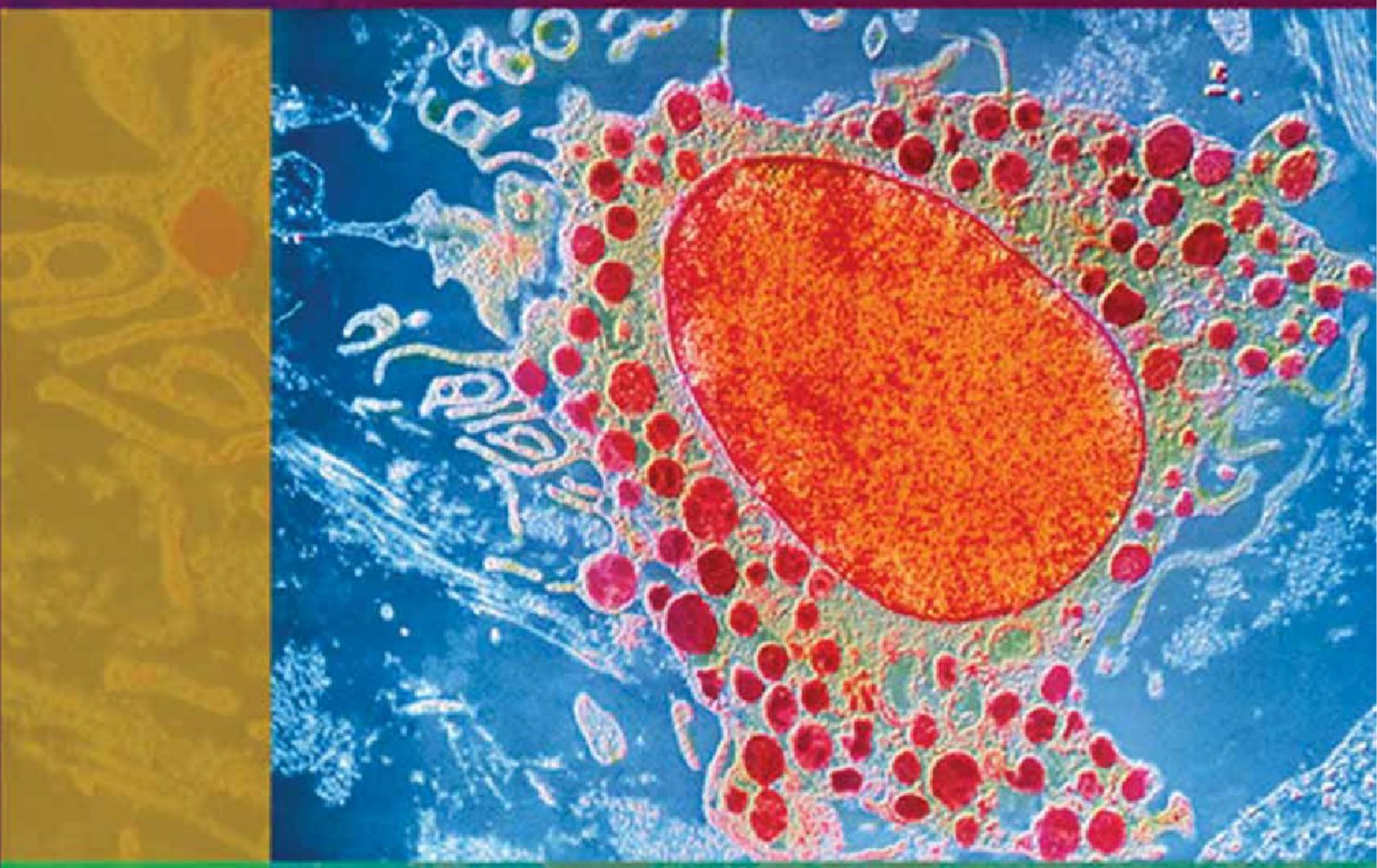
Essentials of Pathophysiology



FOURTH EDITION

Carol Mattson Porth

Wolters Kluwer

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Essentials of Pathophysiology

CONCEPTS OF ALTERED HEALTH STATES

Edition 4

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This book is dedicated to

All the Students who use the book, for it is for them that the book was written.

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Preface

As the 21st century unfolds, more information is available to more people at a faster pace than ever before. This ever-evolving ability to communicate has produced phenomenal advances in the ability to understand and treat disease. Yet despite these advances, we are also reminded that illness and disease continue to occur and impact the physiologic, social, psychological, and economic well-being of individuals, their families, the community, and the world.

As a nurse–physiologist, my major emphasis with this edition, as in previous editions, is to relate normal body functioning to the physiologic changes that participate in disease production and occur as a result of disease, as well as the body's remarkable ability to compensate for these changes. The beauty of physiology is that it integrates all of the aspects of human genetics, molecular and cellular biology, and organ anatomy and physiology into a functional whole that can be used to explain both the physical and psychological aspects of altered health. Indeed, it has been my philosophy to share the beauty of the human body and to emphasize that in disease, as in health, there is more "going right" in the body than is "going wrong."

With the creation of this text, I focused on presenting information that is fundamental to understanding the physiologic processes of altered health states; information that necessary to support an understanding pathophysiology. One of the strengths of *Essentials of Pathophysiology* is that it is a book to grow with. Although intended as a course textbook for students, it is also designed to serve as a reference book that students can take with them and use in their practice once the course is finished.

Updated to reflect state-of-the-art science, content remains organized in a manner that is logical, understandable, and draws readers into the wonders of the human body. Concepts build on one another, with concepts from physiology, biochemistry, physics, and other sciences reviewed as deemed appropriate. A conceptual model that integrates the developmental and preventative aspects of health has been used. Selection of content was based on common health problems, including the special needs of children, pregnant women, and elderly persons. The fourth edition expands the art program, increasing the number of photographs depicting clinical manifestations of selected disorders while also providing more than 500 full-color illustrations, many created specifically to supplement and expand the concepts presented.

Newly created Summary Concepts follow each section and provide a review of material that focuses on integrating and linking concepts rather than fostering rote memorization. Once again, the "Understanding" feature depicts physiologic processes and phenomena, breaking them down into an easy-to-follow sequence for easier learning. "Clinical Features" are illustrations that depict the clinical features of persons with selected diseases. As with other types of illustrations in this edition, they are designed to help the reader develop a visual memory—in this case, the memory of the entire spectrum of clinical manifestations that are associated with a disease state.

Review exercises appear at the end of each chapter and assist the reader in using the conceptual approach to solving problems related to chapter content. The glossary defines the specialized terms of pathophysiology. Tables of normal laboratory values provide a handy reference of conventional and SI units, as well as conversion units.

As with previous editions, every effort has been taken to make the text as accurate and up to date as possible. This was accomplished through an extensive review of the literature and through the use of critiques provided by students, faculty, and content specialists. This book is an extension of my career and, as such, of my philosophy. It is my hope that readers will learn to appreciate the marvelous potential of the body, incorporating it into their own philosophy and ultimately sharing it with their clients.

Carol Mattson Porth

A Comprehensive Package for Teaching and Learning

To further facilitate teaching and learning, a carefully designed ancillary package has been developed to assist faculty and students.

Instructor Resources

Tools to assist you with teaching your course are available upon adoption of this text at http://thePoint.lww.com/PorthEssentials4e.

- A thoroughly revised and augmented **Test Generator** contains more than 1,100 NCLEX-style questions mapped to chapter learning objectives.
- An extensive collection of materials is provided for each book chapter:
  - **Pre-Lecture Quizzes** (and answers) allow you to check students' reading.
- **PowerPoint Presentations** provide an easy way to integrate the textbook with your students' classroom experience; multiple-choice questions are included to promote class participation.
- **Guided Lecture Notes** offer corresponding PowerPoint slide numbers to simplify preparation for lecture.
- **Discussion Topics** (and suggested answers) can be used in the classroom or in online discussion boards to facilitate interaction with your students.

- **Assignments** (and suggested answers) include group, written, clinical, and Web assignments to engage students in varied activities and assess their learning.
- **Case Studies** with related questions (and suggested answers) give students an opportunity to apply their knowledge to a client case similar to one they might encounter in practice.

- A **QSEN Competency Map** identifies content and special features in the book related to competencies identified by the QSEN Institute.
- An **Image Bank** lets you use the photographs and illustrations from this textbook in your course materials.
- **Strategies for Effective Teaching** provide general tips for instructors related to preparing course materials and meeting student needs.
- Access to all **Student Resources** is provided so that you can understand the student experience and use these resources in your course as well.

Student Resources

An exciting set of free learning resources is available to help students review and apply vital concepts of pathophysiology. For the fourth edition, multimedia engines have been optimized so that students can access many of these resources on mobile devices. Students can activate the codes printed in the front of their textbooks at http://thePoint.lww.com/activate to access these resources:

- **Student Review Questions** for each chapter, totaling more than 900 questions, help students review important concepts and practice for certification examinations.
- Interactive learning resources appeal to a variety of learning styles. Icons in the text direct readers to relevant resources:
  - **Concepts in Action Animations** bring physiologic and pathophysiologic concepts to life.
  - Interactive **Clinical Simulation Case Studies** present case scenarios and offer interactive exercises and questions to help students apply what they have learned.
- A **Spanish–English Audio Glossary** provides helpful terms and phrases for communicating with patients who speak Spanish.
- **Journal articles** offer access to current articles relevant to each chapter and available in Lippincott Williams & Wilkins journals to familiarize students with health care literature.

Study Guide

A comprehensive study aid for reviewing key concepts, Study Guide for Porth's Essentials of Pathophysiology, **4th edition**, has been thoroughly revised and presents a variety of exercises, including case studies and practice NCLEX-style questions, to reinforce textbook content and enhance learning.

Adaptive Learning | Powered by PrepU

Updated to accompany the 4th edition, Lippincott Adaptive Learning | Powered by PrepU helps every student learn more, while giving instructors the data they need to monitor each student's progress, strengths, and weaknesses. The adaptive learning system allows instructors to assign quizzes or students to take quizzes on their own—quizzes that adapt to each student's individual mastery level. Visit at http://thePoint.lww.com/PrepU to learn more.

A Comprehensive, Digital, Integrated Course Solution

Lippincott CoursePoint is the only integrated digital course solution for health care education, combining the power of digital course content, interactive resources, and Adaptive Learning | Powered by PrepU. Pulling these resources together into one solution, the integrated product offers a seamless experience for learning, studying, applying, and remediating.

Lippincott CoursePoint provides a personalized learning experience that is structured in the way students study. It drives students to immediate remediation in their text; digital course content and interactive course resources like case studies, videos, and journal articles are also immediately available in the same digitally integrated course solution to help expand on concepts and bring them to life. After students complete an adaptive, formative assessment on the reading, the results identify students' specific weaknesses and, at the moment it's identified they don't understand the material, they can immediately remediate to that content. Instructors also have a powerful and measurable way to assess their students' understanding and to help engage them in the course content. Knowing where students are struggling allows instructors to adapt class time as appropriate.

Lippincott CoursePoint can bring Adaptive Learning | Powered by PrepU and digital resources together on the same platform to provide all of the aids that students need to study more effectively, score higher on exams, and prepare for clinical practice. The SmartSense links feature included throughout CoursePoint integrates all of the content, offering immediate remediation and additional learning resources at the click of a mouse. With Lippincott CoursePoint, instructors can collaborate with students at any time, identify common misunderstandings, evaluate student comprehension, and differentiate instruction as needed. This unique offering creates an unparalleled learning experience for students because they can learn and retain course material in an adaptive, personalized way.

Contact your Wolters Kluwer Health sales representative or visit http://thePoint.lww.com/coursepoint-porthessentials4e for more information about Lippincott CoursePoint solution.

It is with pleasure that we introduce these resources—the textbook, ancillary resources, and additional

supplements and learning tools—to you. One of our primary goals in creating these resources has been to help students learn how to provide quality care to patients and families across health care settings. We hope that we have succeeded in that goal, and we welcome feedback from our readers.

To the Reader

This book was written with the intent of making the subject of pathophysiology an exciting exploration that relates normal body functioning to the physiologic changes that occur as a result of disease, as well as the body's remarkable ability to compensate for these changes. Indeed, it is these changes that represent many of the signs and symptoms of disease.

Using a book such as this can be simplified by taking time out to find what is in the book and how to locate information when it is needed. The *Table of Contents* provides an overall view of the organization and content of the book. The *Index* can be viewed as a roadmap for locating content. Using the Index, readers can quickly locate related content in different chapters of the book or answer questions that come up in other courses.

Organization

The book is organized into units and chapters. The *units* identify broad areas of content, such as alterations in the circulatory system. Many of the units have *introductory chapters* that contain information about the normal structure and function of the body systems discussed in the unit. These chapters, which are intended as a review of content from previous courses as well as an update on recent scientific advances in genetic and molecular biology, provide the foundation for understanding the pathophysiology content presented in the subsequent chapters. The *disorder chapters* focus on specific areas of pathophysiology content, such as heart failure and circulatory shock. The *chapter outline* that appears at the beginning of each chapter provides an overall view of the chapter content and organization. *Icons* identify specific content related to infants and children  , pregnant women  , and older adults  .

Reading and Learning Aids

In an ever-expanding world of information, you will not be able to read, let alone remember, everything that is in this (or any other) book. With this in mind, we have developed a number of special features that will help you focus on and master the essential content for your current as well as future needs.

It is essential for any professional to use and understand the vocabulary of his or her profession. Throughout the text, you will encounter terms in *italics*. This is a signal that a word and the ideas associated with it are important to learn. To help, the *Glossary* contains concise definitions of frequently encountered terms. If you are unsure of the meaning of a term you encounter in your reading, check the Glossary in the back of the book before proceeding.

Summary Concepts

Summary concepts at the end of each section provide a review and a reinforcement of the main content that has been covered. One of the ways to approach learning is to focus on the major ideas or concepts rather than trying to memorize significant amounts of information. As you have probably already discovered, it is impossible to memorize everything that is in a particular section or chapter of the book. Not only does your brain have a difficult time trying to figure out where to store all the different bits of information, your brain doesn't know how to retrieve the information when you need it. Most important of all, memorized lists of content can seldom, if ever, be applied directly to an actual clinical situation. Summary concepts guide you in identifying the major ideas or concepts that form the foundation for truly understanding the major areas of content. When you understand the concepts in these sections, you will have a framework for remembering and using the facts given in the text.

SUMMARY CONCEPTS

- Chromosomal disorders result from a change in chromosome structure or number. They reflect events that occur at the time of meiosis, such as defective movement of an entire chromosome or breakage of a chromosome with loss, gain, or translocation of genetic material.
- A change in chromosome number is called *aneuploidy*. *Monosomy* involves the presence of only one member of a chromosome pair as is seen in Turner syndrome, in which there is monosomy of the X chromosome in females. *Polysomy* refers to the presence of more than two chromosomes in a set, as occurs in Klinefelter syndrome, which involves polysomy of the X chromosome in males. Trisomy 21 (i.e., Down syndrome) is the most common disorder of the autosomal chromosomes, and occurs in both sexes.

Tables, Charts, and Boxes

Tables, charts, and *boxes* are designed to present complex information in a format that makes it more meaningful and easier to remember. Tables have two or more

columns, and are often used for the purpose of comparing or contrasting information. Charts have one column and are used to summarize information. Boxes highlight key information.

TABLE 6-2 Some Disorders of Organ Systems Associated with Mitochondrial DNA Mutations

Disorder	Manifestations
Chronic progressive external ophthalmoplegia	Progressive weakness of the extraocular muscles
Deafness	Progressive sensorineural deafness, often associated with aminoglycoside antibiotics
Kearns-Sayre syndrome	Progressive weakness of the extraocular muscles of early onset with heart block, retinal pigmentation
Leber hereditary optic neuropathy	Painless, subacute, bilateral visual loss, with central blind spots (scotomas) and abnormal color vision
Leigh disease	Proximal muscle weakness, sensory neuropathy, developmental delay, ataxia, seizures, dementia, and visual impairment due to retinal pigment degeneration
MELAS	Mitochondrial Encephalomyopathy (cerebral structural changes), Lactic Acidosis, and Strokelike syndrome, seizures, and other clinical and laboratory abnormalities; may manifest only as diabetes mellitus
Myoclonic epilepsy with ragged red fibers	Myoclonic Epilepsy, Ragged Red Fibers in muscle; ataxia; sensorineural deafness
	Myoclonic seizures, cerebellar ataxia, mitochondrial myopathy (muscle weakness, fatigue)

CHART 6-1 Teratogenic Agents*

Radiation

Drugs and Chemical Substances
- Alcohol
- Anticoagulants
  - Warfarin
- Anticonvulsants
- Cancer drugs
  - Aminopterin
  - Methotrexate
  - 6-Mercaptopurine
- Isotretinoin (Accutane)
- Propylthiouracil
- Tetracycline
- Thalidomide

Infectious Agents

Viruses
- Cytomegalovirus
- Herpes simplex virus
- Measles (rubella)
- Mumps
- Varicella-zoster virus (chickenpox)

Nonviral factors
- Syphilis
- Toxoplasmosis

*Not inclusive.

BOX 8-1 Measurement Units

Laboratory measurements of electrolytes in body fluids are expressed as a concentration or amount of solute in a given volume of fluid, such as milligrams per deciliter (mg/dL), milliequivalents per liter (mEq/L), or millimoles per liter (mmol/L).

The use of *milligrams (mg) per deciliter* expresses the weight of the solute in one tenth of a liter (dL). The concentration of electrolytes such as calcium, phosphate, and magnesium is often expressed in mg/dL.

The *milliequivalent* is used to express the charge equivalency for a given weight of an electrolyte: 1 mEq of sodium has the same number of charges as 1 mEq of chloride, regardless of molecular weight. The number of milliequivalents of an electrolyte in a liter of solution can be derived from the following equation:

$$\text{mEq} = \frac{\text{mg/100 mL} \times 10 \times \text{valence}}{\text{atomic weight}}$$

The Système Internationale (SI) units express electrolyte concentration in *millimoles per liter* (mmol/L). A millimole is one thousandth of a mole, or the molecular weight of a substance expressed in milligrams. The number of millimoles of an electrolyte in a liter of solution can be calculated using the following equation:

$$\text{mmol/L} = \frac{\text{mEq/L}}{\text{valence}}$$

Illustrations and Photographs

The full-color *illustrations* will help you to build your own mental image of the content that is being presented. Each drawing has been developed to fully support and build upon the ideas in the text. Some illustrations are used to help you picture the complex interactions of the multiple phenomena that are involved in the development of a particular disease; others can help you visualize normal function or understand the mechanisms whereby the disease processes exert their effects. In addition, *photographs* depicting clinical manifestations and detailing pathologic processes provide a realistic view of selected disorders and pathologic processes.

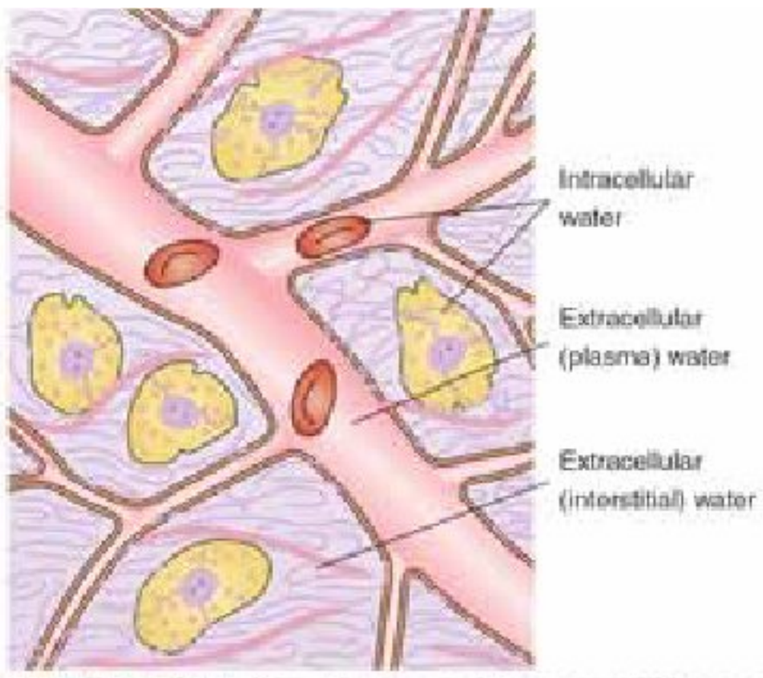


FIGURE 8-1. Distribution of body water. The extracellular space includes the vascular compartment and the interstitial spaces.

Clinical Features

This edition retains the illustrations that depict the *clinical features* of persons with selected diseases. This feature is designed to help you visualize the entire spectrum of clinical manifestations that are associated with these disease states.

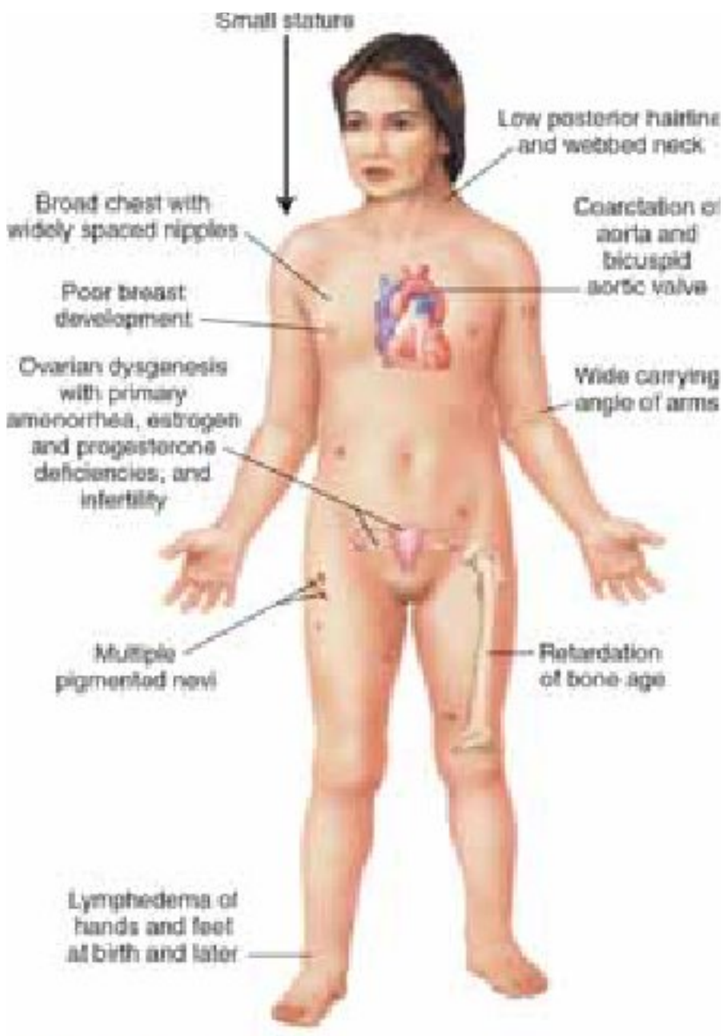
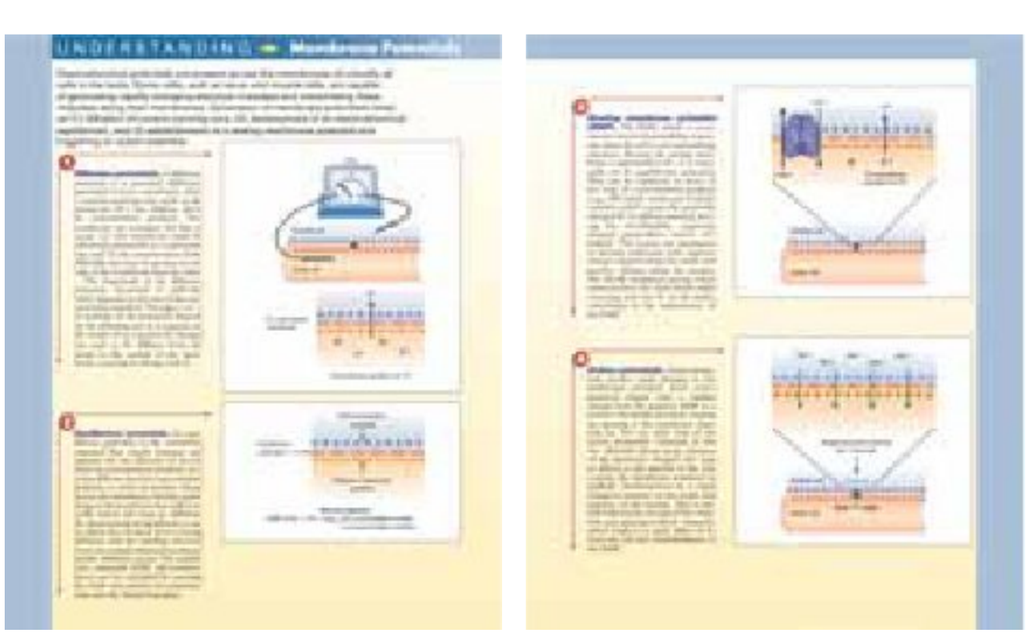


FIGURE 6-11. Clinical features of Turner syndrome.

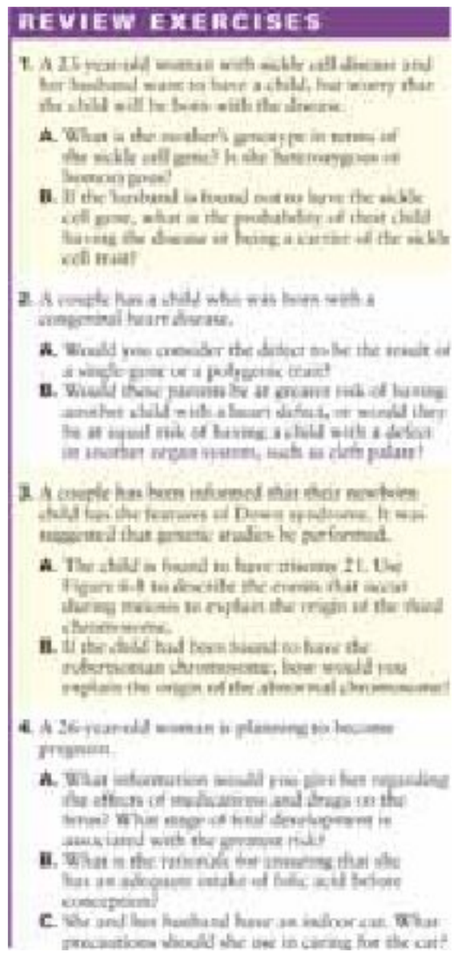
Understanding Physiologic Processes

Included in a number of chapters is an *Understanding* feature that focuses on the physiologic processes and phenomena that form the basis for understanding disorders presented in the text. This feature breaks a process or phenomenon down to its component parts and presents them in a sequential manner, providing an insight into the many opportunities for disease processes to disrupt the sequence.



Material for Review

An important feature has been built into the text to help you verify your understanding of the material presented. After you have finished reading and studying the chapter, work on answering the *Review Exercises* at the end of the chapter. They are designed to help you integrate, conceptualize, and apply material from the text. If you are unable to answer a question, reread the relevant section in the chapter.



Appendix

The *Lab Values* tables in the appendix provide rapid access to normal values for many laboratory tests in conventional and SI units, as well as a description of the prefixes, symbols, and factors (e.g., micro, μ, 10^{-6}) used for describing these values. Knowledge of normal values can help you put abnormal values in context.

We hope that this guide has given you a clear picture of how to use this book. Good luck and enjoy the journey!

Acknowledgments

As in past editions, many persons participated in the creation of this work. The contributing authors deserve a special mention. Dr. Gaspard, in particular, deserves thanks. Her wide breadth of knowledge and skillful assistance were invaluable in preparing the text and developing the illustrations for the book. Another person who deserves recognition is Georgianne Heymann, who assisted in editing the manuscript. As with previous editions, she provided not only excellent editorial assistance but also encouragement and support when the tasks associated with manuscript preparation became most frustrating. I would also like to acknowledge Jody Erickson, RN, BSN, DNP, FNP, BC for her assistance with selected work in the text.

Special thanks also to those at Wolters Kluwer Health who participated in the development of this edition: Sherry Dickinson, executive editor; Dawn Lagrosa, associate product development editor; Joan Wendt, design coordinator; and Marian Bellus, production project manager. Thanks also to Wendy Beth Jackelow, MFA, CMI, for her talent and expertise in creating and modifying the illustrations.

The students in the classes I have taught over the years also deserve a special salute, for they are the inspiration upon which this book was founded. They provided the questions, suggestions, and contact with the "real world" of patient care that directed the organization and selection of content for the book.

Last, but certainly not least, I would like to acknowledge my family and friends for their unlimited patience, understanding, and encouragement throughout the entire process.

Contents

Introduction to Pathophysiology

Pathophysiology, which is the focus of this book, may be defined as the physiology of altered health. The term combines the words *pathology* and *physiology*. Pathology (from the Greek *pathos*, meaning "disease") deals with the study of the structural and functional changes in cells, tissues, and organs of the body that cause or are caused by disease. Physiology deals with the functions of the human body. Thus, pathophysiology deals not only with the cellular and organ changes that occur with disease, but also with the effects that these changes have on total body function. In addition, pathophysiology focuses on the mechanisms of the underlying disease process and provides the background for preventive as well as therapeutic health care measures and practices.

Disease

Disease may be defined as an interruption, cessation, or disorder of a body system or organ structure that is characterized usually by a recognized etiologic agent or agents, an identifiable group of signs and symptoms, or consistent anatomic alterations.[1] The aspects of the disease process include etiology, pathogenesis, morphologic changes, and clinical manifestations.

Etiology

The causes of disease are known as *etiologic factors*.[2] Among the recognized etiologic agents are biologic agents (e.g., bacteria, viruses), physical forces (e.g., trauma, burns, radiation), chemical agents (e.g., poisons, alcohol), and nutritional excesses or deficits. At the molecular level, it is important to distinguish between abnormal molecules and molecules that cause disease.[3] This is true of diseases such as cystic fibrosis, sickle cell anemia, and familial hypercholesterolemia, in which the genetic abnormality of a single amino acid, transporter molecule, or receptor protein produces widespread effects on health.

Most disease-causing agents are nonspecific, and many different agents can cause disease of a single organ. A single agent or traumatic event can, however, lead to disease of a number of organs or systems. Although a disease-causing agent can affect more than a single organ and a number of disease-causing agents can affect the same organ, most disease states do not have a single cause. Instead, the majority of diseases are multifactorial in origin. This is particularly true of diseases such as cancer, heart disease, and diabetes. The multiple factors that predispose to a particular disease often are referred to as *risk factors*.[4]

One way to view the factors that cause disease is to group them into categories according to whether they were present at birth or acquired later in life. *Congenital conditions* are defects that are present at birth, although they may not be evident until later in life. Congenital conditions may be caused by genetic influences, environmental factors (e.g., viral infections in the mother, maternal drug use, irradiation, or intrauterine crowding), or a combination of genetic and environmental factors. *Acquired defects* are those that are caused by events that occur after birth. These include injury, exposure to infectious agents, inadequate nutrition, lack of oxygen, inappropriate immune responses, and neoplasia. Many diseases are thought to be the result of a genetic predisposition and an environmental event or events that serve as a trigger to initiate disease development.

Pathogenesis

Pathogenesis is the sequence of cellular and tissue events that take place from the time of initial contact with an etiologic agent until the ultimate expression of a disease.[2] Etiology describes what sets the disease process in motion, while pathogenesis describes how the disease process evolves. Although the two terms often are used interchangeably, their meanings are quite different. For example, atherosclerosis often is cited as the cause or etiology of coronary heart disease. In reality, the progression from fatty streak to the occlusive vessel lesion seen in persons with coronary heart disease represents the pathogenesis of the disorder. The true etiology of atherosclerosis remains largely uncertain.

Morphology

Morphology refers to the fundamental structure or form of cells or tissues. *Morphologic changes* are concerned with both the gross anatomic and microscopic changes that are characteristic of a disease.[2] *Histology* deals with the study of the cells and extracellular matrix of body tissues. The most common method used in the study of tissues is the preparation of histologic sections—thin, translucent sections of human tissues and organs—that can be examined with the aid of a microscope. Histologic sections play an important role in the diagnosis of many types of cancer. A *lesion* represents a pathologic or traumatic discontinuity of a body organ or tissue. Descriptions of lesion size and characteristics often can be obtained through the use of radiographs, ultrasonography, and other imaging methods. Lesions also may be sampled by biopsy and the tissue samples subjected to histologic study.

Clinical Manifestations

Diseases can manifest in a number of ways. Sometimes the condition produces manifestations, such as fever, that make it evident that the person is sick. In other cases, the condition is silent at the onset and is detected during examination for other purposes or after the disease is far advanced.

Signs and *symptoms* are terms used to describe the structural and functional changes that accompany a disease.[3] A *symptom* is a subjective complaint that is noted

by the person with a disorder, whereas a *sign* is a manifestation that is noted by an observer. Pain, difficulty in breathing, and dizziness are symptoms of a disease. An elevated temperature, a swollen extremity, and changes in pupil size are objective signs that can be observed by someone other than the person with the disease. Signs and symptoms may be related to the primary disorder or they may represent the body's attempt to compensate for the altered function caused by the pathologic condition. Many pathologic states are not observed directly—one cannot see a sick heart or a failing kidney. Instead, what can be observed is the body's attempt to compensate for changes in function brought about by the disease, such as the tachycardia that accompanies blood loss or the increased respiratory rate that occurs with pneumonia.

A *syndrome* is a compilation of signs and symptoms (e.g., chronic fatigue syndrome) that are characteristic of a specific disease state. *Complications* are possible adverse extensions of a disease or outcomes from treatment. *Sequelae* are lesions or impairments that follow or are caused by a disease.

Diagnosis

A *diagnosis* is the designation as to the nature or cause of a health problem (e.g., bacterial pneumonia or hemorrhagic stroke). The diagnostic process usually requires a careful history and physical examination. The history is used to obtain a person's account of his or her symptoms and their progression, and the factors that contribute to a diagnosis. The physical examination is done to observe for signs of altered body structure or function.

The development of a diagnosis involves weighing competing possibilities and selecting the most likely one from among the conditions that might be responsible for the person's clinical presentation.[4] The clinical probability of a given disease in a person of a given age, gender, race, lifestyle, and locality often is influential in arriving at a presumptive diagnosis. Laboratory tests, radiologic studies, computed tomography (CT) scans, and other tests often are used to confirm a diagnosis.

An important factor when interpreting diagnostic test results is the determination of whether they are normal or abnormal. Is a blood count above normal, within the normal range, or below normal? What is termed a *normal* value for a laboratory test is established statistically from test results obtained from a selected sample of people. The normal values refer to the 95% distribution (mean plus or minus two standard deviations [mean ± 2 SD]) of test results for the reference population.[4–6] Thus, the normal levels for serum sodium (136 to 145 mEq/L) represent the mean serum level for the reference population ± 2 SD. The normal values for some laboratory tests are adjusted for sex or age. For example, the normal hemoglobin range for women is 12.0 to 16.0 g/dL, and for men, 14.0 to 17.4 g/dL.[7] Serum creatinine levels often are adjusted for age in the elderly, and normal values for serum phosphate differ between adults and children.

The quality of data on which a diagnosis is based may be judged for their validity, reliability, sensitivity, specificity, and predictive value.[4,7,8] *Validity* refers to the extent to which a measurement tool measures what it is intended to measure. This often is assessed by comparing a measurement method with the best possible method of measure that is available. For example, the validity of blood pressure measurements obtained by a sphygmomanometer might be compared with those obtained by intra-arterial measurements. *Reliability* refers to the extent to which an observation, if repeated, gives the same result. A poorly calibrated blood pressure machine may give inconsistent measurements of blood pressure, particularly of pressures in either the high or low range. Reliability also depends on the persons making the measurements. For example, blood pressure measurements may vary from one observer to another because of the technique used (e.g., different observers may deflate the cuff at a different rate, thus obtaining different values), the way the numbers on the manometer are read, or differences in hearing acuity.

In the field of clinical laboratory measurements, *standardization* is aimed at increasing the trueness and reliability of measured values. Standardization relies on the use of written standards, reference measurement procedures, and reference materials.[9] In the United States, the Food and Drug Administration (FDA) regulates in vitro diagnostic devices, including clinical laboratory instruments, test kits, and reagents. Manufacturers who propose to market new diagnostic devices must submit information on their instrument, test kit, or reagent to the FDA, as required by existing statutes and regulations. The FDA reviews this information to decide whether the product may be marketed in the United States.

Measures of sensitivity and specificity are concerned with determining how likely or how well the test or observation will identify people with or without the disease.[4] *Sensitivity* refers to the proportion of people with a disease who are positive for that disease on a given test or observation (called a *true-positive* result). If the result of a very sensitive test is negative, it tells us the person does not have the disease and the disease has been excluded or "ruled out." *Specificity* refers to the proportion of people without the disease who are negative on a given test or observation (called a *true-negative* result). Specificity can be calculated only from among people who do not have the disease. A test that is 95% specific correctly identifies 95 of 100 normal people. The other 5% are *false-positive* results. A false-positive test result can be unduly stressful for the person being tested, whereas a *false-negative* test result can delay diagnosis and jeopardize the outcome of treatment.

Predictive value is the extent to which an observation or test result is able to predict the presence of a given disease or condition.[4,10] A *positive predictive value* refers to the proportion of true-positive results that occurs in a given population. In a group of women found to have "suspect breast nodules" in a cancer screening program, the proportion later determined to have breast cancer would constitute the positive predictive value. A *negative predictive value* refers to the true-negative observations in a population. In a screening test for breast cancer, the negative predictive value represents the proportion of women without suspect nodules who do not

have breast cancer. Although predictive values rely in part on sensitivity and specificity, they depend more heavily on the prevalence of the condition in the population. Despite unchanging sensitivity and specificity, the positive predictive value of an observation rises with prevalence, whereas the negative predictive value falls.

Clinical Course

The clinical course describes the evolution of a disease. A disease can have an acute, subacute, or chronic course. An *acute disorder* is one that is relatively severe, but self-limiting. *Chronic disease* implies a continuous, long-term process. A chronic disease can run a continuous course or can present with exacerbations (aggravation of symptoms and severity of the disease) and remissions (a period during which there is a decrease in severity and symptoms). *Subacute disease* is intermediate or between acute and chronic: it is not as severe as an acute disease and not as prolonged as a chronic disease.

The spectrum of disease severity for infectious diseases, such as hepatitis B, can range from preclinical to persistent chronic infection. During the *preclinical stage*, the disease is not clinically evident but is destined to progress to clinical disease. As with hepatitis B, it is possible to transmit a virus during the preclinical stage. *Subclinical disease* is not clinically apparent and is not destined to become clinically apparent. It is diagnosed with antibody or culture tests. Most cases of tuberculosis are not clinically apparent, and evidence of their presence is established by skin tests. *Clinical disease* is manifested by signs and symptoms. A persistent chronic infectious disease persists for years—sometimes for life. *Carrier status* refers to an individual who harbors an organism but is not infected, as evidenced by antibody response or clinical manifestations. This person still can infect others. Carrier status may be of limited duration or it may be chronic, lasting for months or years.

Perspectives and Patterns of Disease

The health of individuals is closely linked to the health of the community and to the population it encompasses. The ability to traverse continents in a matter of hours has opened the world to issues of populations at a global level. Diseases that once were confined to limited areas of the world now pose a threat to populations throughout the world.

As we move through the 21st century, we are continually reminded that the health care system and the services it delivers are targeted to particular populations. Managed care systems are focused on a population-based approach to planning, delivering, providing, and evaluating health care. The focus of health care also has begun to emerge as a partnership in which individuals are asked to assume greater responsibility for their own health.

Epidemiology and Patterns of Disease

Epidemiology is the study of disease occurrence in human populations.[4] It was initially developed to explain the spread of infectious diseases during epidemics and has emerged as a science to study risk factors for multifactorial diseases, such as heart disease and cancer. Epidemiology looks for patterns, such as age, race, dietary habits, lifestyle, or geographic location, of persons affected with a particular disorder. In contrast to biomedical researchers, who seek to elucidate the mechanisms of disease production, epidemiologists are more concerned with whether something happens than how it happens. For example, the epidemiologist is more concerned with whether smoking itself is related to cardiovascular disease and whether the risk of heart disease decreases when smoking ceases. The biomedical researcher, however, is more concerned about the causative agent in cigarette smoke and the pathway by which it contributes to heart disease.

Much of our knowledge about disease comes from epidemiologic studies. Epidemiologic methods are used to determine how a disease is spread, how to control it, how to prevent it, and how to eliminate it. Epidemiologic methods also are used to study the natural history of disease, to evaluate new preventative and treatment strategies, to explore the impact of different patterns of health care delivery, and to predict future health care needs. As such, epidemiologic studies serve as a basis for clinical decision making, allocation of health care dollars, and development of policies related to public health issues.

Measures of disease frequency are an important aspect of epidemiology. They establish a means for predicting what diseases are present in a population and provide an indication of the rate at which they are increasing or decreasing. A *disease case* can be either an existing case or the number of new episodes of a particular illness that are diagnosed within a given period. *Incidence* reflects the number of new cases arising in a population at risk during a specified time. The population at risk is considered to be persons who are without the disease but are at risk for developing it. It is determined by dividing the number of new cases of a disease by the population at risk for development of the disease during the same period (e.g., new cases per 1000 or 100,000 persons in the population who are at risk). The cumulative incidence estimates the risk of developing the disease during that period of time. *Prevalence* is a measure of existing disease in a population at a given point in time (e.g., number of existing cases divided by the current population).[9] The prevalence is not an estimate of risk of developing a disease because it is a function of both new cases and how long the cases remain in the population. Incidence and prevalence are always reported as rates (e.g., cases per 100 or cases per 100,000).

Morbidity and mortality statistics provide information about the functional effects (morbidity) and death-producing (mortality) characteristics of a disease. These statistics are useful in terms of anticipating health care needs, planning of public education programs, directing health research efforts, and allocating health care dollars.

Mortality statistics provide information about the causes of death in a given population. In most countries, people are legally required to record certain facts such as age, sex, and cause of death on a death certificate.

Internationally agreed-upon classification procedures (the International Classification of Diseases [ICD] by the World Health Organization) are used for coding the cause of death, and these data are expressed as death rates.[11] Crude mortality rates (i.e., number of deaths in a given period) do not account for age, sex, race, socioeconomic status, and other factors. For this reason, mortality often is expressed as death rates for a specific population, such as the infant mortality rate. Mortality also can be described in terms of the leading causes of death according to age, sex, race, and ethnicity.

Morbidity describes the effects an illness has on a person's life. Many diseases, such as arthritis, have low death rates but a significant impact on quality of life. Morbidity is concerned not only with the occurrence or incidence of a disease but also the persistence and long-term consequences of the disease.

Determination of Risk Factors

Conditions suspected of contributing to the development of a disease are called *risk factors*. They may be inherent to the person (high blood pressure or overweight) or external (smoking or drinking alcohol). There are different types of studies used to determine risk factors, including cross-sectional studies, case–control studies, and cohort studies. *Cross-sectional studies* use the simultaneous collection of information necessary for classification of exposure and outcome status. They can be used to compare the prevalence of a disease in those with the factor (or exposure) with the prevalence of a disease in those who are unexposed to the factor, such as the prevalence of coronary heart disease in smokers and nonsmokers. *Case–control studies* are designed to compare persons known to have the outcome of interest (*cases*) with those known not to have the outcome of interest (*controls*).[4] Information on exposures or characteristics of interest is then collected from persons in both groups. For example, the characteristics of maternal alcohol consumption in infants born with a fetal alcohol spectrum disorder (cases) can be compared with those in infants born without one of these disorders (controls).

A *cohort* is a group of persons who were born at approximately the same time or share some characteristics of interest.[4] Persons enrolled in a cohort study (also called a *longitudinal study*) are followed over a period of time to observe a specific health outcome. A cohort may consist of a single group of persons chosen because they have or have not been exposed to suspected risk factors; two groups specifically selected because one has been exposed and the other has not; or a single exposed group in which the results are compared with the general population.

One of the best-known examples of a cohort study is the Framingham Study, which was carried out in Framingham, Massachusetts.[12] Framingham was selected because of the size of its population, the relative ease with which the people could be contacted, and the stability of the population in terms of moving into and out of the area. This longitudinal study, which began in 1950, was set up by the U.S. Public Health Service to study the characteristics of people who would later develop coronary heart disease. The study consisted of 5000 persons, aged 30 to 59 years, selected at random and followed for an initial period of 20 years, during which time it was predicted that 1500 of them would develop coronary heart disease. The advantage of such a study is that it can explore a number of risk factors at the same time and determine the relative importance of each. Another advantage is that the risk factors can later be related to other diseases, such as stroke.

A second well-known cohort study is the Nurses' Health Study, which was developed by Harvard University and Brigham and Women's Hospital. The study began in 1976 with a cohort of 121,700 female nurses, 30 to 55 years of age, living in the United States.[13] Initially designed to explore the relationship between oral contraceptives and breast cancer, nurses in the study have provided answers to detailed questions about their menstrual cycle, smoking habits, diet, weight and waist measurements, activity patterns, health problems, and medication use. They have given urine and blood samples, and even provided researchers with their toenail clippings. In selecting the cohort, it was reasoned that nurses would be well-organized, accurate, and observant in their responses, and that physiologically they would be no different from other groups of women. It also was anticipated that their childbearing, eating, and smoking patterns would be similar to those of other working women.

Natural History

The *natural history* of a disease refers to the progression and projected outcome of the disease without medical intervention.[4] By studying the patterns of a disease over time in populations, epidemiologists can better understand its natural history. Knowledge of the natural history can be used to determine disease outcome, establish priorities for health care services, determine the effects of screening and early detection programs on disease outcome, and compare the results of new treatments with the expected outcome without treatment.

There are some diseases for which there are no effective treatment methods available, or for which the current treatment measures are only effective in certain people. In this case, the natural history of the disease can be used as a predictor of outcome. For example, the natural history of hepatitis C indicates that 80% of people who become infected with the virus fail to clear the virus and progress to chronic infection.[14] Information about the natural history of a disease and the availability of effective treatment methods provides directions for preventive measures. In the case of hepatitis C, careful screening of blood donations and education of intravenous drug abusers can be used to prevent transfer of the virus. At the same time, scientists are striving to develop a vaccine that will prevent infection in persons exposed to the virus. The development of vaccines to prevent the spread of infectious diseases such as polio and hepatitis B undoubtedly has been motivated by knowledge about

the natural history of these diseases and the lack of effective intervention measures. With other diseases, such as breast cancer, early detection through use of clinical breast examination and mammography increases the chances for a cure.

Prognosis refers to the probable outcome and prospect of recovery from a disease. It can be designated as chances for full recovery, possibility of complications, or anticipated survival time. Prognosis often is presented in relation to treatment options—that is, the expected outcomes or chances for survival with or without a certain type of treatment. The prognosis associated with a given type of treatment usually is presented along with the risk associated with the treatment.

Levels of Prevention

Leading a healthy life contributes to the prevention of disease. There are three fundamental types of prevention: primary prevention, secondary prevention, and tertiary prevention.[4,15] It is important to note that all three levels are aimed at prevention. *Primary prevention* is directed at keeping disease from occurring by removing all risk factors. Examples of primary prevention include the administration of folic acid to pregnant women and women who may become pregnant to prevent fetal neural tube defects, giving immunizations to children to prevent communicable disease, and counseling people to adopt healthy lifestyles as a means of preventing heart disease. Primary prevention is often accomplished outside the health care system at the community level. Some primary prevention measures are mandated by law (e.g., wearing seat belts in automobiles and helmet use on motorcycles). Other primary prevention activities (e.g., use of earplugs or dust masks) occur in specific occupations. *Secondary prevention* detects disease early when it is still asymptomatic and treatment measures can affect a cure or stop the disease from progressing. The use of a Papanicolaou (Pap) smear for early detection of cervical cancer is an example of secondary prevention. Screening also includes history taking (asking if a person smokes), physical examination (blood pressure measurement), laboratory tests (cholesterol level determination), and other procedures (colonoscopy) that can be applied to asymptomatic people. Most secondary prevention is done in clinical settings. All types of health care professionals (e.g., physicians, nurses, dentists, audiologists, optometrists) participate in secondary prevention. *Tertiary prevention* is directed at clinical interventions that prevent further deterioration or reduce the complications of a disease once it has been diagnosed.

REFERENCES

1. *Stedman's Medical Dictionary*. 28th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:855.
2. Kumar V, Abbas AK, Fausto N, et al. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2012:4,5.
3. Waldenstrom J. Sick molecules and our concepts of illness. *J Intern Med*. 1989;225:221–227.
4. Fletcher RH, Fletcher SW, Fletcher G. *Clinical Epidemiology: The Essentials*. 5th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1–16, 17–29, 31–49, 50–59, 93–104, 108–130.
5. Brigden ML, Heathcote JC. Problems with interpreting laboratory tests. *Postgrad Med*. 2000;107(7):145–162.
6. Mayer D. *Essentials of Evidence-Based Medicine*. New York, NY: Cambridge University Press; 2004.
7. Fischbach F, Dunning MB. *A Manual of Laboratory and Diagnostic Tests*. 8th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009;74:964.
8. Dawson B, Trapp RG, Trapp R. *Basic and Clinical Biostatistics*. New York, NY: Lange Medical Books/McGraw-Hill; 2004.
9. Michaud GY. The role of standards in the development and implementation of clinical laboratory tests: A domestic and global perspective. *Cancer Biomark*. 2005;1:209–216.
10. Montori VM, Wyer P, Newman TB, et al. Tips for learning of evidence-based medicine: 5. The effect of spectrum of disease on performance of diagnostic tests. *Can Med Assoc J*. 2005;173:385–390.
11. World Health Organization. About WHO: Definition of health; disease eradication/elimination goals. 2007. Available at: http://www.who.int/about/definition/en/. Accessed September 2, 2013.
12. Framingham Heart Study. Framingham Heart Study: Design, rationale, objectives, and research milestones. 2011. Available at: http://www.framinghamheartstudy.org. Accessed September 2, 2013.
13. Channing Laboratory. Nurses' Health Study. 2011. Available at: http://www.channing.harvard.edu/nhs/. Accessed September 2, 2013.
14. Liang J, Reherman B, Seeff LB, et al. Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med*. 2000;132:296–305.
15. Neis MA, McEwan M. *Community Health Nursing*. 5th ed. St. Louis, MO: Mosby; 2011:1–90.

UNIT 1

Cell and Tissue Function

Chapter 1

Cell Structure and Function

The cell is the smallest functional unit of life. Cells are the smallest unit capable of self-reproduction and are vehicles for transmitting genetic information that defines the organism. Cells with similar specialized functions are often organized into larger functional aggregates called *tissues*. These tissues in turn combine to form the various body structures and organs. Although the cells of different tissues and organs vary in structure and function, they are remarkably similar in their ability to exchange materials with their immediate environment, obtain energy from organic nutrients, synthesize complex molecules, and replicate themselves. Because most diseases begin at the cellular level, an understanding of cell function is crucial to understanding the disease process. Some diseases affect the cells of a single organ, others affect the cells of a particular tissue type, and still others affect the cells of the entire organism.

This chapter discusses the structural and functional components of the cell, basic cellular mechanisms, and tissue types.

Functional Components of the Cell

Although diverse in their organization, all eukaryotic cells (cells with a true nucleus) have in common structures that perform unique functions. Under a light microscope, three primary components of the eukaryotic cell become evident: the plasma membrane, the nucleus, and the cytoplasm, while numerous structures are visible by higher magnification electron microscopy (Fig. 1-1).

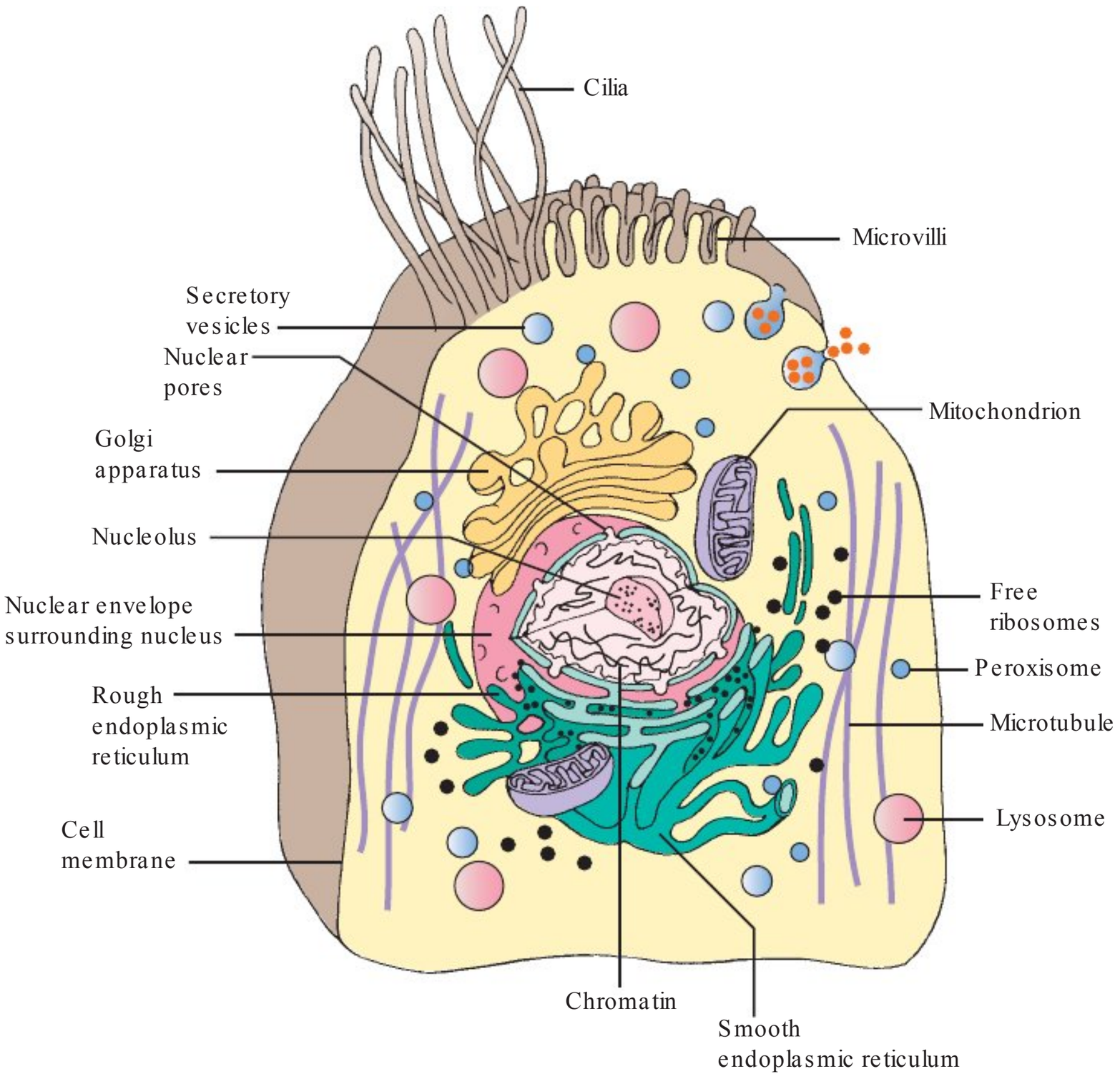


FIGURE 1-1. Composite cell designed to show in one cell all of the various components of the nucleus and cytoplasm.

Two distinct regions exist in the cell: the *cytoplasm*, which lies outside the nucleus, and the *nucleoplasm*, which lies inside the nucleus. The cytoplasm contains membrane-enclosed organelles ("little organs") and inclusions in an aqueous gel called the *cytoplasmic matrix*. The matrix consists of a variety of solutes including inorganic ions (Na^+, K^+, Ca^+) and organic molecules such as intermediate metabolites, carbohydrates, lipids, proteins, and RNA. The nucleus is the largest organelle within the cell and its nucleoplasm contains the genome along with the enzymes necessary for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) transcription.

The Cell Membrane

In many respects, the cell membrane (also called the plasma membrane) is one of the most important parts of the cell. It acts as a semipermeable structure that separates the intracellular and extracellular environments. It controls the transport of materials from the extracellular fluids to the interior of the cell, holds and binds receptors for hormones and other biologically active substances, participates in the generation and conduction of electrical currents in nerve and muscle cells, and aids in the regulation of cell growth and proliferation.

The cell membrane is a dynamic and fluid structure consisting of an organized arrangement of lipids, carbohydrates, and proteins (Fig. 1-2). A main structural component of the membrane is its lipid bilayer that consists primarily of phospholipids, cholesterol, and glycoproteins. This lipid bilayer provides the basic fluid structure of the membrane and serves as a relatively impermeable barrier to all but lipid-soluble substances. The most abundant lipids are phospholipids, each with a hydrophilic (water-soluble) head and a hydrophobic (water-insoluble) tail. Phospholipid molecules along with the glycolipids are aligned such that their hydrophilic heads face outward on each side of the membrane and their hydrophobic tails project toward the middle of the membrane. The presence of cholesterol makes the membrane regionally less deformable and less permeable to small water soluble molecules.

Although the lipid bilayer provides the basic structure of the cell membrane, proteins carry out most of the specific functions. The *integral proteins* span the entire lipid bilayer and are part of the membrane. Because most of the integral proteins pass directly through the membrane, they are also referred to as *transmembrane proteins*. Other proteins, called the *peripheral proteins*, are bound to one or the other side of the membrane and do not pass into the lipid bilayer.

The manner in which proteins are associated with the cell membrane often determines their function. Thus, peripheral proteins are associated with functions involving the inner or outer side of the membrane where they

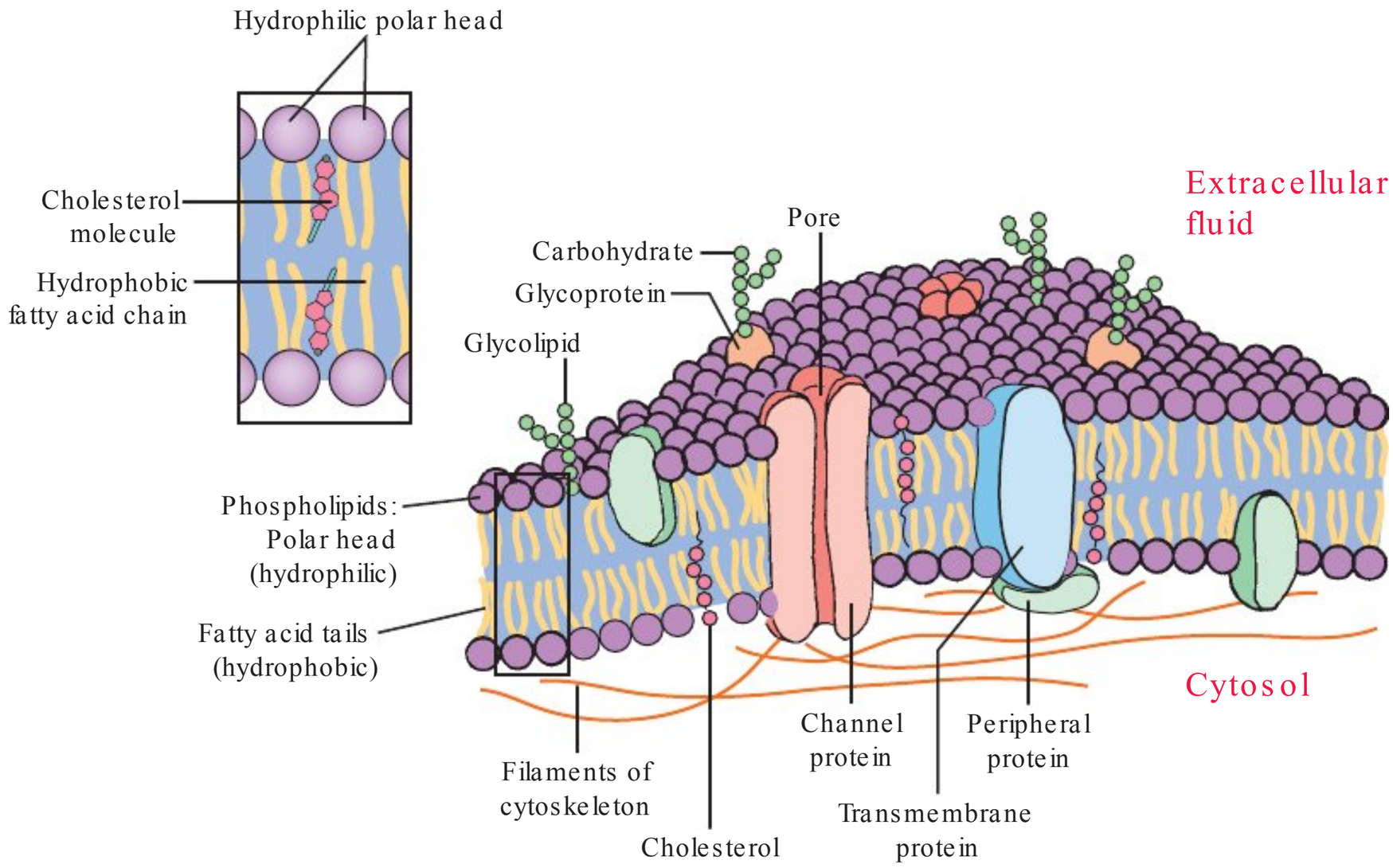


FIGURE 1-2. Structure of the plasma (cell) membrane showing the hydrophilic (polar) heads and the hydrophobic (fatty acid) tails (inset), and the position of the integral and peripheral proteins in relation to the interior and exterior of the cell.

are found. Several peripheral proteins serve as receptors or are involved in intracellular signaling systems. By contrast, only the transmembrane proteins can function on both sides of the membrane or transport molecules across it. Many integral transmembrane proteins form the ion channels found on the cell surface. These channel proteins have a complex morphology and are selective with respect to the substances they transmit.

A fuzzy-looking layer, called the *cell coat* or *glycocalyx*, surrounds the cell surface. It consists of long, complex carbohydrate chains attached to protein molecules that penetrate the outside portion of the membrane (i.e., glycoproteins); outward-facing membrane lipids (i.e., glycolipids); and carbohydrate-binding proteins called lectins. The cell coat participates in cell-to-cell recognition due to antigens that label cells as self or nonself and are important in tissue transplantation. The cell coat of a red blood cell contains the ABO blood group antigens.

The Nucleus

The nucleus of a nondividing cell appears as a rounded or elongated structure situated near the center of the cell (see Fig. 1-1). It is enclosed in a nuclear envelope and contains chromatin, the genetic material of the nucleus, and a distinct region called the *nucleolus*. All eukaryotic cells have at least one nucleus (prokaryotic cells, such as bacteria, lack a nucleus and nuclear membrane).

The nucleus is regarded as the control center for the cell. It contains the DNA that is essential to the cell because its genes encode the information necessary for the synthesis of proteins that the cell must produce to stay alive. The genes also represent the individual units of inheritance that transmit information from one generation to another. The nucleus also is the site for the synthesis of the three types of RNA that move to the cytoplasm and carry out the actual synthesis of proteins. Messenger RNA (mRNA) copies and carries the DNA instructions for protein synthesis to the cytoplasm; ribosomal RNA (rRNA) is the site of protein synthesis; and transfer RNA (tRNA) transports amino acids to the site of protein synthesis for incorporation into the protein being synthesized (see Chapter 5).

The complex structure of DNA and DNA-associated proteins dispersed in the nuclear matrix is called *chromatin*. Depending on its transcriptional activity, chromatin may be condensed as an inactive form of chromatin called *heterochromatin* or extended as a more active form called *euchromatin*. Because heterochromatic regions of the nucleus stain more intensely than regions consisting of euchromatin, nuclear staining can be a guide to cell activity. The nucleus also contains the darkly stained round body called the *nucleolus* that is the site of rRNA synthesis and initial ribosomal assembly. Cells that are actively synthesizing proteins can be recognized because their nucleoli are large and prominent and the nucleus as a whole is euchromatic or slightly stained.

Surrounding the nucleus is the *nuclear envelope* formed by an inner and outer nuclear membrane containing a *perinuclear* space between them (Fig. 1-3). The inner nuclear membrane is supported by a rigid network of protein filaments called *nuclear lamina* that bind to chromosomes and secure their position in the nucleus. The outer nuclear membrane resembles and is continuous with the membrane of the endoplasmic reticulum.

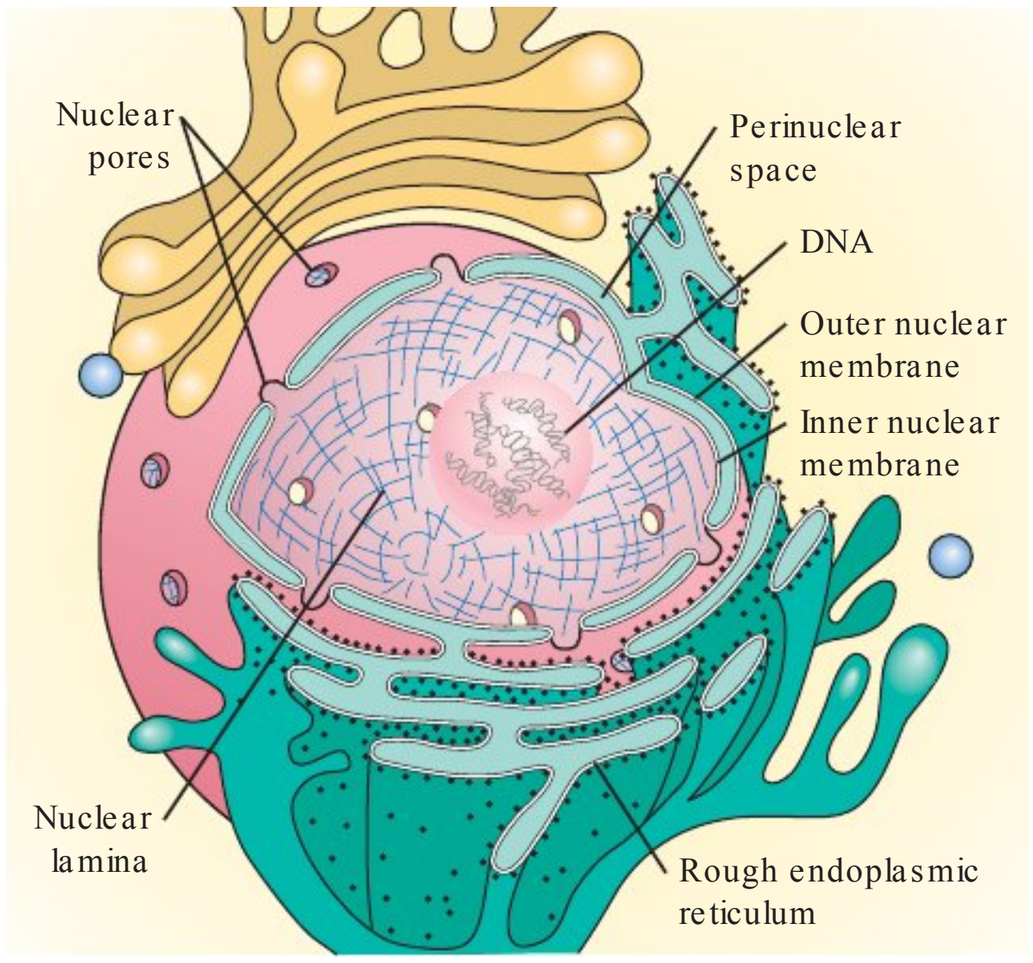


FIGURE 1-3. Schematic drawing of the inner and outer membranes of the nuclear envelope. The double-membrane envelope is penetrated by pores in which nuclear pore complexes are positioned and continuous with the rough endoplasmic reticulum. The nuclear lamina on the surface of the inner membrane binds to DNA and holds the chromosomes in place. DNA, deoxyribonucleic acid.

At the site where the inner and outer membranes fuse, the nuclear envelope is penetrated by pores containing *nuclear pore complexes*. Structures of the nuclear pore complexes act as barriers and enable selective transportation of RNA, ribosomes, and lipids and proteins with signaling functions between the nucleus and cytoplasm to coordinate events such as gene transcription and metabolic activities.

The Cytoplasm and Its Membrane-Bound Organelles

The cytoplasm surrounds the nucleus, and it is in the cytoplasm that the work of the cell takes place. Embedded in the cytoplasm are various membrane-enclosed organelles (e.g., endoplasmic reticulum [ER], Golgi apparatus, mitochondria, and lysosomes) and complexes without membranes (e.g., ribosomes and proteasomes) that have important functions in cells.

Ribosomes, Endoplasmic Reticulum, and Golgi Apparatus

The endoplasmic reticulum (with its associated ribosomes) and Golgi apparatus represent the primary sites of protein synthesis in the cell (Fig. 1-4). Following protein synthesis in the ribosomes, the endoplasmic reticulum and Golgi apparatus use transport vesicles to move newly synthesized proteins, membrane components, and soluble molecules from one organelle to another.

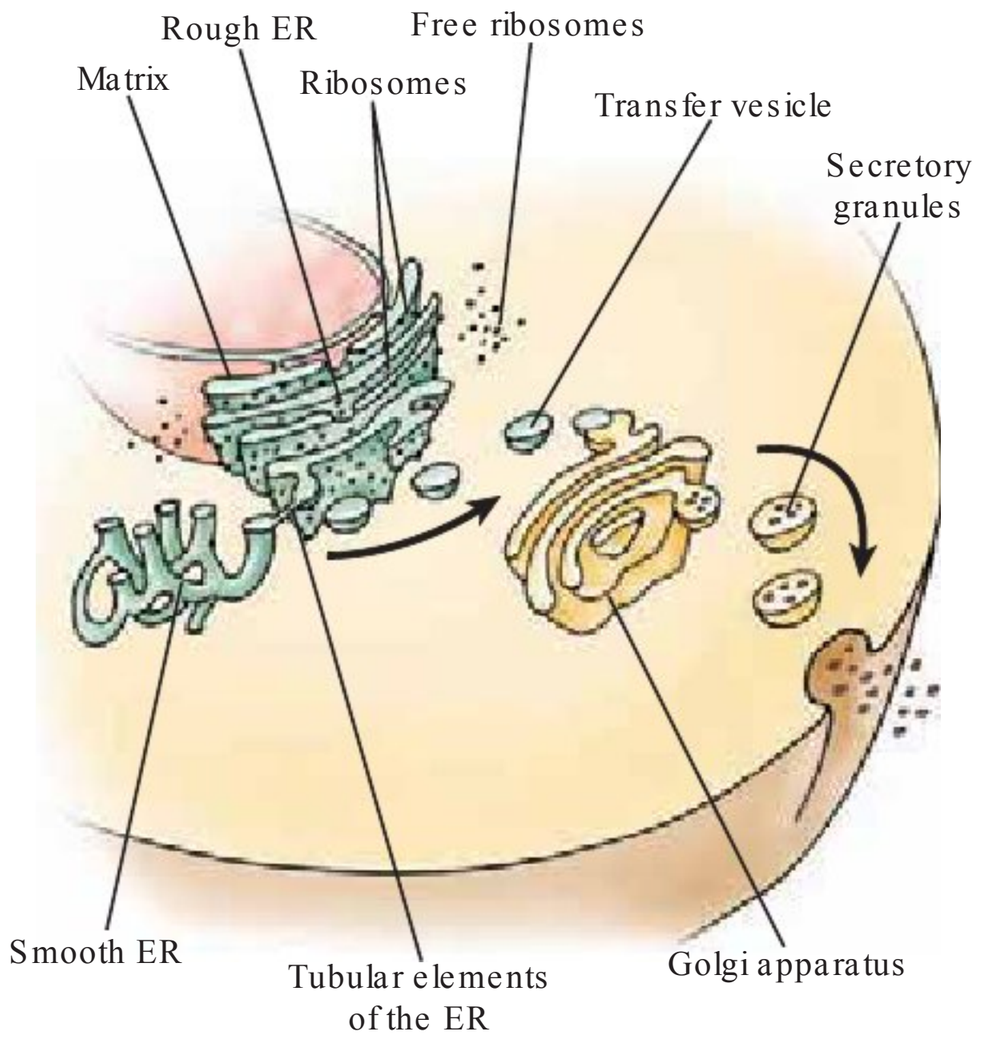


FIGURE 1-4. Three-dimensional view of the rough and the smooth endoplasmic reticula (ER) and the Golgi apparatus. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and lipid (smooth ER) synthesis. Most of the proteins synthesized by the rough ER are sealed into transfer vesicles and transported to the Golgi apparatus, where they are modified and packaged into secretory granules.

Ribosomes. The ribosomes are small particles of nucleoproteins (rRNA and proteins) that are held together by a strand of mRNA. Poly Ribosomes exist as isolated clusters of free ribosomes within the cytoplasm or attached to the membrane of the ER (see Fig. 1-4). Free ribosomes are involved in the synthesis of proteins that remain in the cell as cytoplasmic structural or functional elements, whereas those attached to the ER translate mRNAs that code for proteins to be bound in membranes or destined for secretion.

Endoplasmic Reticulum. The endoplasmic reticulum is an extensive dynamic system of interconnected membranous tubes and sac-like cisternae (see Figs. 1-3 and 1-4). Within the lumen of the ER is a matrix that connects the space between the two membranes of the nuclear envelope to the cell periphery. The ER functions as a tubular communication system for transporting various substances from one part of the cell to another. A large surface area and multiple enzyme systems attached to the ER membranes also provide the machinery for many cellular metabolic functions.

Two forms of ER exist in cells: rough and smooth. *Rough ER* is studded with ribosomes attached to specific binding sites on the membrane. These ribosomes, with their accompanying strand of mRNA, synthesize proteins destined to be incorporated into cell membranes, used in the generation of lysosomal enzymes, or exported

from the cell. The *smooth ER* is free of ribosomes and is continuous with the rough ER. It does not participate in protein synthesis; instead, its enzymes are involved in the synthesis of lipid and steroid hormone molecules, regulation of intracellular calcium, and metabolism and detoxification of certain hormones and drugs. The sarcoplasmic reticulum of skeletal and cardiac muscle cells is a form of smooth ER. Calcium ions needed for muscle contraction are stored and released from cisternae of the sarcoplasmic reticulum. The smooth ER of the liver is involved in glycogen storage and metabolism of lipid-soluble drugs.

Golgi Apparatus. The Golgi apparatus, sometimes called the *Golgi complex*, consists of stacks of thin, flattened vesicles or sacs (see Fig. 1-4). These Golgi bodies are found near the nucleus and function in association with the ER. Substances produced in the ER are transported to the Golgi complex in small, membrane-bound transport vesicles. Many cells synthesize proteins that are larger than the active product. The Golgi complex modifies these substances and packages them into secretory granules or vesicles. Insulin, for example, is synthesized as a large, inactive proinsulin molecule that is cleaved to produce a smaller, active insulin molecule within the Golgi complex of the beta cells of the pancreas. In addition to producing secretory granules, the Golgi complex is thought to produce large carbohydrate molecules that are added to proteins produced by the rough ER to form glycoproteins.

Lysosomes

The lysosomes, which can be viewed as digestive organelles in the cell, are small, membrane-bound sacs filled with hydrolytic enzymes. These enzymes can break down excess and worn-out cell parts as well as foreign substances that are taken into the cell. All of the lysosomal enzymes are acid hydrolases, which means that they require an acid environment. The lysosomes provide this environment by maintaining a pH of approximately 5.0 in their interior. The pH of the cytosol and other cellular components is approximately 7.2. Like all other cellular organelles, lysosomes not only contain a unique collection of enzymes, but also have a unique surrounding membrane that prevents the release of its digestive enzymes into the cytosol.

Lysosomes are formed from digestive vesicles called *endosomes*. These vesicles fuse to form multivesicular bodies called *early endosomes* (Fig. 1-5). The early endosomes mature into *late endosomes* as they recycle lipids, proteins, and other membrane components back to the plasma membrane in vesicles called *recycling vesicles*. Lysosomal enzymes are synthesized in the rough ER and then transported to the Golgi apparatus, where they are biochemically modified and packaged for transport to the endosomes. The late endosomes mature into lysosomes as they progressively accumulate newly synthesized acid hydrolases from the Golgi apparatus and attain digestive abilities.

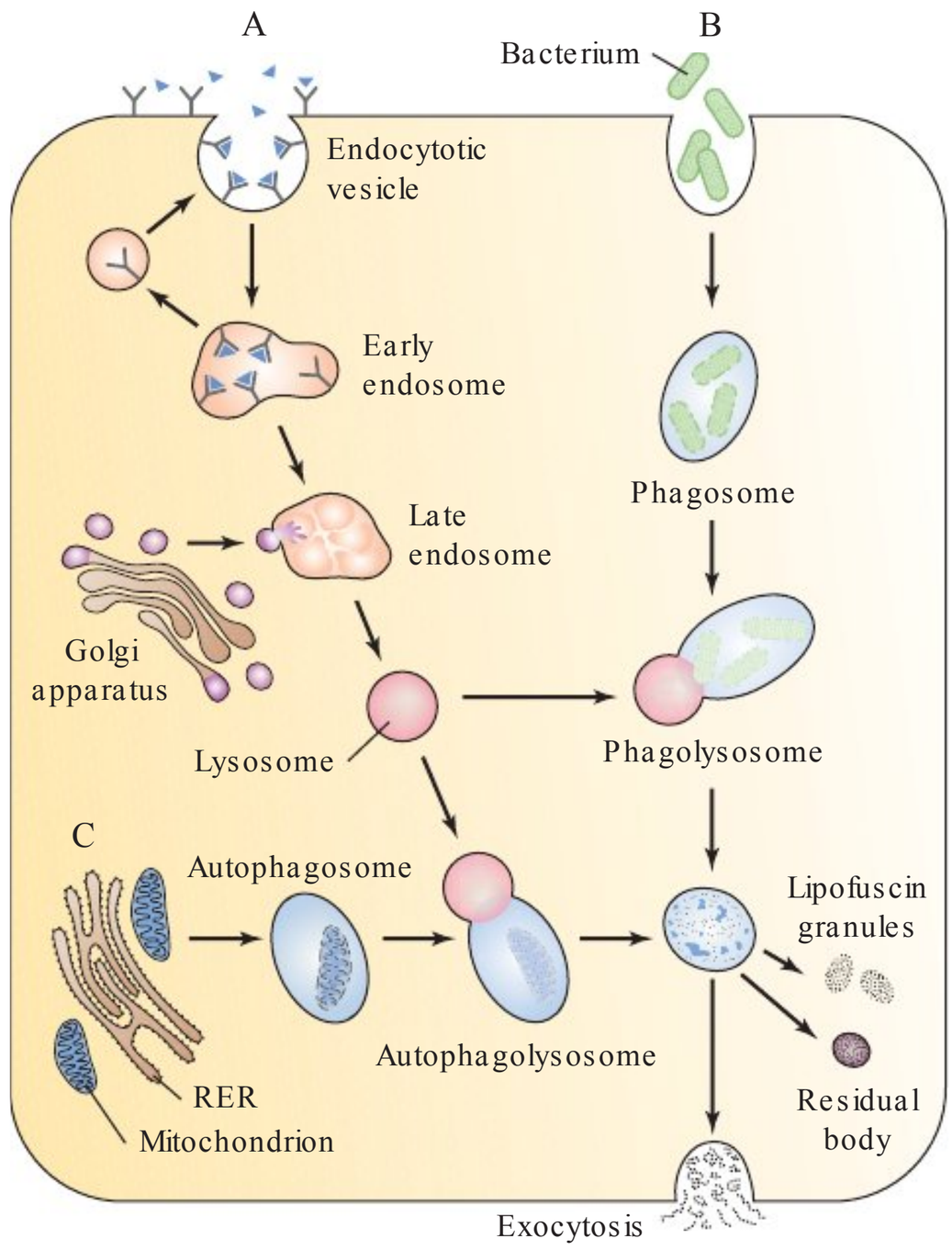


FIGURE 1-5. Pathways for digestion of materials by lysosomes. **(A)** Receptor-mediated endocytosis with formation of lysosome from early and late endosomes. Vesicle contents are sorted in the early endosome with receptors and lipids being sent back to the membrane. Transport vesicles carry lysosomal enzymes to the late endosomes, converting them into lysosomes that digest proteins and other components acquired from the endocytotic vesicles. **(B)** Phagocytosis involving the delivery of large extracellular particles such as bacteria and cellular debris to the lysosomes via phagosomes. **(C)** Autophagy is the process in which worn-out mitochondria and other cell parts are surrounded by a membrane derived from the rough endoplasmic reticulum (RER). The resulting autophagosome then fuses with a lysosome to form an authophagolysosome. Undigested material may be extruded from the cell or remain in the cytoplasm as lipofuscin granules or membrane-bound residual bodies.

Depending on the nature of the substance, different pathways are used for lysosomal degradation of unwanted materials (see Fig. 1-5). Small extracellular particles such as extracellular proteins and plasma membrane proteins form endocytotic vesicles after being internalized by pinocytosis or receptor-mediated endocytosis. These vesicles are converted into early and late endosomes, after which they mature into lysosomes. Large extracellular particles such as bacteria, cell debris, and other foreign particles are engulfed in a process called *phagocytosis*. A *phagosome*, formed as the material is internalized within the cell, fuses with a lysosome to form a *phagolysosome*. Intracellular particles, such as entire organelles, cytoplasmic proteins, and other

cellular components, are engulfed in a process called autophagy. These particles are isolated from the cytoplasmic matrix by ER membranes to form an *autophagosome*, which then fuses with a lysosome to form an *autophagolysosome*.

Although the lysosomal enzymes can break down most proteins, carbohydrates, and lipids to their basic constituents, some materials remain undigested. These undigested materials may remain in the cytoplasm as *residual bodies* or be extruded from the cell. In some long-lived cells, such as neurons and heart muscle cells, large quantities of residual bodies accumulate as lipofuscin granules or age pigments. Other indigestible pigments, such as inhaled carbon particles and tattoo pigments, also accumulate and may persist in residual bodies for decades.

Lysosomes are also repositories where cells accumulate abnormal substances that cannot be completely digested or broken down. In some genetic diseases known as *lysosomal storage diseases*, a specific lysosomal enzyme is absent or inactive, in which case the digestion of certain cellular substances (e.g., glucocerebrosides, gangliosides, sphingomyelin) does not occur. As a result, these substances accumulate in the cell. In Tay-Sachs disease (see Chapter 6), an autosomal recessive disorder, hexosaminidase A, which is the lysosomal enzyme needed for degrading the GM_2 ganglioside found in nerve cell membranes, is absent. Although the GM_2 ganglioside accumulates in many tissues, such as the heart, liver, and spleen, its accumulation in the nervous system and retina of the eye causes the most damage.

Peroxisomes

Spherical membrane-bound organelles called *peroxisomes* contain enzymes that are used in oxidative reactions. Reactions occurring in peroxisomes use oxygen to produce peroxides and convert hydrogen peroxide to water. Unless degraded, these highly unstable reactive oxygen species and free radicals (see Chapter 2) would damage other cellular molecules and structures. Peroxisomes also contain the enzymes needed for breaking down very–long-chain fatty acids, which are ineffectively degraded by mitochondrial enzymes. In liver cells, peroxisomal enzymes are involved in the formation of the bile acids.

Proteasomes

Proteasomes are cytoplasmic protein complexes that are not bound by membranes. Proteasomes are responsible for proteolysis of malformed and misfolded proteins and have roles in many cellular responses and events. The process of cytosolic proteolysis is carefully controlled by the cell and requires that the protein be targeted for degradation. This process involves *ubiquitination*, a process whereby several small ubiquitin molecules (a small 76-amino-acid polypeptide chain) are attached to an amino acid residue of the targeted protein. Once a protein is so tagged, it is degraded by proteasomes. After the targeted protein has been degraded, the resultant amino acids join the intracellular pool of free amino acids and the ubiquitin molecules are released and recycled.

Mitochondria

The mitochondria are literally the "power plants" of the cell because they contain the enzymes needed for capturing most of the energy in foodstuffs and converting it into cellular energy. This multistep process requires oxygen and is often referred to as *aerobic metabolism*. Much of this energy is stored in the high-energy phosphate bonds of adenosine triphosphate (ATP) that serves to power various cell activities. Mitochondria are found close to the site of energy consumption in the cell (e.g., near the myofibrils in muscle cells). The number of mitochondria in a given cell type is largely determined by the type of activity the cell performs and how much energy is needed to undertake the activity. For example, a dramatic increase in mitochondria occurs in skeletal muscle repeatedly stimulated to contract.

The mitochondria are composed of two membranes: an outer membrane that encloses the periphery of the mitochondrion and an inner membrane that forms shelflike projections, called *cristae* (Fig. 1-6). The narrow space between the outer and inner membranes is called the *intermembrane space*, whereas the large space enclosed by the inner membrane is termed the *matrix space*. The outer mitochondrial membrane contains a large number of transmembrane porins, through which inorganic ions and metabolites may pass. The inner membrane contains the respiratory chain enzymes and transport proteins needed for the synthesis of ATP.

Mitochondria contain their own DNA and ribosomes and are self-replicating. The DNA is found in the mitochondrial matrix and is distinct from the chromosomal DNA found in the nucleus. Mitochondrial DNA, known as the "other human genome," is a double-stranded, circular molecule that encodes the rRNA and tRNA required for intramitochondrial synthesis of the proteins needed for the energy-generating function of the mitochondria. Although mitochondrial DNA directs the synthesis of 13 of the proteins required for mitochondrial function, the DNA of the nucleus encodes the structural

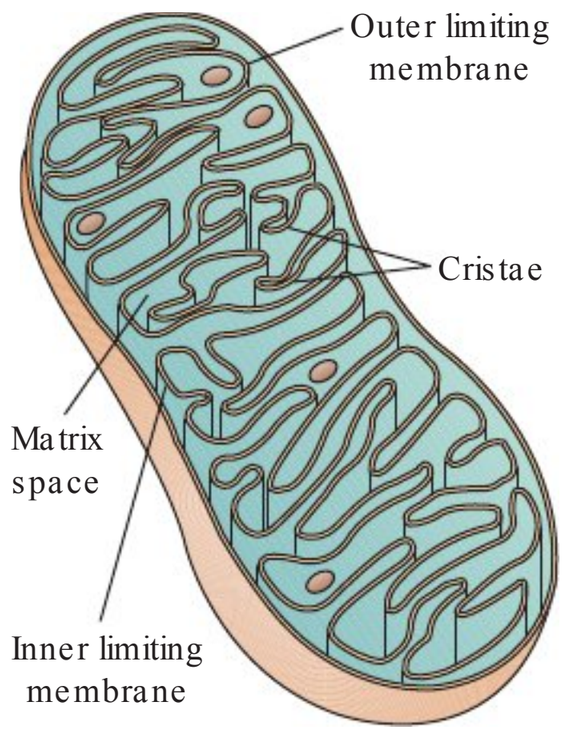


FIGURE 1-6. Mitochondrion. The inner membrane forms transverse folds called cristae, where the enzymes needed for the final step in adenosine triphosphate (ATP) production (i.e., oxidative phosphorylation) are located.