane* and an *inner membrane.* Many infoldings of the inner membrane form

shelves or tubules called *cristae* onto which oxidative enzymes are attached. The cristae provide a large surface area for chemical reactions to occur. In addition, the inner cavity of the mitochondrion is filled with a *matrix* that contains large quantities of dissolved enzymes that are necessary for extracting energy from nutrients. These enzymes operate in association with the oxidative enzymes on the cristae to cause oxidation of the nutrients, thereby forming carbon dioxide and water and at the same time releasing energy. The liberated energy is used to synthesize a "high-energy" substance called *adenosine triphosphate* (ATP). ATP is then transported out of the mitochondrion and diffuses throughout the cell to release its own energy wherever it is needed for performing cellular functions. The chemical details of ATP formation by the mitochondrion are provided in Chapter 68, but some of the basic functions of ATP in the cell are introduced later in this chapter.

Mitochondria are self-replicative, which means that one mitochondrion can form a second one, a third one, and so on, whenever there is a need in the cell for increased amounts of ATP. Indeed, the mitochondria contain *DNA* similar to that found in the cell nucleus. In Chapter 3 we will see that DNA is the basic chemical of the nucleus that controls replication of the cell. The DNA of the mitochondrion plays a similar role, controlling replication of the mitochondrion. Cells that are faced with increased energy demands—which occurs, for example, in skeletal muscles subjected to chronic exercise training—may increase the density of mitochondria to supply the additional energy required.

Cell Cytoskeleton—Filament and Tubular Structures

The cell cytoskeleton is a network of fibrillar proteins organized into filaments or tubules. These originate as precursor protein molecules synthesized by ribosomes in the cytoplasm. The precursor molecules then polymerize to form *filaments.* As an example, large numbers of actin filaments frequently occur in the outer zone of the cytoplasm, called the *ectoplasm,* to form an elastic support for the cell membrane. Also, in muscle cells, actin and myosin filaments are organized into a special contractile machine that is the basis for muscle contraction, as is discussed in detail in Chapter 6.

A special type of stiff filament composed of polymerized *tubulin* molecules is used in all cells to construct strong tubular structures, the *microtubules.* **Figure 2-8** shows typical microtubules from the flagellum of a sperm.

Another example of microtubules is the tubular skeletal structure in the center of each cilium that radiates upward from the cell cytoplasm to the tip of the cilium. This structure is discussed later in the chapter and is illustrated in **Figure 2-18**. Also, both the *centrioles* and the *mitotic spindle* of the mitosing cell are composed of stiff microtubules.

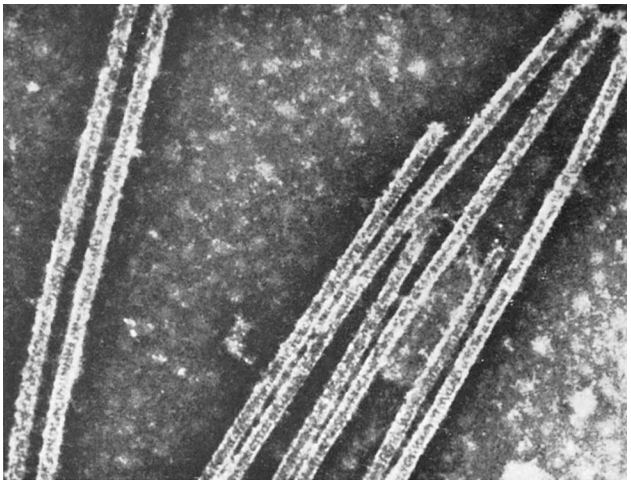


Figure 2-8. Microtubules teased from the flagellum of a sperm. *(From Wolstenholme GEW, O'Connor M, and the publisher, JA Churchill, 1967. Figure 4, page 314. Copyright the Novartis Foundation, formerly the Ciba Foundation.)*

Thus, a primary function of microtubules is to act as a *cytoskeleton,* providing rigid physical structures for certain parts of cells. The cytoskeleton of the cell not only determines cell shape but also participates in cell division, allows cells to move, and provides a track-like system that directs the movement of organelles within the cells.

Nucleus

The nucleus, which is the control center of the cell, sends messages to the cell to grow and mature, to replicate, or to die. Briefly, the nucleus contains large quantities of DNA, which comprise the *genes.* The genes determine the characteristics of the cell's proteins, including the structural proteins, as well as the intracellular enzymes that control cytoplasmic and nuclear activities.

The genes also control and promote reproduction of the cell. The genes first reproduce to create two identical sets of genes; then the cell splits by a special process called *mitosis* to form two daughter cells, each of which receives one of the two sets of DNA genes. All these activities of the nucleus are considered in detail in Chapter 3.

Unfortunately, the appearance of the nucleus under the microscope does not provide many clues to the mechanisms by which the nucleus performs its control activities. **Figure 2-9** shows the light microscopic appearance of the *interphase* nucleus (during the period between mitoses), revealing darkly staining *chromatin material* throughout the nucleoplasm. During mitosis, the chromatin material organizes in the form of highly structured *chromosomes,* which can then be easily identified using the light microscope, as illustrated in Chapter 3.

Nuclear Membrane. The *nuclear membrane,* also called the *nuclear envelope,* is actually two separate bilayer membranes, one inside the other. The outer membrane is

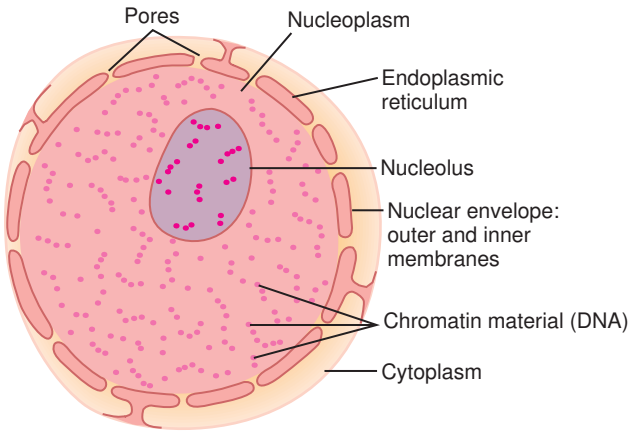


Figure 2-9. Structure of the nucleus.

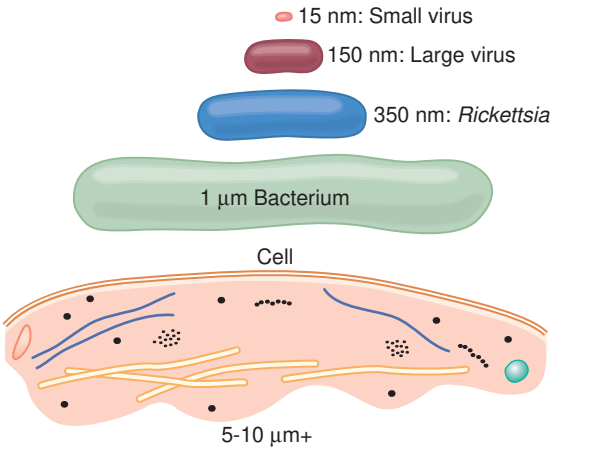


Figure 2-10. Comparison of sizes of precellular organisms with that of the average cell in the human body.

continuous with the endoplasmic reticulum of the cell cytoplasm, and the space between the two nuclear membranes is also continuous with the space inside the endoplasmic reticulum, as shown in **Figure 2-9**.

The nuclear membrane is penetrated by several thousand *nuclear pores.* Large complexes of protein molecules are attached at the edges of the pores so that the central area of each pore is only about 9 nanometers in diameter. Even this size is large enough to allow molecules up to 44,000 molecular weight to pass through with reasonable ease.

Nucleoli and Formation of Ribosomes. The nuclei of most cells contain one or more highly staining structures called *nucleoli.* The nucleolus, unlike most other organelles discussed here, does not have a limiting membrane. Instead, it is simply an accumulation of large amounts of RNA and proteins of the types found in ribosomes. The nucleolus becomes considerably enlarged when the cell is actively synthesizing proteins.

Formation of the nucleoli (and of the ribosomes in the cytoplasm outside the nucleus) begins in the nucleus. First, specific DNA genes in the chromosomes cause RNA to be synthesized. Some of this synthesized RNA is stored in the nucleoli, but most of it is transported outward through the nuclear pores into the cytoplasm. Here it is used in conjunction with specific proteins to assemble "mature" ribosomes that play an essential role in forming cytoplasmic proteins, as discussed more fully in Chapter 3.

COMPARISON OF THE ANIMAL CELL WITH PRECELLULAR FORMS OF LIFE

The cell is a complicated organism that required many hundreds of millions of years to develop after the earliest form of life, an organism similar to the present-day *virus,* first appeared on earth. **Figure 2-10** shows the relative sizes of (1) the smallest known virus, (2) a large virus, (3) a *Rickettsia,* (4) a *bacterium,* and (5) a *nucleated cell,* demonstrating that the cell has a diameter about 1000 times that of the smallest virus and therefore a volume about 1 billion times that of the smallest virus. Correspondingly, the functions and anatomical organization of the cell are also far more complex than those of the virus.

The essential life-giving constituent of the small virus is a *nucleic acid* embedded in a coat of protein. This nucleic acid is composed of the same basic nucleic acid constituents (DNA or RNA) found in mammalian cells, and it is capable of reproducing itself under appropriate conditions. Thus, the virus propagates its lineage from generation to generation and is therefore a living structure in the same way that the cell and the human being are living structures.

As life evolved, other chemicals besides nucleic acid and simple proteins became integral parts of the organism, and specialized functions began to develop in different parts of the virus. A membrane formed around the virus, and inside the membrane, a fluid matrix appeared. Specialized chemicals then developed inside the fluid to perform special functions; many protein enzymes appeared that were capable of catalyzing chemical reactions, thus determining the organism's activities.

In still later stages of life, particularly in the rickettsial and bacterial stages, *organelles* developed inside the organism, representing physical structures of chemical aggregates that perform functions in a more efficient manner than can be achieved by dispersed chemicals throughout the fluid matrix.

Finally, in the nucleated cell, still more complex organelles developed, the most important of which is the *nucleus.* The nucleus distinguishes this type of cell from all lower forms of life; the nucleus provides a control center for all cellular activities, and it provides for reproduction of new cells generation after generation, with each new cell having almost exactly the same structure as its progenitor.

FUNCTIONAL SYSTEMS OF THE CELL

In the remainder of this chapter, we discuss several representative functional systems of the cell that make it a living organism.

INGESTION BY THE CELL—ENDOCYTOSIS

If a cell is to live and grow and reproduce, it must obtain nutrients and other substances from the surrounding fluids. Most substances pass through the cell membrane by *diffusion* and *active transport.*

Diffusion involves simple movement through the membrane caused by the random motion of the molecules of the substance; substances move either through cell membrane pores or, in the case of lipid-soluble substances, through the lipid matrix of the membrane.

Active transport involves the actual carrying of a substance through the membrane by a physical protein structure that penetrates all the way through the membrane. These active transport mechanisms are so important to cell function that they are presented in detail in Chapter 4.

Very large particles enter the cell by a specialized function of the cell membrane called *endocytosis.* The principal forms of endocytosis are *pinocytosis* and *phagocytosis.* Pinocytosis means ingestion of minute particles that form vesicles of extracellular fluid and particulate constituents inside the cell cytoplasm. Phagocytosis means ingestion of large particles, such as bacteria, whole cells, or portions of degenerating tissue.

Pinocytosis. Pinocytosis occurs continually in the cell membranes of most cells, but it is especially rapid in some cells. For instance, it occurs so rapidly in macrophages that about 3 percent of the total macrophage membrane is engulfed in the form of vesicles each minute. Even so, the pinocytotic vesicles are so small—usually only 100 to 200 nanometers in diameter—that most of them can be seen only with an electron microscope.

Pinocytosis is the only means by which most large macromolecules, such as most protein molecules, can enter cells. In fact, the rate at which pinocytotic vesicles form is usually enhanced when such macromolecules attach to the cell membrane.

Figure 2-11 demonstrates the successive steps of pinocytosis, showing three molecules of protein attaching to the membrane. These molecules usually attach to specialized protein *receptors* on the surface of the membrane that are specific for the type of protein that is to be absorbed. The receptors generally are concentrated in small pits on the outer surface of the cell membrane, called *coated pits.* On the inside of the cell membrane beneath these pits is a latticework of fibrillar protein called *clathrin,* as well as other proteins, perhaps including contractile filaments of *actin* and *myosin.* Once the protein molecules have bound with the receptors, the

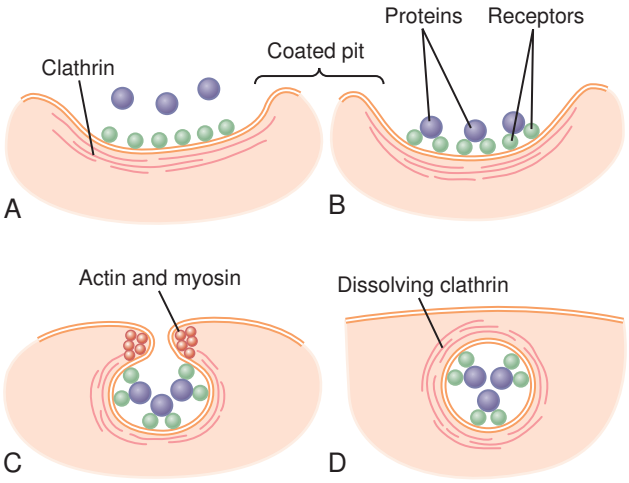


Figure 2-11. Mechanism of pinocytosis.

surface properties of the local membrane change in such a way that the entire pit invaginates inward and the fibrillar proteins surrounding the invaginating pit cause its borders to close over the attached proteins, as well as over a small amount of extracellular fluid. Immediately thereafter, the invaginated portion of the membrane breaks away from the surface of the cell, forming a *pinocytotic vesicle* inside the cytoplasm of the cell.

What causes the cell membrane to go through the necessary contortions to form pinocytotic vesicles is still unclear. This process requires energy from within the cell, which is supplied by ATP, a high-energy substance discussed later in this chapter. This process also requires the presence of calcium ions in the extracellular fluid, which probably react with contractile protein filaments beneath the coated pits to provide the force for pinching the vesicles away from the cell membrane.

Phagocytosis. Phagocytosis occurs in much the same way as pinocytosis occurs, except that it involves large particles rather than molecules. Only certain cells have the capability of phagocytosis, most notably the tissue macrophages and some white blood cells.

Phagocytosis is initiated when a particle such as a bacterium, a dead cell, or tissue debris binds with receptors on the surface of the phagocyte. In the case of bacteria, each bacterium is usually already attached to a specific antibody, and it is the antibody that attaches to the phagocyte receptors, dragging the bacterium along with it. This intermediation of antibodies is called *opsonization,* which is discussed in Chapters 34 and 35.

Phagocytosis occurs in the following steps:

1. The cell membrane receptors attach to the surface ligands of the particle.
2. The edges of the membrane around the points of attachment evaginate outward within a fraction of a second to surround the entire particle; then, progressively more and more membrane receptors attach to the particle ligands. All this occurs

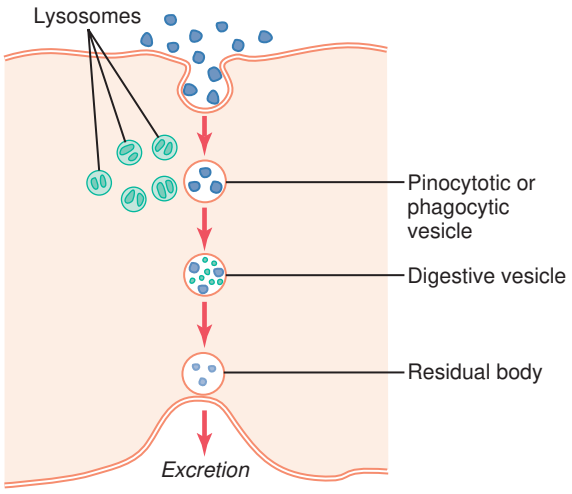


Figure 2-12. Digestion of substances in pinocytotic or phagocytic vesicles by enzymes derived from lysosomes.

suddenly in a zipper-like manner to form a closed *phagocytic vesicle.*

3. Actin and other contractile fibrils in the cytoplasm surround the phagocytic vesicle and contract around its outer edge, pushing the vesicle to the interior.
4. The contractile proteins then pinch the stem of the vesicle so completely that the vesicle separates from the cell membrane, leaving the vesicle in the cell interior in the same way that pinocytotic vesicles are formed.

PINOCYTOTIC AND PHAGOCYTIC FOREIGN SUBSTANCES ARE DIGESTED INSIDE THE CELL BY LYSOSOMES

Almost immediately after a pinocytotic or phagocytic vesicle appears inside a cell, one or more *lysosomes* become attached to the vesicle and empty their *acid hydrolases* to the inside of the vesicle, as shown in **Figure 2-12**. Thus, a *digestive vesicle* is formed inside the cell cytoplasm in which the vesicular hydrolases begin hydrolyzing the proteins, carbohydrates, lipids, and other substances in the vesicle. The products of digestion are small molecules of amino acids, glucose, phosphates, and so forth that can diffuse through the membrane of the vesicle into the cytoplasm. What is left of the digestive vesicle, called the *residual body,* represents indigestible substances. In most instances, the residual body is finally excreted through the cell membrane by a process called *exocytosis,* which is essentially the opposite of endocytosis.

Thus, the pinocytotic and phagocytic vesicles containing lysosomes can be called the *digestive organs* of the cells.

Regression of Tissues and Autolysis of Damaged Cells. Tissues of the body often regress to a smaller size. For instance, this regression occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regression.

Another special role of the lysosomes is removal of damaged cells or damaged portions of cells from tissues. Damage to the cell—caused by heat, cold, trauma, chemicals, or any other factor—induces lysosomes to rupture. The released hydrolases immediately begin to digest the surrounding organic substances. If the damage is slight, only a portion of the cell is removed and the cell is then repaired. If the damage is severe, the entire cell is digested, a process called *autolysis.* In this way, the cell is completely removed and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one.

The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include (1) *lysozyme,* which dissolves the bacterial cell membrane; (2) *lysoferrin,* which binds iron and other substances before they can promote bacterial growth; and (3) acid at a pH of about 5.0, which activates the hydrolases and inactivates bacterial metabolic systems.

Recycling of Cell Organelles—Autophagy. Lysosomes play a key role in the process of *autophagy,* which literally means "to eat oneself." Autophagy is a housekeeping process by which obsolete organelles and large protein aggregates are degraded and recycled (**Figure 2-13**). Worn-out cell organelles are transferred to lysosomes by double membrane structures called *autophagosomes* that are formed in the cytosol. Invagination of the lysosomal membrane and the formation of vesicles provides another pathway for cytosolic structures to be transported into the lumen of the lysosomes. Once inside the lysosomes, the organelles are digested and the nutrients are reused by the cell. Autophagy contributes to the routine turnover of cytoplasmic components and is a key mechanism for tissue development, for cell survival when nutrients are scarce, and for maintaining homeostasis. In liver cells, for example, the average mitochondrion normally has a life span of only about 10 days before it is destroyed.

SYNTHESIS OF CELLULAR STRUCTURES BY ENDOPLASMIC RETICULUM AND GOLGI APPARATUS

Specific Functions of the Endoplasmic Reticulum

The extensiveness of the endoplasmic reticulum and the Golgi apparatus in secretory cells has already been emphasized. These structures are formed primarily of lipid bilayer membranes similar to the cell membrane, and their walls are loaded with protein enzymes that catalyze the synthesis of many substances required by the cell.

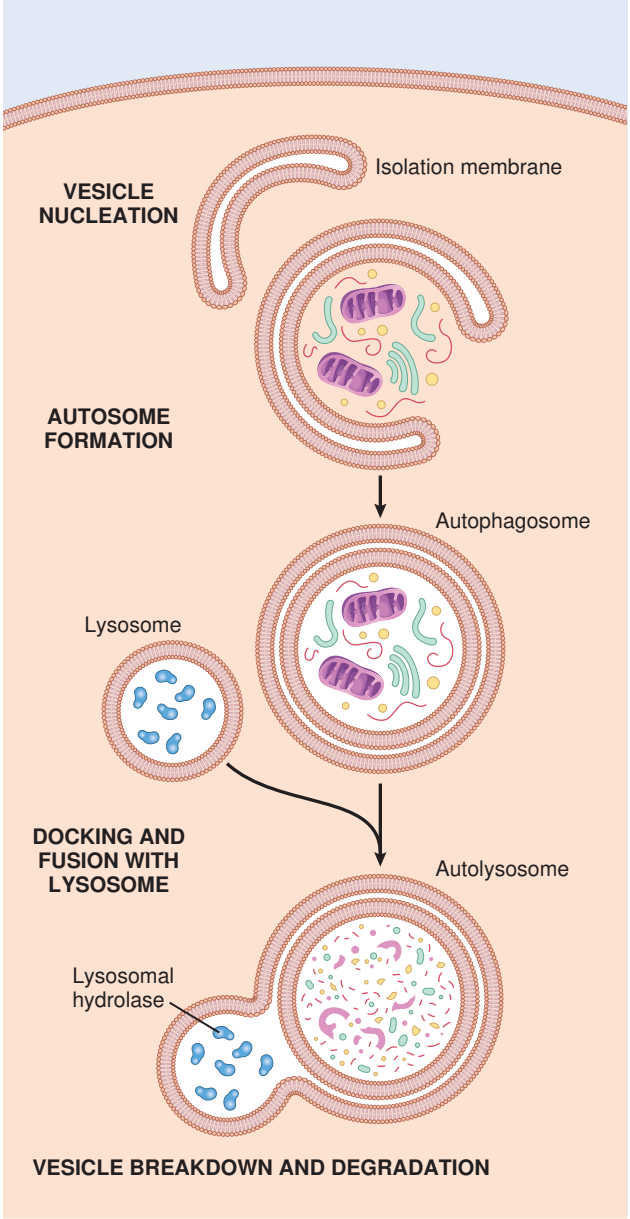


Figure 2-13. Schematic diagram of autophagy steps.

Most synthesis begins in the endoplasmic reticulum. The products formed there are then passed on to the Golgi apparatus, where they are further processed before being released into the cytoplasm. First, however, let us note the specific products that are synthesized in specific portions of the endoplasmic reticulum and the Golgi apparatus.

Proteins Are Formed by the Granular Endoplasmic Reticulum. The granular portion of the endoplasmic reticulum is characterized by large numbers of ribosomes attached to the outer surfaces of the endoplasmic reticulum membrane. As discussed in Chapter 3, protein molecules are synthesized within the structures of the ribosomes. The ribosomes extrude some of the synthesized protein molecules directly into the cytosol, but they also extrude many more through the wall of the endoplasmic reticulum to the interior of the endoplasmic vesicles and tubules, into the *endoplasmic matrix.*

Synthesis of Lipids by the Smooth Endoplasmic Reticulum. The endoplasmic reticulum also synthesizes lipids, especially phospholipids and cholesterol. These lipids are rapidly incorporated into the lipid bilayer of the endoplasmic reticulum itself, thus causing the endoplasmic reticulum to grow more extensive. This process occurs mainly in the smooth portion of the endoplasmic reticulum.

To keep the endoplasmic reticulum from growing beyond the needs of the cell, small vesicles called *ER vesicles* or *transport vesicles* continually break away from the smooth reticulum; most of these vesicles then migrate rapidly to the Golgi apparatus.

Other Functions of the Endoplasmic Reticulum. Other significant functions of the endoplasmic reticulum, especially the smooth reticulum, include the following:

1. It provides the enzymes that control glycogen breakdown when glycogen is to be used for energy.
2. It provides a vast number of enzymes that are capable of detoxifying substances, such as drugs, that might damage the cell. It achieves detoxification by coagulation, oxidation, hydrolysis, conjugation with glycuronic acid, and in other ways.

Specific Functions of the Golgi Apparatus

Synthetic Functions of the Golgi Apparatus. Although the major function of the Golgi apparatus is to provide additional processing of substances already formed in the endoplasmic reticulum, it also has the capability of synthesizing certain carbohydrates that cannot be formed in the endoplasmic reticulum. This is especially true for the formation of large saccharide polymers bound with small amounts of protein; important examples include *hyaluronic acid* and *chondroitin sulfate.*

A few of the many functions of hyaluronic acid and chondroitin sulfate in the body are as follows: (1) they are the major components of proteoglycans secreted in mucus and other glandular secretions; (2) they are the major components of the *ground substance*, or nonfibrous components of the extracellular matrix, outside the cells in the interstitial spaces, acting as fillers between collagen fibers and cells; (3) they are principal components of the organic matrix in both cartilage and bone; and (4) they are important in many cell activities, including migration and proliferation.

Processing of Endoplasmic Secretions by the Golgi Apparatus—Formation of Vesicles. Figure 2-14 summarizes the major functions of the endoplasmic reticulum and Golgi apparatus. As substances are formed in the endoplasmic reticulum, especially the proteins, they are transported through the tubules toward portions of the

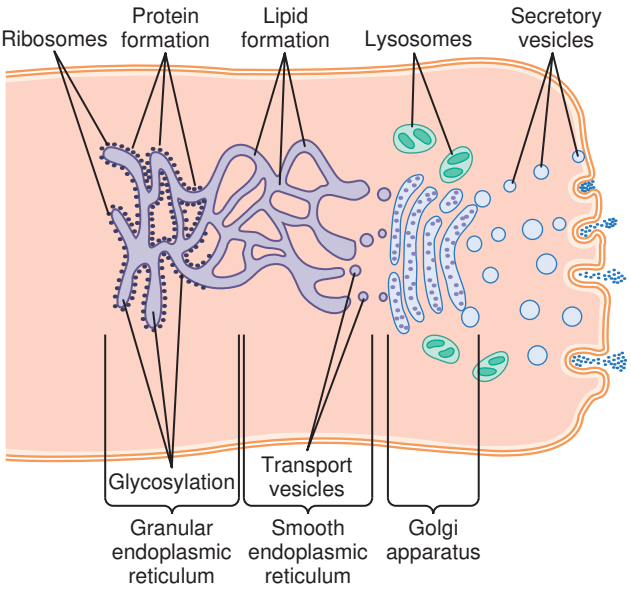


Figure 2-14. Formation of proteins, lipids, and cellular vesicles by the endoplasmic reticulum and Golgi apparatus.

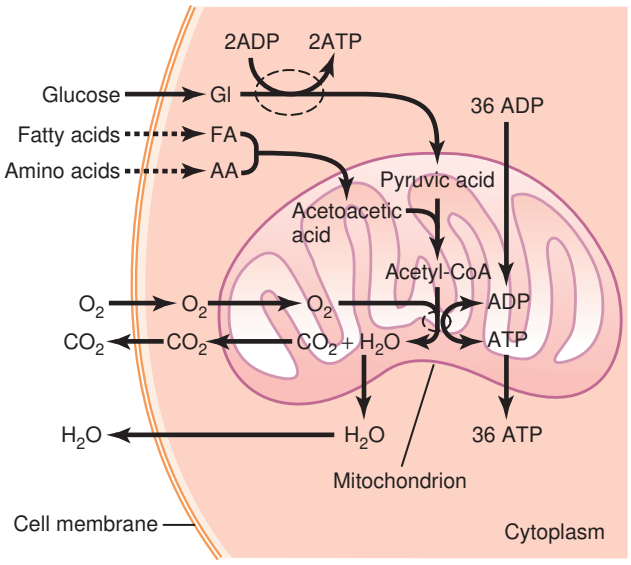


Figure 2-15. Formation of adenosine triphosphate *(ATP)* in the cell, showing that most of the ATP is formed in the mitochondria. ADP, adenosine diphosphate; CoA, coenzyme A.

smooth endoplasmic reticulum that lie nearest the Golgi apparatus. At this point, small *transport vesicles* composed of small envelopes of smooth endoplasmic reticulum continually break away and diffuse to the *deepest layer* of the Golgi apparatus. Inside these vesicles are the synthesized proteins and other products from the endoplasmic reticulum.

The transport vesicles instantly fuse with the Golgi apparatus and empty their contained substances into the vesicular spaces of the Golgi apparatus. Here, additional carbohydrate moieties are added to the secretions. Also, an important function of the Golgi apparatus is to compact the endoplasmic reticular secretions into highly concentrated packets. As the secretions pass toward the outermost layers of the Golgi apparatus, the compaction and processing proceed. Finally, both small and large vesicles continually break away from the Golgi apparatus, carrying with them the compacted secretory substances, and in turn, the vesicles diffuse throughout the cell.

The following example provides an idea of the timing of these processes: When a glandular cell is bathed in radioactive amino acids, newly formed radioactive protein molecules can be detected in the granular endoplasmic reticulum within 3 to 5 minutes. Within 20 minutes, newly formed proteins are already present in the Golgi apparatus, and within 1 to 2 hours, the proteins are secreted from the surface of the cell.

Types of Vesicles Formed by the Golgi Apparatus—Secretory Vesicles and Lysosomes. In a highly secretory cell, the vesicles formed by the Golgi apparatus are mainly *secretory vesicles* containing protein substances that are to be secreted through the surface of the cell membrane. These secretory vesicles first diffuse to the cell membrane, then fuse with it and empty their substances to the exterior by the mechanism called *exocytosis.* Exocytosis, in most cases, is stimulated by the entry of calcium ions into the cell; calcium ions interact with the vesicular membrane in some way that is not understood and cause its fusion with the cell membrane, followed by exocytosis—that is, opening of the membrane's outer surface and extrusion of its contents outside the cell. Some vesicles, however, are destined for intracellular use.

Use of Intracellular Vesicles to Replenish Cellular Membranes. Some of the intracellular vesicles formed by the Golgi apparatus fuse with the cell membrane or with the membranes of intracellular structures such as the mitochondria and even the endoplasmic reticulum. This fusion increases the expanse of these membranes and thereby replenishes the membranes as they are used up. For instance, the cell membrane loses much of its substance every time it forms a phagocytic or pinocytotic vesicle, and the vesicular membranes of the Golgi apparatus continually replenish the cell membrane.

In summary, the membranous system of the endoplasmic reticulum and Golgi apparatus represents a highly metabolic organ capable of forming new intracellular structures, as well as secretory substances to be extruded from the cell.

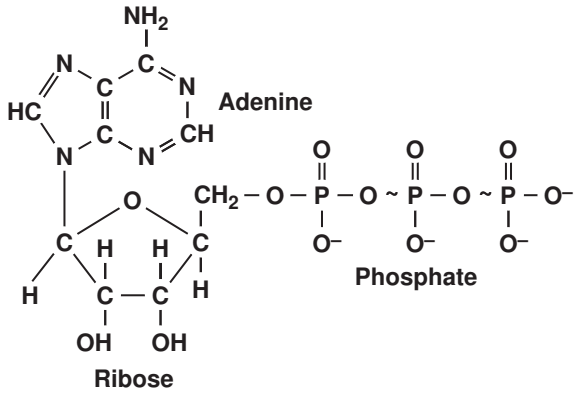
THE MITOCHONDRIA EXTRACT ENERGY FROM NUTRIENTS

The principal substances from which cells extract energy are foodstuffs that react chemically with oxygen—carbohydrates, fats, and proteins. In the human body, essentially all carbohydrates are converted into *glucose* by the digestive tract and liver before they reach the other cells of the body. Similarly, proteins are converted into *amino acids* and fats are converted into *fatty acids.* **Figure 2-15** shows oxygen and the foodstuffs—glucose,

fatty acids, and amino acids—all entering the cell. Inside the cell, the foodstuffs react chemically with oxygen, under the influence of enzymes that control the reactions and channel the energy released in the proper direction. The details of all these digestive and metabolic functions are provided in Chapters 63 through 73.

Briefly, almost all these oxidative reactions occur inside the mitochondria, and the energy that is released is used to form the high-energy compound *ATP.* Then, ATP, not the original foodstuffs, is used throughout the cell to energize almost all of the subsequent intracellular metabolic reactions.

Functional Characteristics of ATP



ATP is a nucleotide composed of (1) the nitrogenous base *adenine,* (2) the pentose sugar *ribose,* and (3) three *phosphate radicals.* The last two phosphate radicals are connected with the remainder of the molecule by so-called *high-energy phosphate bonds,* which are represented in the formula shown by the symbol ~. *Under the physical and chemical conditions of the body,* each of these high-energy bonds contains about 12,000 calories of energy per mole of ATP, which is many times greater than the energy stored in the average chemical bond, thus giving rise to the term *high-energy bond.* Further, the high-energy phosphate bond is very labile so that it can be split instantly on demand whenever energy is required to promote other intracellular reactions.

When ATP releases its energy, a phosphoric acid radical is split away and *adenosine diphosphate* (ADP) is formed. This released energy is used to energize many of the cell's other functions, such as synthesis of substances and muscular contraction.

To reconstitute the cellular ATP as it is used up, energy derived from the cellular nutrients causes ADP and phosphoric acid to recombine to form new ATP, and the entire process is repeated over and over again. For these reasons, ATP has been called the *energy currency* of the cell because it can be spent and remade continually, having a turnover time of only a few minutes.

Chemical Processes in the Formation of ATP—Role of the Mitochondria. Upon entry into the cells, glucose is subjected to enzymes in the *cytoplasm* that convert it into *pyruvic acid* (a process called *glycolysis*). A small amount of ADP is changed into ATP by the energy released during this conversion, but this amount accounts for less than 5 percent of the overall energy metabolism of the cell.

About 95 percent of the cell's ATP formation occurs in the mitochondria. The pyruvic acid derived from carbohydrates, fatty acids from lipids, and amino acids from proteins is eventually converted into the compound *acetyl-coenzyme A (CoA)* in the matrix of mitochondria. This substance, in turn, is further dissoluted (for the purpose of extracting its energy) by another series of enzymes in the mitochondrion matrix, undergoing dissolution in a sequence of chemical reactions called the *citric acid cycle,* or *Krebs cycle.* These chemical reactions are so important that they are explained in detail in Chapter 68.

In this citric acid cycle, acetyl-CoA is split into its component parts, *hydrogen atoms* and *carbon dioxide.* The carbon dioxide diffuses out of the mitochondria and eventually out of the cell; finally, it is excreted from the body through the lungs.

The hydrogen atoms, conversely, are highly reactive, and they combine with oxygen that has also diffused into the mitochondria. This combination releases a tremendous amount of energy, which is used by the mitochondria to convert large amounts of ADP to ATP. The processes of these reactions are complex, requiring the participation of many protein enzymes that are integral parts of mitochondrial *membranous shelves* that protrude into the mitochondrial matrix. The initial event is removal of an electron from the hydrogen atom, thus converting it to a hydrogen ion. The terminal event is combination of hydrogen ions with oxygen to form water plus release of tremendous amounts of energy to large globular proteins that protrude like knobs from the membranes of the mitochondrial shelves; this process is called *ATP synthetase.* Finally, the enzyme ATP synthetase uses the energy from the hydrogen ions to cause the conversion of ADP to ATP. The newly formed ATP is transported out of the mitochondria into all parts of the cell cytoplasm and nucleoplasm, where its energy is used to energize multiple cell functions.

This overall process for formation of ATP is called the *chemiosmotic mechanism* of ATP formation. The chemical and physical details of this mechanism are presented in Chapter 68, and many of the detailed metabolic functions of ATP in the body are presented in Chapters 68 through 72.

Uses of ATP for Cellular Function. Energy from ATP is used to promote three major categories of cellular functions: (1) *transport* of substances through multiple membranes in the cell, (2) *synthesis of chemical compounds* throughout the cell, and (3) *mechanical work.* These uses of ATP are illustrated by examples in **Figure 2-16**: (1) to supply energy for the transport of sodium through the

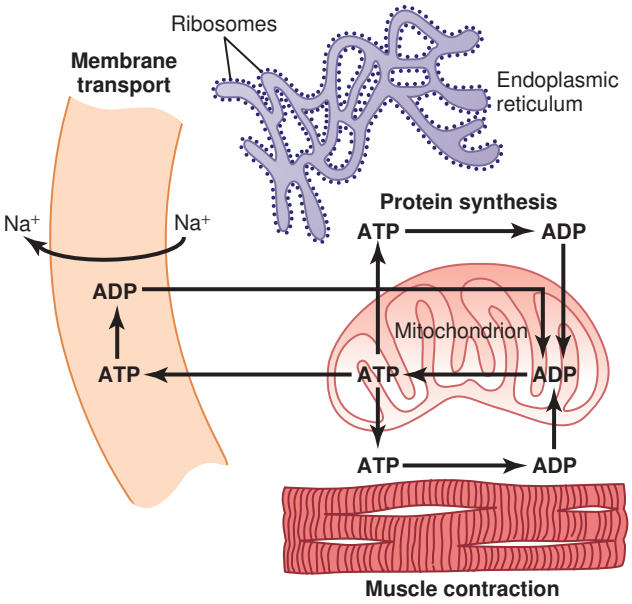


Figure 2-16. Use of adenosine triphosphate (*ATP*; formed in the mitochondrion) to provide energy for three major cellular functions: membrane transport, protein synthesis, and muscle contraction. ADP, adenosine diphosphate.

cell membrane, (2) to promote protein synthesis by the ribosomes, and (3) to supply the energy needed during muscle contraction.

In addition to membrane transport of sodium, energy from ATP is required for membrane transport of potassium ions, calcium ions, magnesium ions, phosphate ions, chloride ions, urate ions, hydrogen ions, and many other ions and various organic substances. Membrane transport is so important to cell function that some cells—the renal tubular cells, for instance—use as much as 80 percent of the ATP that they form for this purpose alone.

In addition to synthesizing proteins, cells make phospholipids, cholesterol, purines, pyrimidines, and a host of other substances. Synthesis of almost any chemical compound requires energy. For instance, a single protein molecule might be composed of as many as several thousand amino acids attached to one another by peptide linkages. The formation of each of these linkages requires energy derived from the breakdown of four high-energy bonds; thus, many thousand ATP molecules must release their energy as each protein molecule is formed. Indeed, some cells use as much as 75 percent of all the ATP formed in the cell simply to synthesize new chemical compounds, especially protein molecules; this is particularly true during the growth phase of cells.

The final major use of ATP is to supply energy for special cells to perform mechanical work. We see in Chapter 6 that each contraction of a muscle fiber requires expenditure of tremendous quantities of ATP energy. Other cells perform mechanical work in other ways, especially by *ciliary* and *ameboid motion,* described later in this chapter. The source of energy for all these types of mechanical work is ATP.

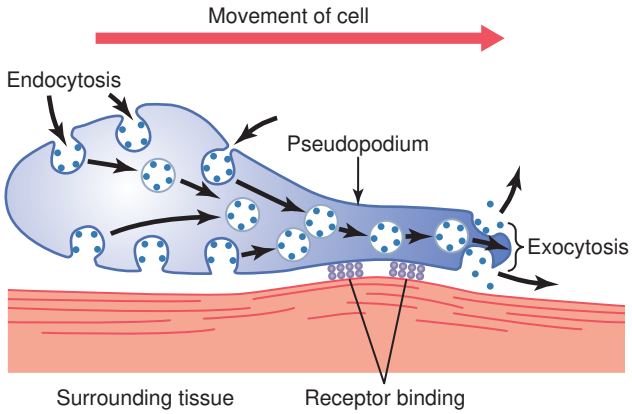


Figure 2-17. Ameboid motion by a cell.

In summary, ATP is always available to release its energy rapidly and almost explosively wherever in the cell it is needed. To replace the ATP used by the cell, much slower chemical reactions break down carbohydrates, fats, and proteins and use the energy derived from these processes to form new ATP. More than 95 percent of this ATP is formed in the mitochondria, which accounts for the mitochondria being called the "powerhouses" of the cell.

LOCOMOTION OF CELLS

The most obvious type of movement that occurs in the body is that of the muscle cells in skeletal, cardiac, and smooth muscle, which constitute almost 50 percent of the entire body mass. The specialized functions of these cells are discussed in Chapters 6 through 9. Two other types of movement—*ameboid locomotion* and *ciliary movement*—occur in other cells.

AMEBOID MOVEMENT

Ameboid movement is movement of an entire cell in relation to its surroundings, such as movement of white blood cells through tissues. It receives its name from the fact that amebae move in this manner, and amebae have provided an excellent tool for studying the phenomenon.

Typically, ameboid locomotion begins with protrusion of a *pseudopodium* from one end of the cell. The pseudopodium projects away from the cell body and partially secures itself in a new tissue area, and then the remainder of the cell is pulled toward the pseudopodium. **Figure 2-17** demonstrates this process, showing an elongated cell, the right-hand end of which is a protruding pseudopodium. The membrane of this end of the cell is continually moving forward, and the membrane at the left-hand end of the cell is continually following along as the cell moves.

Mechanism of Ameboid Locomotion. **Figure 2-17** shows the general principle of ameboid motion. Basically,

it results from continual formation of new cell membrane at the leading edge of the pseudopodium and continual absorption of the membrane in mid and rear portions of the cell. Two other effects are also essential for forward movement of the cell. The first effect is attachment of the pseudopodium to surrounding tissues so that it becomes fixed in its leading position, while the remainder of the cell body is pulled forward toward the point of attachment. This attachment is effected by *receptor proteins* that line the insides of exocytotic vesicles. When the vesicles become part of the pseudopodial membrane, they open so that their insides evert to the outside, and the receptors now protrude to the outside and attach to ligands in the surrounding tissues.

At the opposite end of the cell, the receptors pull away from their ligands and form new endocytotic vesicles. Then, inside the cell, these vesicles stream toward the pseudopodial end of the cell, where they are used to form new membrane for the pseudopodium.

The second essential effect for locomotion is to provide the energy required to pull the cell body in the direction of the pseudopodium. In the cytoplasm of all cells is a moderate to large amount of the protein *actin.* Much of the actin is in the form of single molecules that do not provide any motive power; however, these molecules polymerize to form a filamentous network, and the network contracts when it binds with an actin-binding protein such as *myosin.* The entire process is energized by the high-energy compound ATP. This mechanism is what happens in the pseudopodium of a moving cell, where such a network of actin filaments forms anew inside the enlarging pseudopodium. Contraction also occurs in the ectoplasm of the cell body, where a preexisting actin network is already present beneath the cell membrane.

Types of Cells That Exhibit Ameboid Locomotion. The most common cells to exhibit ameboid locomotion in the human body are the *white blood cells* when they move out of the blood into the tissues to form *tissue macrophages.* Other types of cells can also move by ameboid locomotion under certain circumstances. For instance, fibroblasts move into a damaged area to help repair the damage, and even the germinal cells of the skin, although ordinarily completely sessile cells, move toward a cut area to repair the opening. Finally, cell locomotion is especially important in the development of the embryo and fetus after fertilization of an ovum. For instance, embryonic cells often must migrate long distances from their sites of origin to new areas during development of special structures.

Control of Ameboid Locomotion—Chemotaxis. The most important initiator of ameboid locomotion is the process called *chemotaxis,* which results from the appearance of certain chemical substances in the tissues. Any chemical substance that causes chemotaxis to occur is called a *chemotactic substance.* Most cells that exhibit ameboid locomotion move toward the source of a chemotactic substance—that is, from an area of lower concentration toward an area of higher concentration—which is called *positive chemotaxis.* Some cells move away from the source, which is called *negative chemotaxis.*

But how does chemotaxis control the direction of ameboid locomotion? Although the answer is not certain, it is known that the side of the cell most exposed to the chemotactic substance develops membrane changes that cause pseudopodial protrusion.

CILIA AND CILIARY MOVEMENTS

A second type of cellular motion, *ciliary movement,* is a whiplike movement of cilia on the surfaces of cells. This movement occurs mainly in two places in the human body: on the surfaces of the respiratory airways and on the inside surfaces of the uterine tubes (fallopian tubes) of the reproductive tract. In the nasal cavity and lower respiratory airways, the whiplike motion of cilia causes a layer of mucus to move at a rate of about 1 cm/min toward the pharynx, in this way continually clearing these passageways of mucus and particles that have become trapped in the mucus. In the uterine tubes, the cilia cause slow movement of fluid from the ostium of the uterine tube toward the uterus cavity; this movement of fluid transports the ovum from the ovary to the uterus.

As shown in **Figure 2-18**, a cilium has the appearance of a sharp-pointed straight or curved hair that projects 2 to 4 micrometers from the surface of the cell. Often many cilia project from a single cell—for instance, as many as 200 cilia on the surface of each epithelial cell inside the respiratory passageways. The cilium is covered by an outcropping of the cell membrane, and it is supported by 11 microtubules—9 double tubules located around the periphery of the cilium and 2 single tubules down the center, as demonstrated in the cross section shown in **Figure 2-18**. Each cilium is an outgrowth of a structure that lies immediately beneath the cell membrane, called the *basal body* of the cilium.

The *flagellum of a sperm* is similar to a cilium; in fact, it has much the same type of structure and the same type of contractile mechanism. The flagellum, however, is much longer and moves in quasi-sinusoidal waves instead of whiplike movements.

In the inset of **Figure 2-18**, movement of the cilium is shown. The cilium moves forward with a sudden, rapid whiplike stroke 10 to 20 times per second, bending sharply where it projects from the surface of the cell. Then it moves backward slowly to its initial position. The rapid forward-thrusting, whiplike movement pushes the fluid lying adjacent to the cell in the direction that the cilium moves; the slow, dragging movement in the backward direction has almost no effect on fluid movement. As a result, the fluid is continually propelled in the direction of the fast-forward stroke. Because most ciliated cells have large numbers of cilia on their surfaces and because

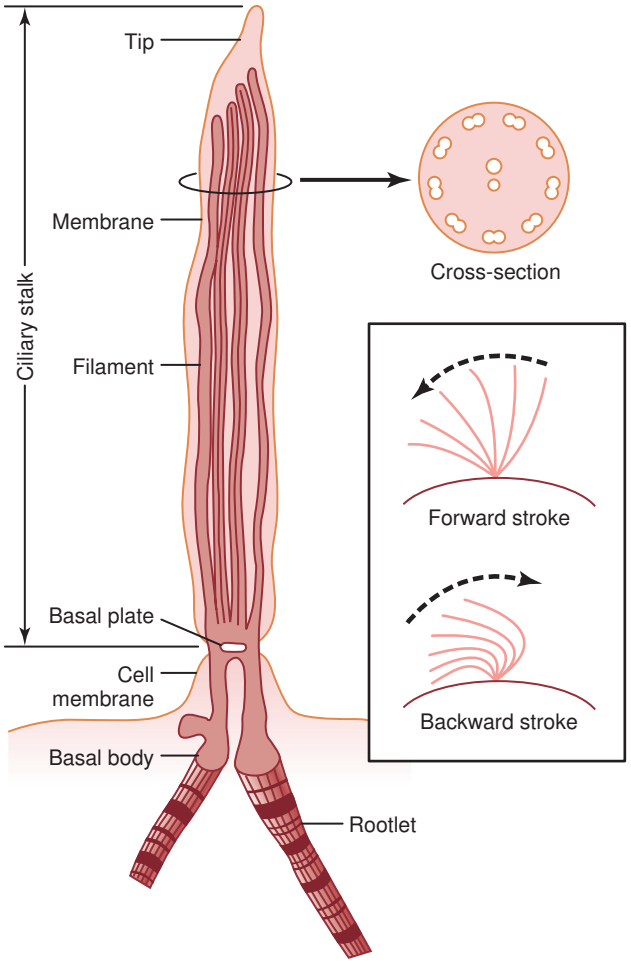


Figure 2-18. Structure and function of the cilium. *(Modified from Satir P: Cilia. Sci Am 204:108, 1961. Copyright Donald Garber: Executor of the estate of Bunji Tagawa.)*

all the cilia are oriented in the same direction, this is an effective means for moving fluids from one part of the surface to another.

Mechanism of Ciliary Movement. Although not all aspects of ciliary movement are known, we are aware of the following elements: First, the nine double tubules and the two single tubules are all linked to one another by a complex of protein cross-linkages; this total complex of tubules and cross-linkages is called the *axoneme.* Second, even after removal of the membrane and destruction of other elements of the cilium besides the axoneme, the cilium can still beat under appropriate conditions. Third, two conditions are necessary for continued beating of the axoneme after removal of the other structures of the cilium: (1) the availability of ATP and (2) appropriate ionic conditions, especially appropriate concentrations of magnesium and calcium. Fourth, during forward motion of the cilium, the double tubules on the front edge of the cilium slide outward toward the tip of the cilium, while those on the back edge remain in place. Fifth, multiple protein arms composed of the protein *dynein,* which has adenosine triphosphatase (ATPase) enzymatic activity, project from each double tubule toward an adjacent double tubule.

Given this basic information, it has been determined that the release of energy from ATP in contact with the ATPase dynein arms causes the heads of these arms to "crawl" rapidly along the surface of the adjacent double tubule. If the front tubules crawl outward while the back tubules remain stationary, bending occurs.

The way in which cilia contraction is controlled is not understood. The cilia of some genetically abnormal cells do not have the two central single tubules, and these cilia fail to beat. Therefore, it is presumed that some signal, perhaps an electrochemical signal, is transmitted along these two central tubules to activate the dynein arms.

Bibliography

Alberts B, Johnson A, Lewis J, et al: Molecular Biology of the Cell, 6th ed. New York: Garland Science, 2007.

Bohdanowicz M, Grinstein S: Role of phospholipids in endocytosis, phagocytosis, and macropinocytosis. Physiol Rev 93:69, 2013.

Boya P, Reggiori F, Codogno P: Emerging regulation and functions of autophagy. Nat Cell Biol 15:713, 2013.

Brandizzi F, Barlowe C: Organization of the ER-Golgi interface for membrane traffic control. Nat Rev Mol Cell Biol 14:382, 2013.

Chen S, Novick P, Ferro-Novick S: ER structure and function. Curr Opin Cell Biol 25:428, 2013.

Drummond IA: Cilia functions in development. Curr Opin Cell Biol 24:24, 2012.

Edidin E: Lipids on the frontier: a century of cell-membrane bilayers. Nat Rev Mol Cell Biol 4: 414, 2003.

Guerriero CJ, Brodsky JL: The delicate balance between secreted protein folding and endoplasmic reticulum-associated degradation in human physiology. Physiol Rev 92:537, 2012.

Hamasaki M, Shibutani ST, Yoshimori T: Up-to-date membrane biogenesis in the autophagosome formation. Curr Opin Cell Biol 25:455, 2013.

Hla T, Dannenberg AJ: Sphingolipid signaling in metabolic disorders. Cell Metab 16:420, 2012.

Insall R: The interaction between pseudopods and extracellular signalling during chemotaxis and directed migration. Curr Opin Cell Biol 25:526, 2013.

Jin T: Gradient sensing during chemotaxis. Curr Opin Cell Biol 25:532, 2013.

Kikkawa M: Big steps toward understanding dynein. J Cell Biol 202:15, 2013.

Lamb CA, Yoshimori T, Tooze SA: The autophagosome: origins unknown, biogenesis complex. Nat Rev Mol Cell Biol 14:759, 2013.

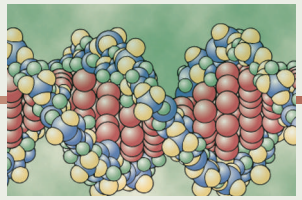
Marzetti E, Csiszar A, Dutta D, et al: Role of mitochondrial dysfunction and altered autophagy in cardiovascular aging and disease: from mechanisms to therapeutics. Am J Physiol Heart Circ Physiol 305:H459, 2013.

Nakamura N, Wei JH, Seemann J: Modular organization of the mammalian Golgi apparatus. Curr Opin Cell Biol 24:467, 2012.

Nixon RA: The role of autophagy in neurodegenerative disease. Nat Med 19:983, 2013.

Smith JJ, Aitchison JD: Peroxisomes take shape. Nat Rev Mol Cell Biol 14:803, 2013.

van der Zand A, Tabak HF: Peroxisomes: offshoots of the ER. Curr Opin Cell Biol 25:449, 2013.



CHAPTER 3

UNIT I

Genetic Control of Protein Synthesis, Cell Function, and Cell Reproduction

Almost everyone knows that the genes, which are located in the nuclei of all cells of the body, control heredity from parents to children, but many people do not realize that these same genes also control the day-to-day function of all the body's cells. The genes control cell function by determining which substances are synthesized within the cell—which structures, which enzymes, which chemicals.

Figure 3-1 shows the general schema of genetic control. Each gene, which is composed of *deoxyribonucleic acid* (DNA), controls the formation of another nucleic acid, *ribonucleic acid* (RNA); this RNA then spreads throughout the cell to control the formation of a specific protein. The entire process, from *transcription* of the genetic code in the nucleus to *translation* of the RNA code and the formation of proteins in the cell cytoplasm, is often referred to as *gene expression.*

Because there are approximately 30,000 different genes in each cell, it is possible to form a large number of different cellular proteins. In fact, RNA molecules transcribed from the same segment of DNA (i.e., the same gene) can be processed in more than one way by the cell, giving rise to alternate versions of the protein. The total number of different proteins produced by the various cell types in humans is estimated to be at least 100,000.

Some of the cellular proteins are *structural proteins,* which, in association with various lipids and carbohydrates, form the structures of the various intracellular organelles discussed in Chapter 2. However, the majority of the proteins are *enzymes* that catalyze the different chemical reactions in the cells. For instance, enzymes promote all the oxidative reactions that supply energy to the cell, along with synthesis of all the cell chemicals, such as lipids, glycogen, and adenosine triphosphate (ATP).

GENES IN THE CELL NUCLEUS CONTROL PROTEIN SYNTHESIS

In the cell nucleus, large numbers of genes are attached end on end in extremely long double-stranded helical molecules of DNA having molecular weights measured in the billions. A very short segment of such a molecule is shown in **Figure 3-2**. This molecule is composed of several simple chemical compounds bound together in a regular pattern, the details of which are explained in the next few paragraphs.

Basic Building Blocks of DNA

Figure 3-3 shows the basic chemical compounds involved in the formation of DNA. These compounds include (1) *phosphoric acid,* (2) a sugar called *deoxyribose,* and (3) four nitrogenous *bases* (two purines, *adenine* and *guanine,* and two pyrimidines, *thymine* and *cytosine*). The phosphoric acid and deoxyribose form the two helical strands that are the backbone of the DNA molecule, and the nitrogenous bases lie between the two strands and connect them, as illustrated in **Figure 3-6**.

Nucleotides

The first stage of DNA formation is to combine one molecule of phosphoric acid, one molecule of deoxyribose,

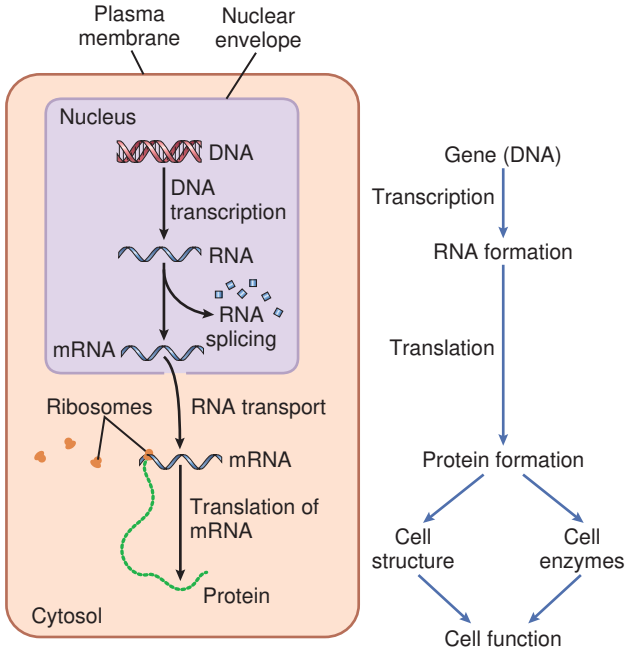


Figure 3-1. The general schema by which genes control cell function. mRNA, messenger RNA.

and one of the four bases to form an acidic nucleotide. Four separate nucleotides are thus formed, one for each of the four bases: *deoxyadenylic, deoxythymidylic, deoxyguanylic,* and *deoxycytidylic acids*. **Figure 3-4** shows the chemical structure of deoxyadenylic acid, and **Figure 3-5** shows simple symbols for the four nucleotides that form DNA.

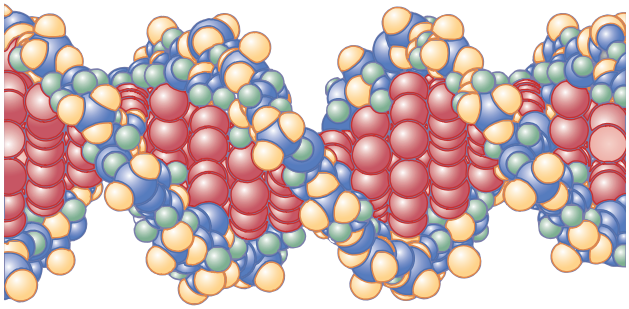


Figure 3-2. The helical, double-stranded structure of the gene. The outside strands are composed of phosphoric acid and the sugar deoxyribose. The internal molecules connecting the two strands of the helix are purine and pyrimidine bases, which determine the "code" of the gene.

Nucleotides Are Organized to Form Two Strands of DNA Loosely Bound to Each Other

Figure 3-6 shows the manner in which multiple numbers of nucleotides are bound together to form two strands of DNA. The two strands are, in turn, loosely bonded with each other by weak cross-linkages, as illustrated in **Figure 3-6** by the central dashed lines. Note that the backbone of each DNA strand is composed of alternating phosphoric acid and deoxyribose molecules. In turn, purine and pyrimidine bases are attached to the sides of the deoxyribose molecules. Then, by means of loose *hydrogen bonds* (dashed lines) between the purine and pyrimidine bases, the two respective DNA strands are held together. Note the following caveats, however:

1. Each purine base *adenine* of one strand always bonds with a pyrimidine base *thymine* of the other strand.
2. Each purine base *guanine* always bonds with a pyrimidine base *cytosine.*

Thus, in **Figure 3-6,** the sequence of complementary pairs of bases is CG, CG, GC, TA, CG, TA, GC, AT, and AT. Because of the looseness of the hydrogen bonds, the

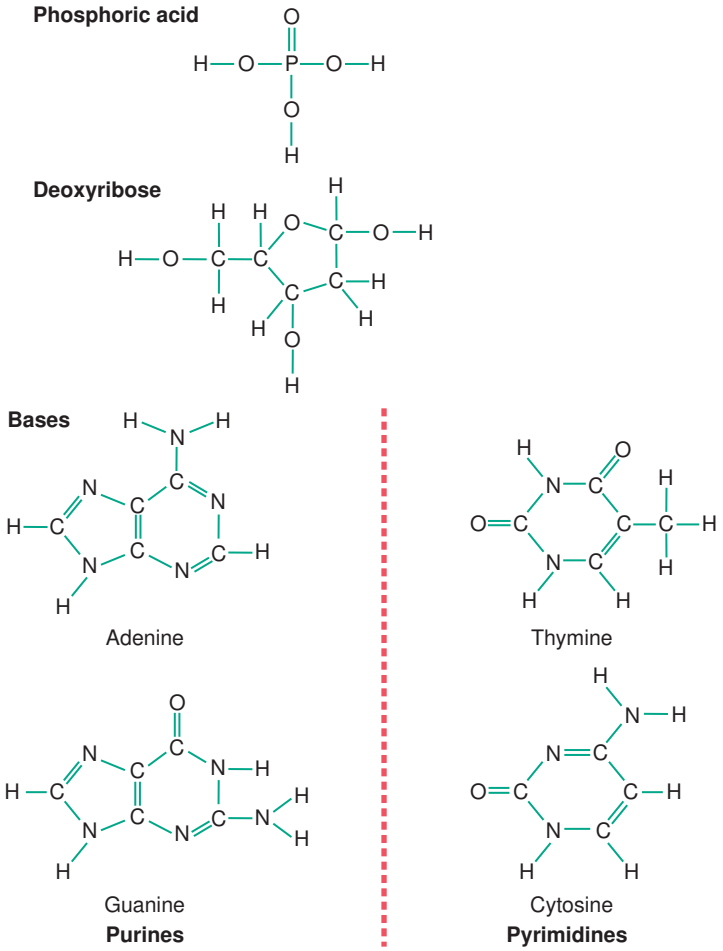


Figure 3-3. The basic building blocks of DNA.

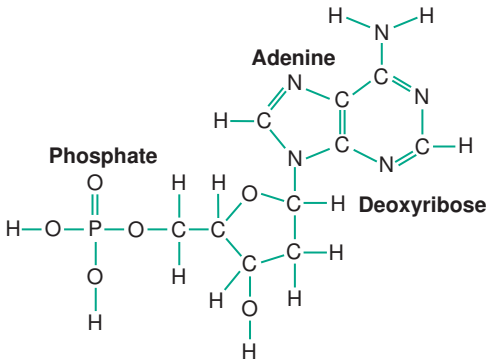


Figure 3-4. Deoxyadenylic acid, one of the nucleotides that make up DNA.

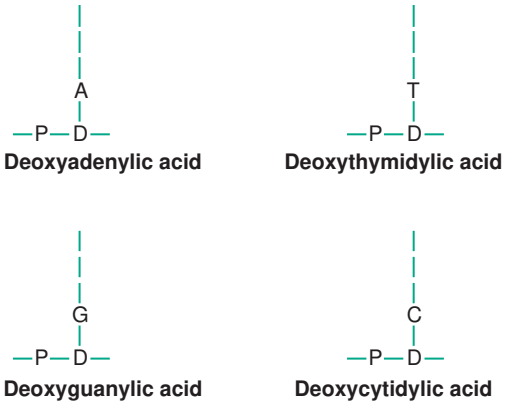


Figure 3-5. Symbols for the four nucleotides that combine to form DNA. Each nucleotide contains phosphoric acid (*P*), deoxyribose (*D*), and one of the four nucleotide bases: *A,* adenine; *T,* thymine; *G,* guanine; or *C,* cytosine.

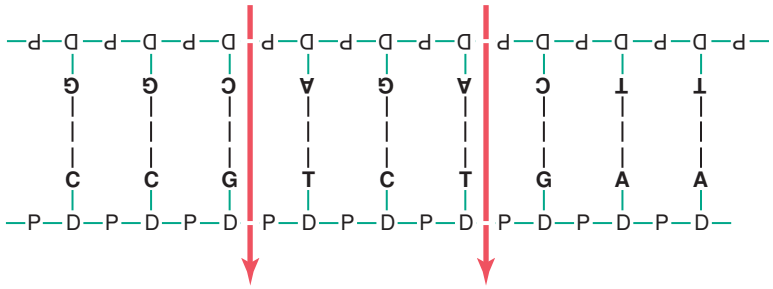


Figure 3-6. Arrangement of deoxyribose nucleotides in a double strand of DNA.

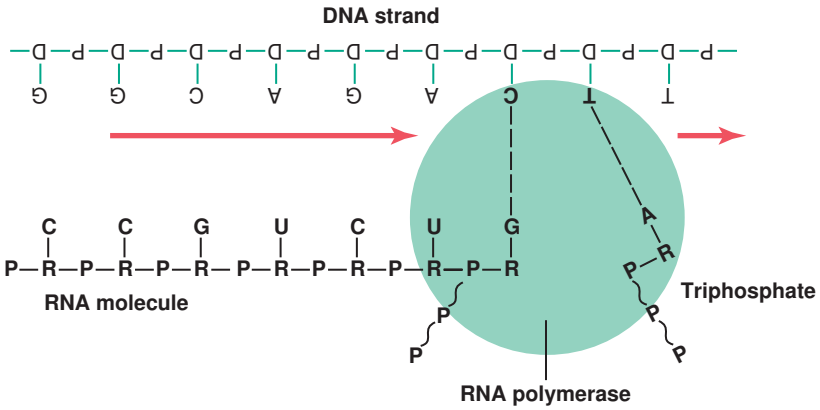


Figure 3-7. Combination of ribose nucleotides with a strand of DNA to form a molecule of RNA that carries the genetic code from the gene to the cytoplasm. The *RNA polymerase* enzyme moves along the DNA strand and builds the RNA molecule.

two strands can pull apart with ease, and they do so many times during the course of their function in the cell.

To put the DNA of **Figure 3-6** into its proper physical perspective, one could merely pick up the two ends and twist them into a helix. Ten pairs of nucleotides are present in each full turn of the helix in the DNA molecule, as shown in **Figure 3-2**.

GENETIC CODE

The importance of DNA lies in its ability to control the formation of proteins in the cell, which it achieves by means of a *genetic code.* That is, when the two strands of a DNA molecule are split apart, the purine and pyrimidine bases projecting to the side of each DNA strand are exposed, as shown by the top strand in **Figure 3-7.** It is these projecting bases that form the genetic code.

The genetic code consists of successive "triplets" of bases—that is, each three successive bases is a *code word.* The successive triplets eventually control the sequence of amino acids in a protein molecule that is to be synthesized in the cell. Note in **Figure 3-6** that the top strand of DNA, reading from left to right, has the genetic code GGC, AGA, CTT, with the triplets being separated from one another by the arrows. As we follow this genetic code through **Figures 3-7** and **3-8**, we see that these three respective triplets are responsible for successive

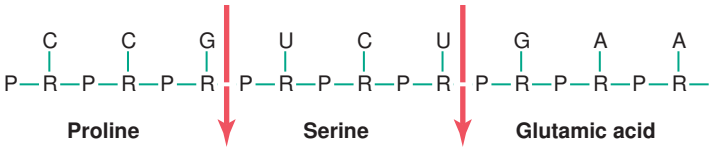


Figure 3-8. A portion of an RNA molecule showing three RNA codons—CCG, UCU, and GAA—that control attachment of the three amino acids, proline, serine, and glutamic acid, respectively, to the growing RNA chain.

placement of the three amino acids, *proline, serine,* and *glutamic acid,* in a newly formed molecule of protein.

THE DNA CODE IN THE CELL NUCLEUS IS TRANSFERRED TO RNA CODE IN THE CELL CYTOPLASM—THE PROCESS OF TRANSCRIPTION

Because the DNA is located in the nucleus of the cell, yet most of the functions of the cell are carried out in the cytoplasm, there must be some means for the DNA genes of the nucleus to control the chemical reactions of the cytoplasm. This control is achieved through the intermediary of another type of nucleic acid, RNA, the formation of which is controlled by the DNA of the nucleus. Thus, as shown in **Figure 3-7**, the code is transferred to the RNA in a process called *transcription.* The RNA, in turn, diffuses from the nucleus through nuclear pores into the cytoplasmic compartment, where it controls protein synthesis.

RNA IS SYNTHESIZED IN THE NUCLEUS FROM A DNA TEMPLATE

During synthesis of RNA, the two strands of the DNA molecule separate temporarily; one of these strands is used as a template for synthesis of an RNA molecule. The code triplets in the DNA cause formation of *complementary* code triplets (called *codons*) in the RNA. These codons, in turn, will control the sequence of amino acids in a protein to be synthesized in the cell cytoplasm.

Basic Building Blocks of RNA. The basic building blocks of RNA are almost the same as those of DNA, except for two differences. First, the sugar deoxyribose is not used in the formation of RNA. In its place is another sugar of slightly different composition, *ribose,* that contains an extra hydroxyl ion appended to the ribose ring structure. Second, thymine is replaced by another pyrimidine, *uracil.*

Formation of RNA Nucleotides. The basic building blocks of RNA form *RNA nucleotides,* exactly as previously described for DNA synthesis. Here again, four separate nucleotides are used in the formation of RNA. These nucleotides contain the bases *adenine, guanine, cytosine,* and *uracil.* Note that these bases are the same bases as in DNA, except that uracil in RNA replaces thymine in DNA.

"Activation" of the RNA Nucleotides. The next step in the synthesis of RNA is "activation" of the RNA nucleotides by an enzyme, *RNA polymerase.* This activation occurs by adding two extra phosphate radicals to each nucleotide to form triphosphates (shown in **Figure 3-7** by the two RNA nucleotides to the far right during RNA chain formation). These last two phosphates are combined with the nucleotide by *high-energy phosphate bonds* derived from ATP in the cell.

The result of this activation process is that large quantities of ATP energy are made available to each of the nucleotides. This energy is used to promote the chemical reactions that add each new RNA nucleotide at the end of the developing RNA chain.

ASSEMBLY OF THE RNA CHAIN FROM ACTIVATED NUCLEOTIDES USING THE DNA STRAND AS A TEMPLATE—THE PROCESS OF TRANSCRIPTION

As shown in **Figure 3-7,** assembly of the RNA molecule is accomplished under the influence of an enzyme, *RNA polymerase.* This large protein enzyme has many functional properties necessary for formation of the RNA molecule. These properties are as follows:

1. In the DNA strand immediately ahead of the gene to be transcribed is a sequence of nucleotides called the *promoter.* The RNA polymerase has an appropriate complementary structure that recognizes this promoter and becomes attached to it, which is the essential step for initiating formation of the RNA molecule.
2. After the RNA polymerase attaches to the promoter, the polymerase causes unwinding of about two turns of the DNA helix and separation of the unwound portions of the two strands.
3. The polymerase then moves along the DNA strand, temporarily unwinding and separating the two DNA strands at each stage of its movement. As it moves along, at each stage it adds a new activated RNA nucleotide to the end of the newly forming RNA chain through the following steps:
   a. First, it causes a hydrogen bond to form between the end base of the DNA strand and the base of an RNA nucleotide in the nucleoplasm.
   b. Then, one at a time, the RNA polymerase breaks two of the three phosphate radicals away from each of these RNA nucleotides, liberating large amounts of energy from the broken high-energy phosphate bonds; this energy is used to cause

covalent linkage of the remaining phosphate on the nucleotide with the ribose on the end of the growing RNA chain.

c. When the RNA polymerase reaches the end of the DNA gene, it encounters a new sequence of DNA nucleotides called the *chain-terminating sequence,* which causes the polymerase and the newly formed RNA chain to break away from the DNA strand. The polymerase then can be used again and again to form still more new RNA chains.

d. As the new RNA strand is formed, its weak hydrogen bonds with the DNA template break away, because the DNA has a high affinity for rebonding with its own complementary DNA strand. Thus, the RNA chain is forced away from the DNA and is released into the nucleoplasm.

Thus, the code that is present in the DNA strand is eventually transmitted in *complementary* form to the RNA chain. The ribose nucleotide bases always combine with the deoxyribose bases in the following combinations:

DNA Base	RNA Base
guanine	cytosine
cytosine	guanine
adenine	uracil
thymine	adenine

There Are Several Different Types of RNA. As research on RNA has continued to advance, many different types of RNA have been discovered. Some types of RNA are involved in protein synthesis, whereas other types serve gene regulatory functions or are involved in post-transcriptional modification of RNA. The functions of some types of RNA, especially those that do not appear to code for proteins, are still mysterious. The following six types of RNA play independent and different roles in protein synthesis:

1. *Precursor messenger RNA* (pre-mRNA) is a large immature single strand of RNA that is processed in the nucleus to form mature messenger RNA (mRNA). The pre-RNA includes two different types of segments called *introns,* which are removed by a process called splicing, and *exons,* which are retained in the final mRNA.
2. *Small nuclear RNA* (snRNA) directs the splicing of pre-mRNA to form mRNA.
3. *Messenger RNA* (mRNA) carries the genetic code to the cytoplasm for controlling the type of protein formed.
4. *Transfer RNA* (tRNA) transports activated amino acids to the ribosomes to be used in assembling the protein molecule.
5. *Ribosomal RNA,* along with about 75 different proteins, forms *ribosomes,* the physical and chemical structures on which protein molecules are actually assembled.
6. *MicroRNA* (miRNA) are single-stranded RNA molecules of 21 to 23 nucleotides that can regulate gene transcription and translation.

MESSENGER RNA—THE CODONS

Messenger RNA molecules are long, single RNA strands that are suspended in the cytoplasm. These molecules are composed of several hundred to several thousand RNA nucleotides in unpaired strands, and they contain *codons* that are exactly complementary to the code triplets of the DNA genes. **Figure 3-8** shows a small segment of mRNA. Its codons are CCG, UCU, and GAA, which are the codons for the amino acids proline, serine, and glutamic acid. The transcription of these codons from the DNA molecule to the RNA molecule is shown in **Figure 3-7**.

RNA Codons for the Different Amino Acids. **Table 3-1** lists the RNA codons for the 22 common amino acids found in protein molecules. Note that most of the amino acids are represented by more than one codon; also, one codon represents the signal "start manufacturing the protein molecule," and three codons represent "stop manufacturing the protein molecule." In **Table 3-1**, these

Table 3-1 RNA Codons for Amino Acids and for Start and Stop

Amino Acid	RNA Codons					
Alanine	GCU	GCC	GCA	GCG		
Arginine	CGU	CGC	CGA	CGG	AGA	AGG
Asparagine	AAU	AAC				
Aspartic acid	GAU	GAC				
Cysteine	UGU	UGC				
Glutamic acid	GAA	GAG				
Glutamine	CAA	CAG				
Glycine	GGU	GGC	GGA	GGG		
Histidine	CAU	CAC				
Isoleucine	AUU	AUC	AUA			
Leucine	CUU	CUC	CUA	CUG	UUA	UUG
Lysine	AAA	AAG				
Methionine	AUG					
Phenylalanine	UUU	UUC				
Proline	CCU	CCC	CCA	CCG		
Serine	UCU	UCC	UCA	UCG	AGC	AGU
Threonine	ACU	ACC	ACA	ACG		
Tryptophan	UGG					
Tyrosine	UAU	UAC				
Valine	GUU	GUC	GUA	GUG		
Start (CI)	AUG					
Stop (CT)	UAA	UAG	UGA			

CI, chain-initiating; CT, chain-terminating.