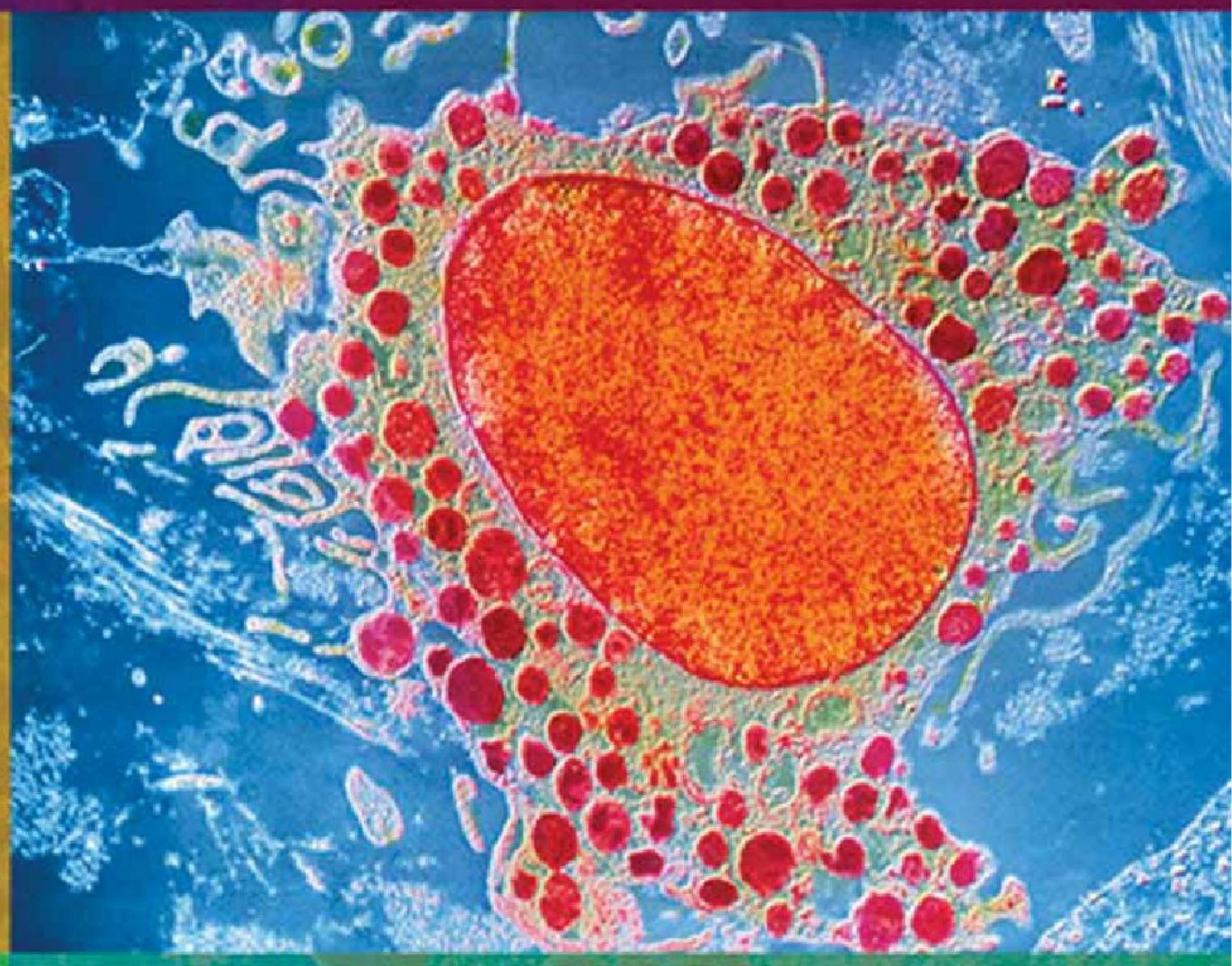
Essentials of Pathophysiology



FOURTH EDITION

Carol Mattson Porth

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Essentials of Pathophysiology

CONCEPTS OF ALTERED HEALTH STATES

Edition 4

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CAROL MATTSON PORTH, RN, MSN, PhD (Physiology), FAHA
Professor Emeritus, College of Nursing
University of Wisconsin–Milwaukee
Milwaukee, Wisconsin

Consultant
KATHRYN J. GASPARD, PhD
Clinical Associate Professor Emeritus
University of Wisconsin–Milwaukee
College of Nursing
Milwaukee, Wisconsin

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Illustrator, 4th Edition: Wendy Beth Jackelow, MFA, CMI
Production Project Manager: Marian A. Bellus
Manufacturing Coordinator: Karin Duffield
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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.

CAROL MATTSON PORTH

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Contributors

Jacqueline M. Akert, RNC, MSN, WHNP-BC
Nurse Practitioner, Women's Health
Aurora Health Care
Waukesha, Wisconsin
(Chapters 40, 41 with Patricia McCowen Mehring)

Aoy Tomita-Mitchell, PhD
Associate Professor
Department of Surgery
Medical College of Wisconsin
Children's Research Institute
Milwaukee, Wisconsin
(Chapters 5, 6)

Diane Book, MD
Associate Professor, Neurology
Co-Director Stroke & Neurovascular Program
Froedtert Hospital & Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 37)

Freddy W. Cao, MD, PhD
Clinical Associate Professor
College of Nursing
University of Wisconsin–Milwaukee
Milwaukee, Wisconsin
(Chapters 18, 34)

Paula Cox-North, PhD, ARNP
Hepatitis & Liver Clinic
Harborview Medical Center
Clinical Assistant Professor
University of Washington School of Nursing
Seattle, Washington
(Chapters 29, 30)

Herodotos Ellinas, MD, FAAP, FACP
Assistant Professor, Department of Anesthesiology
Med–Anesthesia and PGY-1 Program Director
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapters 11, 12, 13)

Jason R. Faulhaber, MD
Division of Infectious Diseases, Carilion Clinic
Assistant Program Director, Fellowship in Infectious Diseases, Carilion Clinic
Assistant Professor, Virginia Tech, Carilion School of Medicine
Adjunct Professor, Department of Biomedical Sciences, Jefferson College of Health Sciences
Roanoke, Virginia
(Chapters 15, 16)

Anne M. Fink, RN, PhD
Postdoctoral Research Associate
University of Illinois–Chicago
College of Nursing
Chicago, Illinois
(Chapters 19, 20 with Karen M. Vuckovic)

Susan A. Fontana, PhD, APRN-BC
Associate Professor and Family Nurse Practitioner
University of Wisconsin–Milwaukee
College of Nursing
Milwaukee, Wisconsin
(Chapter 38)

Kathleen E. Gunta, MSN, RN, OCNS-C
Clinical Nurse Specialist
Aurora St. Luke's Medical Center
Milwaukee, Wisconsin
(Chapter 43)

Nathan A. Ledeboer, PhD, D(ABMM)
Associate Professor of Pathology
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 14)

Kim Litwack, PhD, RN, FAAN, APNP
Associate Dean for Academic Affairs
Family Nurse Practitioner
Advanced Pain Management
University of Wisconsin–Milwaukee
Milwaukee, Wisconsin
(Chapter 35)

Glenn Matfin, MSc (Oxon), MB, ChB, FACE, FACP, FRCP
Medical Director
International Diabetes Center
Clinical Professor of Medicine
University of Minnesota
Minneapolis, Minnesota
(Chapters 10, 31, 32, 33, 39)

Patricia McCowen Mehring, RNC, MSN, WHNP
Nurse Practitioner
Women's Health
Milwaukee, Wisconsin
(Chapter 40, 41 with Jacqueline M. Akert)

Carrie J. Merkle, PhD, RN, FAAN
Associate Professor
College of Nursing
The University of Arizona
Tucson, Arizona
(Chapters 1, 2, 3, 4, 7)

Kathleen Mussatto, PhD, RN
Nurse Scientist, Herma Heart Center
Children's Hospital of Wisconsin
Assistant Clinical Professor of Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapter 19, Heart Disease in Infants and Children)

Debra Bancroft Rizzo, RN, MSN, FNP-BC
Nurse Practitioner
Division of Rheumatology
University of Michigan
Ann Arbor, Michigan
(Chapter 44)

Jonathan Shoopman, MD
Assistant Professor of Anesthesiology and Critical Care
Medical College of Wisconsin
Milwaukee, Wisconsin
(Chapters 22, 23)

Gladys Simandl, RN, PhD
Professor
Columbia College of Nursing
Milwaukee, Wisconsin
(Chapters 45, 46)

Karen M. Vuckovic, RN, PhD, ACNS-BC
Assistant Clinical Professor
University of Illinois–Chicago
College of Nursing
Chicago, Illinois
(Chapters 19, 20 with Anne M. Fink)

Jill M. Winters, RN, PhD, FAHA
President and Dean
Columbia College of Nursing
Milwaukee, Wisconsin
(Chapter 9)

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Reviewers

Louise Boudreault, PhD
Professor of Practical Nursing
Algonquin College
Ottawa, Ontario

Freddy W. Cao, MD, PhD
Clinical Associate Professor
College of Nursing
University of Wisconsin–Milwaukee
Milwaukee, Wisconsin

Lori Hendrickx, MSN, EdD
Professor of Nursing
South Dakota State University
Brookings, South Dakota

Lisa Hight, EdD
Associate Professor of Biology
Baptist College of Health Sciences
Memphis, Tennessee

Mini Jose, PhD, RN
Assistant Professor
University of Texas Medical Branch
School of Nursing
Galveston, Texas

Michelle McDonald, MS
Assistant Professor of Biology
Baptist College of Health Sciences
Memphis, Tennessee

Sandra McLeskey, PhD, RN
Professor
University of Maryland School of Nursing
Baltimore, Maryland

Cheryl Neudauer, PhD
Biology Faculty
Center for Teaching and Learning Co-Leader
Minneapolis Community and Technical College
Minneapolis, Minnesota

Paige Wimberley, MSN, PhD(c)
Assistant Professor of Nursing
Arkansas State University
Jonesboro, Arkansas

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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.

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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 4-2 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
MERRF	Myoclonic Epilepsy, Ragged Red Fibers in muscle; ataxia; sensorineural deafness
Myoclonic epilepsy with ragged red fibers	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:

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

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.

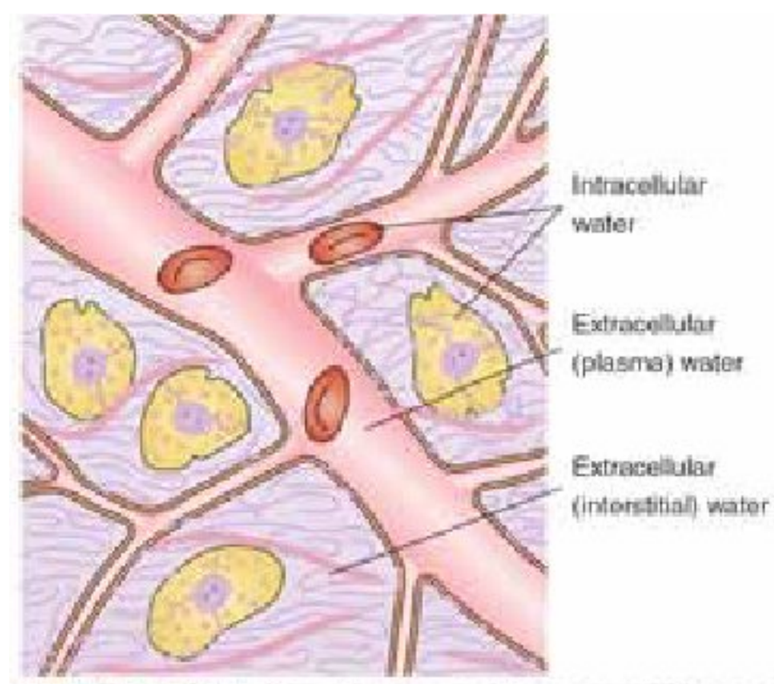


FIGURE 8-1. Distribution of body water. The extracellular space includes the vascular compartment and the interstitial spaces.

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.

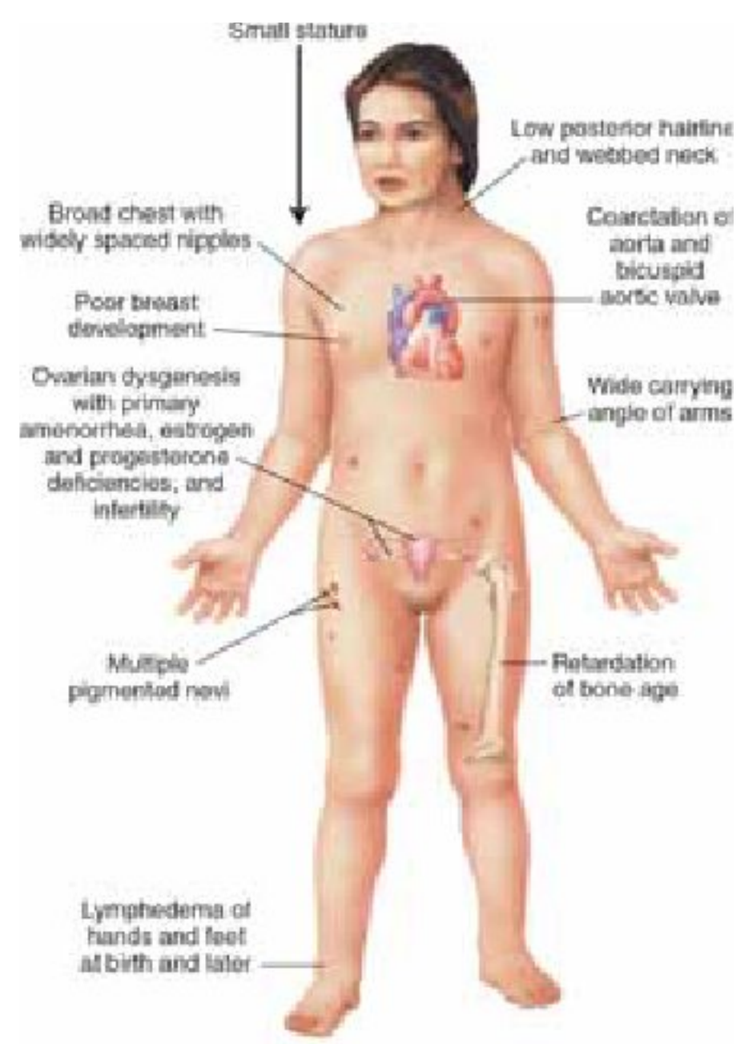
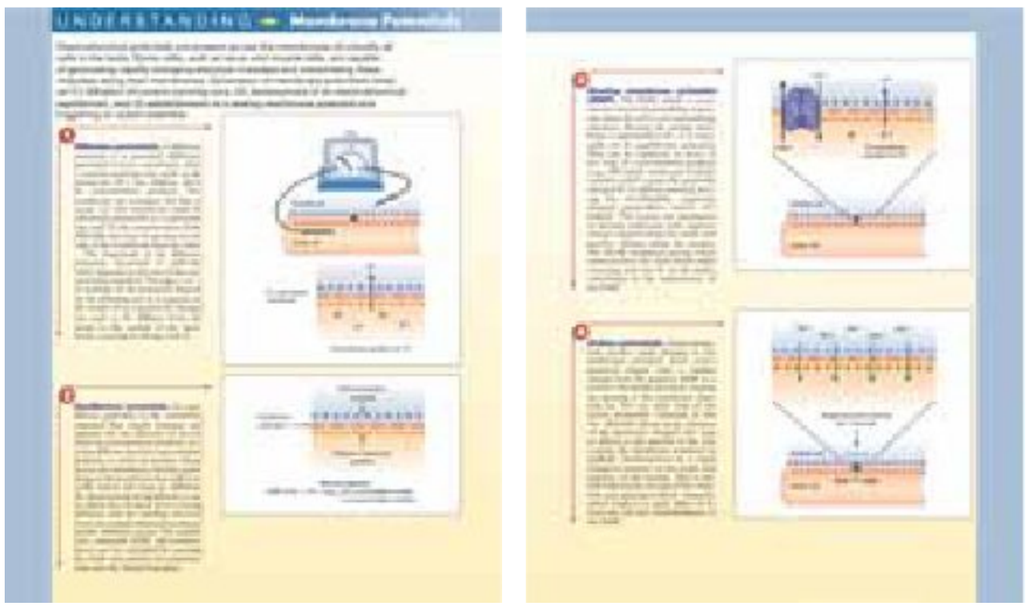


FIGURE 6-11. Clinical features of Turner syndrome.

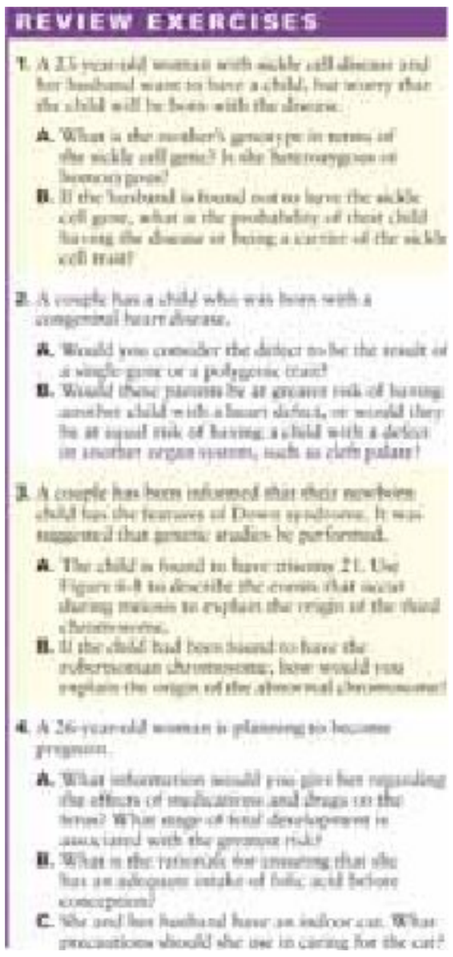
Understanding Physiologic Processes

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!

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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.

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UNIT 1

Cell and Tissue Function

Functional Components of the Cell
- The Cell Membrane
- The Nucleus
- The Cytoplasm and Its Membrane-Bound Organelles
  - Ribosomes, Endoplasmic Reticulum, and Golgi Apparatus
  - Lysosomes
  - Peroxisomes
  - Proteasomes
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  - Adipose Tissue
  - Reticular and Dense Connective Tissue
- Muscle Tissue
  - Skeletal Muscle
  - Smooth Muscle
- Nervous Tissue
- Extracellular Tissue Components
  - Cell Junctions
  - Extracellular Matrix
  - Cell Adhesion Molecules

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).

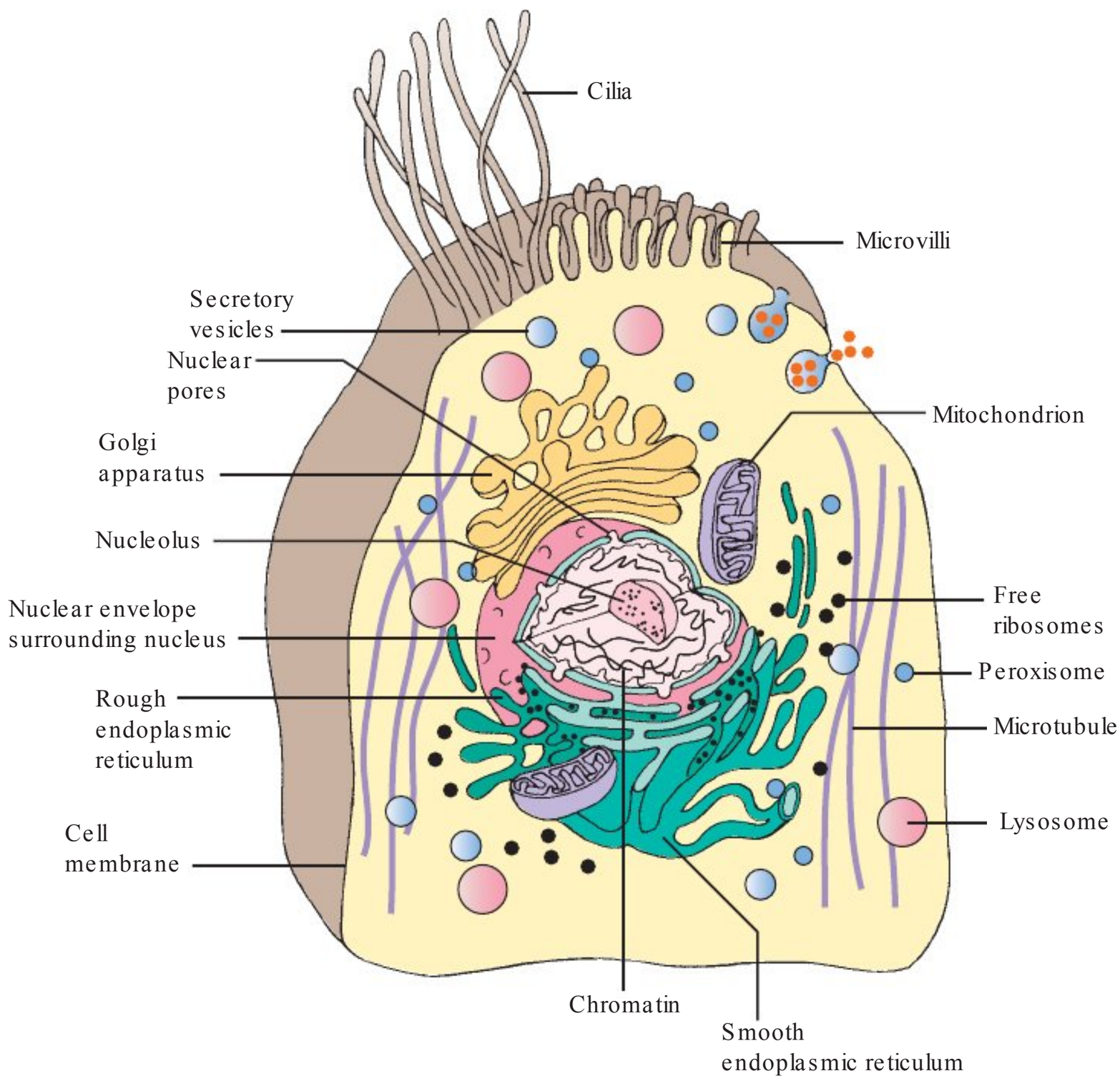


FIGURE 1-1. Composite cell designed to show in one cell all of the various components of the nucleus and cytoplasm.

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

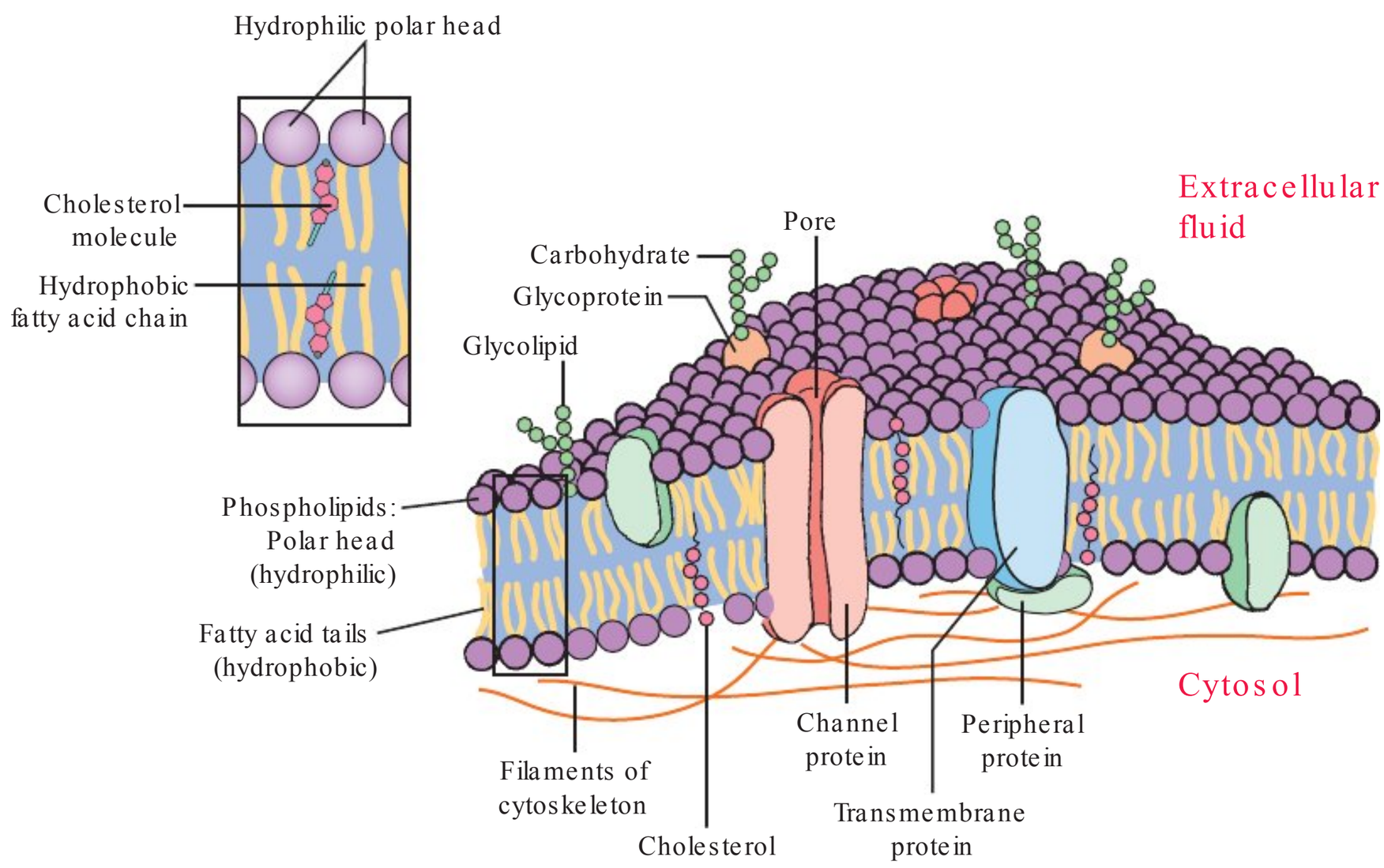


FIGURE 1-2. Structure of the plasma (cell) membrane showing the hydrophilic (polar) heads and the hydrophobic (fatty acid) tails (inset), and the position of the integral and peripheral proteins in relation to the interior and exterior of the cell.

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.

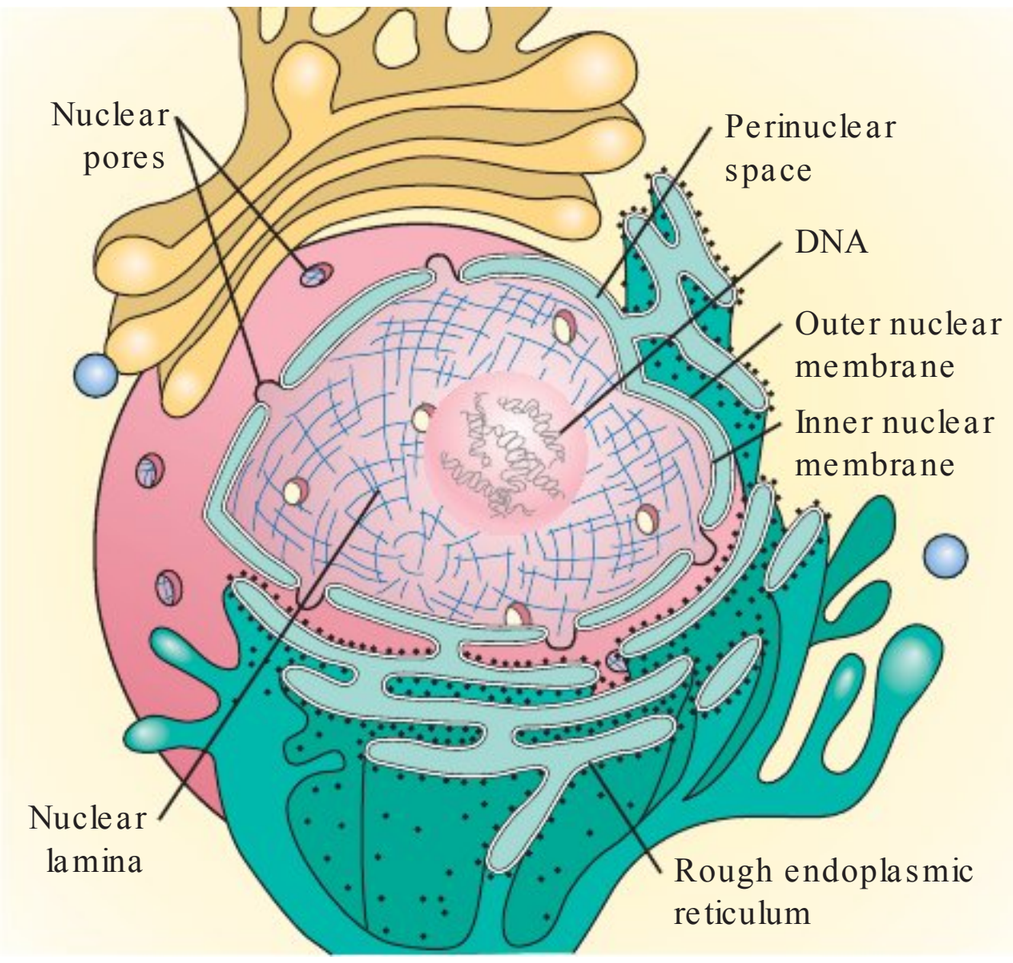


FIGURE 1-3. Schematic drawing of the inner and outer membranes of the nuclear envelope. The double-membrane envelope is penetrated by pores in which nuclear pore complexes are positioned and continuous with the rough endoplasmic reticulum. The nuclear lamina on the surface of the inner membrane binds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

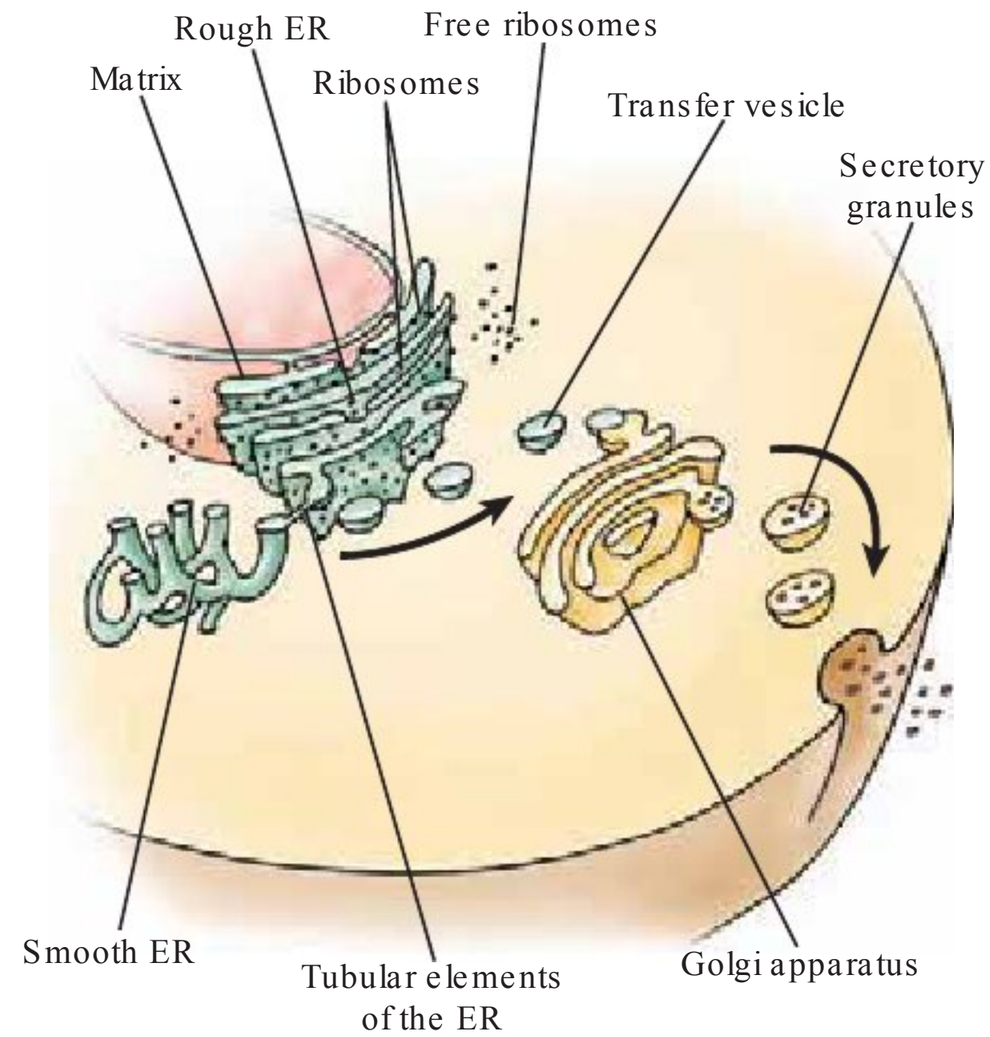


FIGURE 1-4. Three-dimensional view of the rough and the smooth endoplasmic reticula (ER) and the Golgi apparatus. The ER functions as a tubular communication system through which substances can be transported from one part of the cell to another and as the site of protein (rough ER), carbohydrate, and 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.

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.

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.

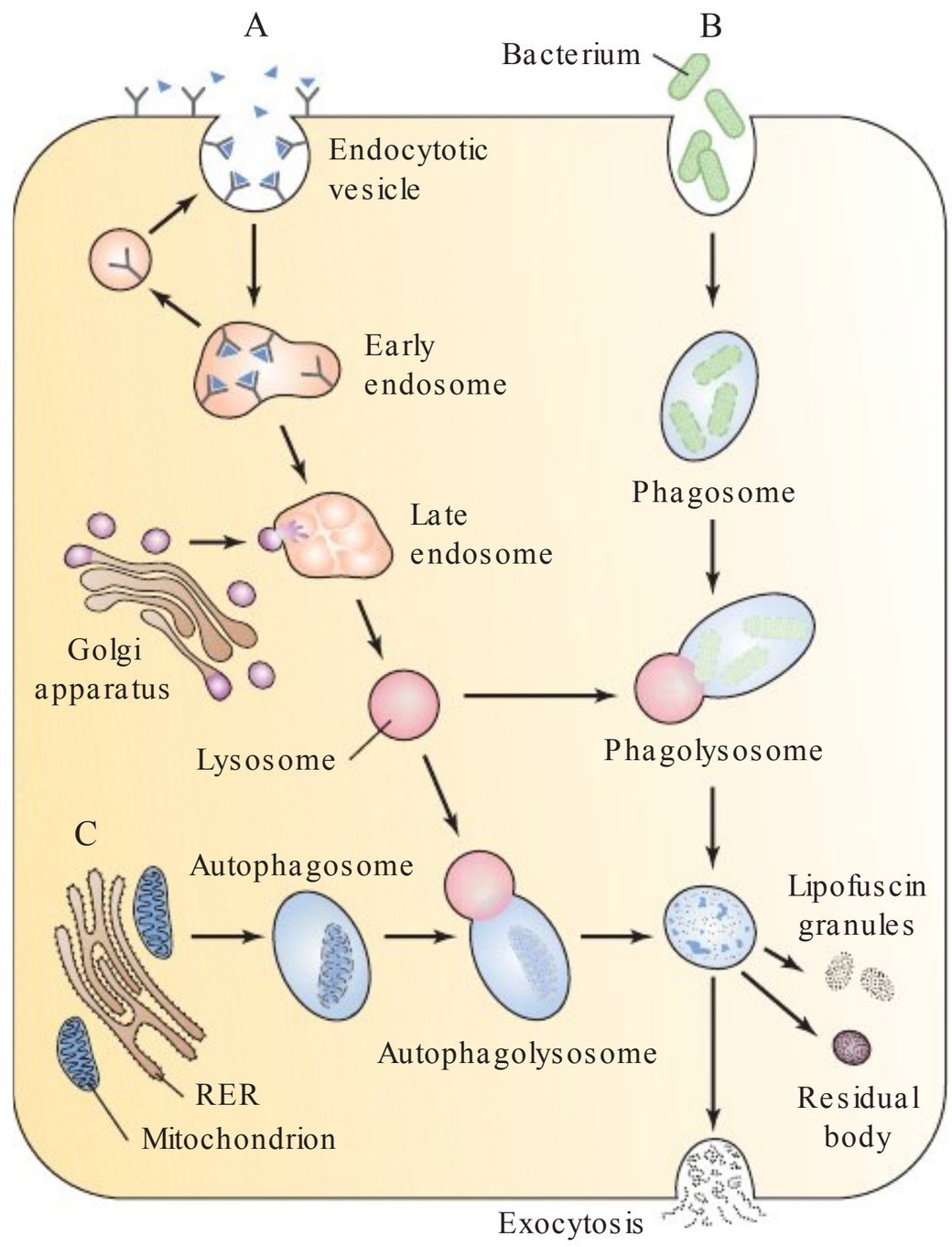


FIGURE 1-5. Pathways for digestion of materials by lysosomes. **(A)** Receptor-mediated endocytosis with formation of lysosome from early and late endosomes. Vesicle contents are sorted in the early endosome with receptors and lipids being sent back to the membrane. Transport vesicles carry lysosomal 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

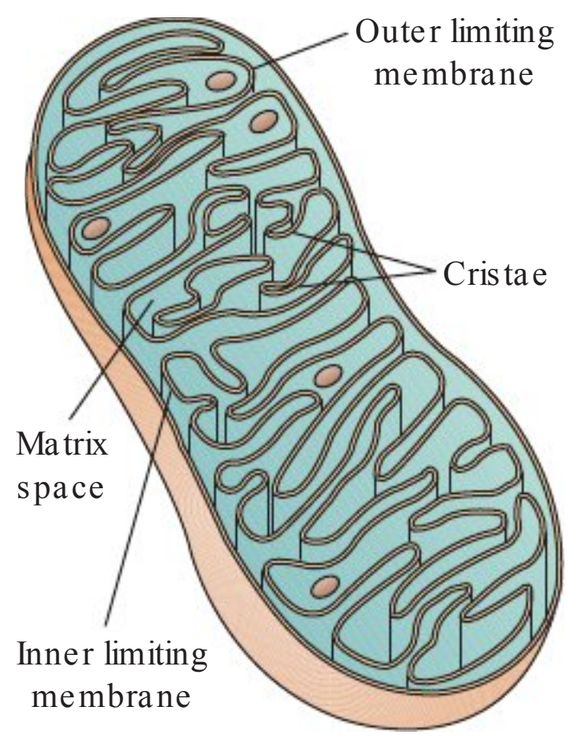


FIGURE 1-6. Mitochondrion. The inner membrane forms transverse folds called cristae, where the enzymes needed for the final step in adenosine triphosphate (ATP) production (i.e., oxidative phosphorylation) are located.

proteins of the mitochondria and other proteins needed to carry out cellular respiration.

Mitochondrial DNA is inherited matrilineally (i.e., from the mother) and provides a basis for familial lineage studies. Mutations have been found in each of the mitochondrial genes, and an understanding of the role of mitochondrial DNA in certain diseases and of mechanisms to maintain the integrity of the mitochondrial genome is beginning to emerge. Most tissues in the body depend to some extent on oxidative metabolism and can therefore be affected by mitochondrial DNA mutations.

Mitochondria also function as key regulators of apoptosis or programmed cell death (discussed in Chapter 2). The initiation of the mitochondrial pathway for apoptosis results from an increase in mitochondrial membrane permeability and the subsequent release of proapoptotic molecules into the cytoplasm. One of these proapoptotic molecules, cytochrome c, is well known for its role in cellular respiration. In the cytosol, cytochrome c binds to a protein called the *apoptosis protease activating factor-1* protein, initiating the molecular events involved in the apoptosis cascade. Other apoptotic proteins also enter the cytoplasm, where they bind to and neutralize the various apoptotic inhibitors, whose normal function consists of blocking the apoptotic cascade. Both the formation of reactive oxygen species (e.g., peroxide) and the activation of the p53 tumor-suppressor gene by DNA damage or other means initiate apoptotic signaling through the mitochondria. Dysregulated apoptosis (too little or too much) has been implicated in a wide range of diseases, including cancer, in which there is an inappropriately low rate of apoptosis, and neurodegenerative diseases, in which there is an increased or excessive rate of apoptosis.

The Cytoskeleton

In addition to its organelles, the cytoplasm contains a network of microtubules, microfilaments, and intermediate filaments (Fig. 1-7). Because they control cell shape and movement, these structures are a major component of the structural elements called the *cytoskeleton*.

Microtubules

Microtubules are slender and rigid tubular structures composed of globular proteins called *tubulin*. Each microtubule consists of parallel protofilaments, each composed of α- and β-tubulin dimers. Microtubules function in many ways, including the development and maintenance of cell form; participation in intracellular transport mechanisms, including axoplasmic transport in neurons; and formation of the basic structure for several complex cytoplasmic organelles, including the cilia, flagella, and centrioles. *Cilia* and *flagella* are microtubule-filled cellular extensions extending from the cell membrane that are capable of sweeping movements. Cilia are found on the apical (luminal) surfaces of many epithelial linings, including the nasal sinuses and passages of the upper respiratory system.

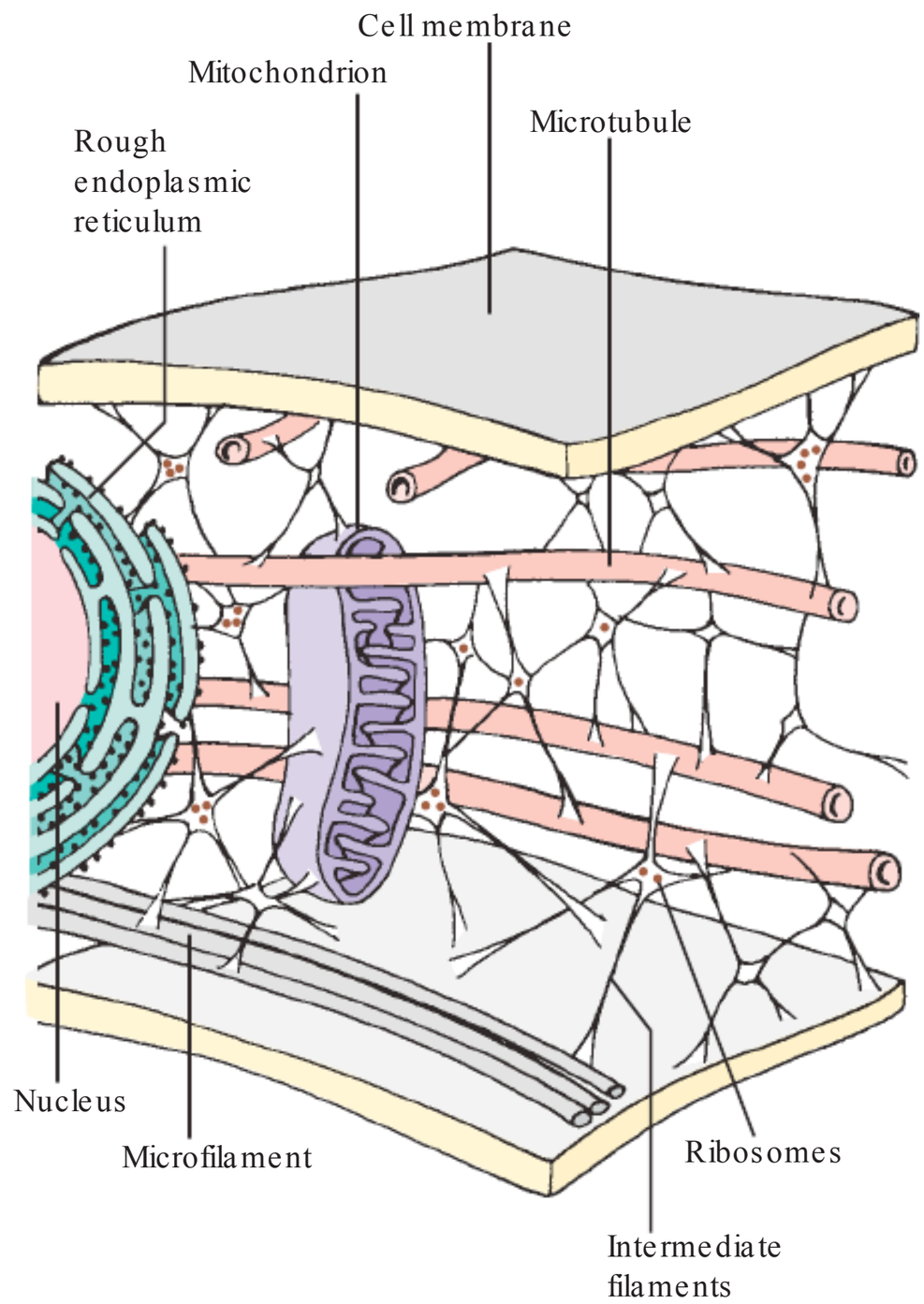


FIGURE 1-7. Three-dimensional view of the network of microtubules, microfilaments, and intermediate filaments that supports the organelles within the cell cytoplasm.

Removal of mucus from the respiratory passages is highly dependent on the proper functioning of the cilia. Flagella form the tail-like structures that provide motility for sperm. Centrioles are small, barrel-shaped bodies oriented at right angles to each other. In dividing cells, the two cylindrical centrioles form the mitotic spindle that aids in the separation and movement of the chromosomes during cell division.

Abnormalities of the microtubules occur in a number of pathologic states. These abnormalities may be manifested by an abnormal appearance and function, aberrant movements of intracellular organelles, and defective cell locomotion. Defective organization of the microtubules can cause sterility by inhibiting sperm motility, as well as defective motility of cilia in the epithelial lining of the respiratory tract, resulting in chronic respiratory tract infections. Proper functioning of the microtubules is also essential for various stages of leukocyte migration. Drugs that bind to tubulin molecules and prevent their assembly of microtubules (*colchicine*) are useful in the treatment of gout, in which symptoms are due to movement of leukocytes toward urate crystals in the tissues. Since microtubules form the mitotic spindle, which is essential for cell proliferation, drugs that bind microtubules (e.g., vinca alkaloids) are useful in the treatment of cancer.

Actin Microfilaments and Intermediate Filaments

In addition to microtubules, two other cytoskeletal structures exist: microfilaments and intermediate filaments. Microfilaments are composed of actin, whereas intermediate filaments are a heterogeneous group of filaments with diameter sizes between those of microtubules and actin filaments.

Actin, which can exist in globular and filamentous forms, is of central importance to cellular biology. It contributes to cell motility, positioning of organelles in the cell, and cell shape and polarity. Many functions of actin filaments are performed in association with myosin motor proteins. Contractile activities involving actin microfilaments and associated thick myosin filaments contribute to muscle contraction.

The intermediate filaments include the cytokeratins, vimentin, and neurofilaments. They have structural and maintenance functions that are important in tissue, cellular, developmental, and differentiation processes. They are also very responsive to cellular stresses, such as heat, radiation, toxins, pathogens and oxidation. *Neurofibrillary tangles* found in the brain in Alzheimer disease contain microtubule-associated proteins and neurofilaments, evidence of a disrupted neuronal cytoskeleton.

SUMMARY CONCEPTS

- Cells are the smallest functional unit of the body. They are autonomous units that contain structures that are strikingly similar to those needed to maintain total body function.
- The cell membrane is a protein-studded lipid bilayer that surrounds the cell and separates it from its surrounding external environment. It contains receptors for hormones and other biologically active substances, participates in the electrical events that occur in nerve and muscle cells, and aids in the regulation of cell growth and proliferation. The cell surface is surrounded by a fuzzy-looking layer called the cell coat or glycocalyx. The cell coat participates in cell-to-cell recognition and adhesion, and it contains tissue transplant antigens.
- The nucleus is the control center for the cell. It contains deoxyribonucleic acid (DNA), which provides the information necessary for the synthesis of the various proteins that the cell must produce to stay alive and to transmit information from one generation to another.
- The cytoplasm contains the cell's organelles. Ribosomes serve as sites for protein synthesis in the cell. The endoplasmic reticulum (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. The Golgi apparatus modifies materials synthesized in the ER and packages them into secretory granules for transport within the cell or export from the cell. Lysosomes, which can be viewed as the digestive system of the cell, contain hydrolytic enzymes that digest worn-out cell parts and foreign materials. The mitochondria serve as power plants for the cell because they transform food energy into ATP, which is used to power cell activities. They contain their own extrachromosomal DNA, which is used in the synthesis of certain proteins required for mitochondrial function.
- In addition to its organelles, the cytoplasm also contains a network of microtubules, actin microfilaments, and intermediate filaments called the cytoskeleton. Microtubules are slender, stiff tubular structures that influence cell shape, provide a means of moving organelles through the cytoplasm, and form cilia, flagella, and centrioles. Actin microfilaments are dynamic, thin, threadlike cytoplasmic structures that are important in cell movement and organelle positioning. Many types of intermediate filaments function in supporting and maintaining the shape of cells and participate in numerous cellular processes.

Cell Metabolism and Energy Storage

Energy metabolism refers to the chemical processes involved in converting carbohydrates, fats, and proteins from the foods we eat into the energy needed for cell functions. Cells use oxygen to transform the breakdown products of the foods we eat into the energy needed for muscle contraction; the transport of ions and other molecules across cell membranes; and the synthesis of enzymes, hormones, and other macromolecules.

The special "unit of currency" for transferring energy in living cells is ATP. Adenosine triphosphate molecules consist of adenosine, a nitrogenous base; ribose, a five-carbon sugar; and three phosphate groups (Fig. 1-8). The last two phosphate groups are attached to the remainder of the molecule by two high-energy bonds. Each bond releases a large amount of energy when hydrolyzed. Adenosine triphosphate is hydrolyzed to form adenosine

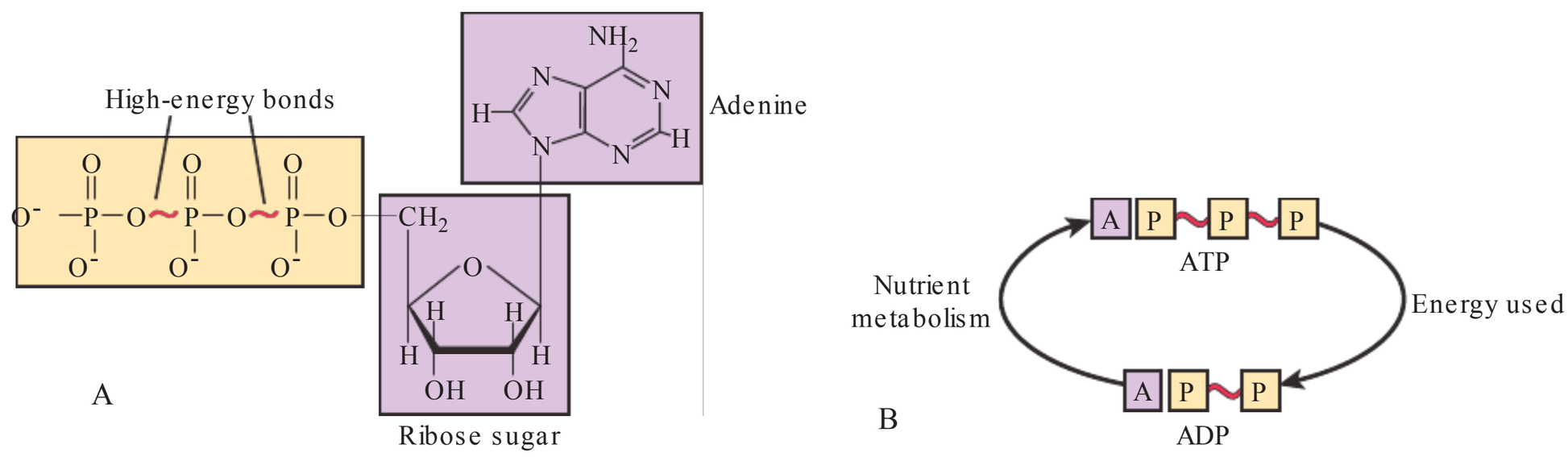


FIGURE 1-8. Adenosine triphosphate (ATP) is the major source of cellular energy. **(A)** Each molecule of ATP contains two high-energy bonds, each containing about 12 kcal of potential energy. **(B)** The high-energy ATP bonds are in constant flux. They are generated by substrate (glucose, amino acid, and fat) metabolism and are consumed as the energy is expended. ADP, adenosine diphosphate.

diphosphate (ADP) with the loss of one high-energy bond and to adenosine monophosphate (AMP) with the loss of two such bonds. The energy liberated from the hydrolysis of ATP is used to drive reactions that require free energy, such as muscle contraction and active transport mechanisms. Energy from foodstuffs is used to convert ADP back to ATP. Hence ATP is often called the *energy currency* of the cell; energy can be "saved" or "spent" using ATP as an exchange currency.

Two types of energy production are present in the cell: the *anaerobic* (i.e., without oxygen) glycolytic pathway, occurring in the cytoplasm, and the *aerobic* (i.e., with oxygen) pathway, occurring in the mitochondria. The glycolytic pathway serves as the prelude to the aerobic pathway.

Anaerobic Metabolism

Glycolysis is the anaerobic process by which energy is liberated from glucose. It is an important source of energy for cells that lack mitochondria. The process also provides a temporary source of energy for cells that are deprived of an adequate supply of oxygen. Glycolysis involves a sequence of reactions that convert glucose to pyruvic acid, with the concomitant production of ATP from ADP. The net gain of energy from the glycolytic metabolism of one molecule of glucose is two ATP molecules. Although relatively inefficient as to energy yield, the glycolytic pathway is important during periods of decreased oxygen delivery, such as occurs in skeletal muscle during the first few minutes of exercise.

Glycolysis requires the presence of nicotinamide adenine dinucleotide (NAD^+), a hydrogen carrier. The end products of glycolysis are pyruvate and NADH (the reduced form of NAD^+) plus H^+. When oxygen is present, pyruvic acid moves into the aerobic mitochondrial pathway, and NAD^+ is regenerated as NADH delivers its electron and proton (H^+) to the oxidative electron transport system. Under anaerobic conditions, such as cardiac arrest or circulatory shock, pyruvic acid is converted to lactic acid, which diffuses out of the cells into the extracellular fluid. Conversion of pyruvate to lactic acid is reversible, and once the oxygen supply has been restored, lactic acid is converted back to pyruvic acid and used directly for energy or to synthesize glucose.

Aerobic Metabolism

Aerobic metabolism, which supplies 90% of the body's energy needs, occurs in the cell's mitochondria and requires oxygen. It is here that the hydrogen and carbon molecules from dietary fats, proteins, and carbohydrates are broken down and combined with molecular oxygen to form carbon dioxide and water as energy is released. Unlike lactic acid, which is an end product of anaerobic metabolism, carbon dioxide and water are relatively harmless and easily eliminated from the body. In a 24-hour period, oxidative metabolism produces 150 to 300 mL of water.

The citric acid cycle, sometimes called the *tricarboxylic acid* (TCA) or *Krebs* cycle, provides the final common pathway for the metabolism of nutrients. In the citric acid cycle, which takes place in the matrix of the mitochondria, an activated two-carbon molecule of acetyl-coenzyme A (acetyl-CoA) condenses with a four-carbon molecule of oxaloacetic acid and moves through a series of enzyme-mediated steps. This process produces hydrogen atoms and carbon dioxide. As hydrogen is generated, it combines with NAD^+ or flavin adenine dinucleotide (FAD) for transfer to the electron transport system. Besides pyruvate from the glycolysis of glucose, products of amino acid and fatty acid degradation enter the citric acid cycle and contribute to the generation of ATP.

Oxidation of electrons from the hydrogen atoms generated during glycolysis and the citric acid cycle takes place in the electron transport system located on the inner mitochondrial membrane. The electrons are used to reduce elemental oxygen, which combines with hydrogen to form water. During this sequence of oxidative reactions, large amounts of energy are released and used to convert ADP to ATP. Because the formation of ATP involves the addition of a high-energy phosphate bond to ADP, the process is called *oxidative phosphorylation*.

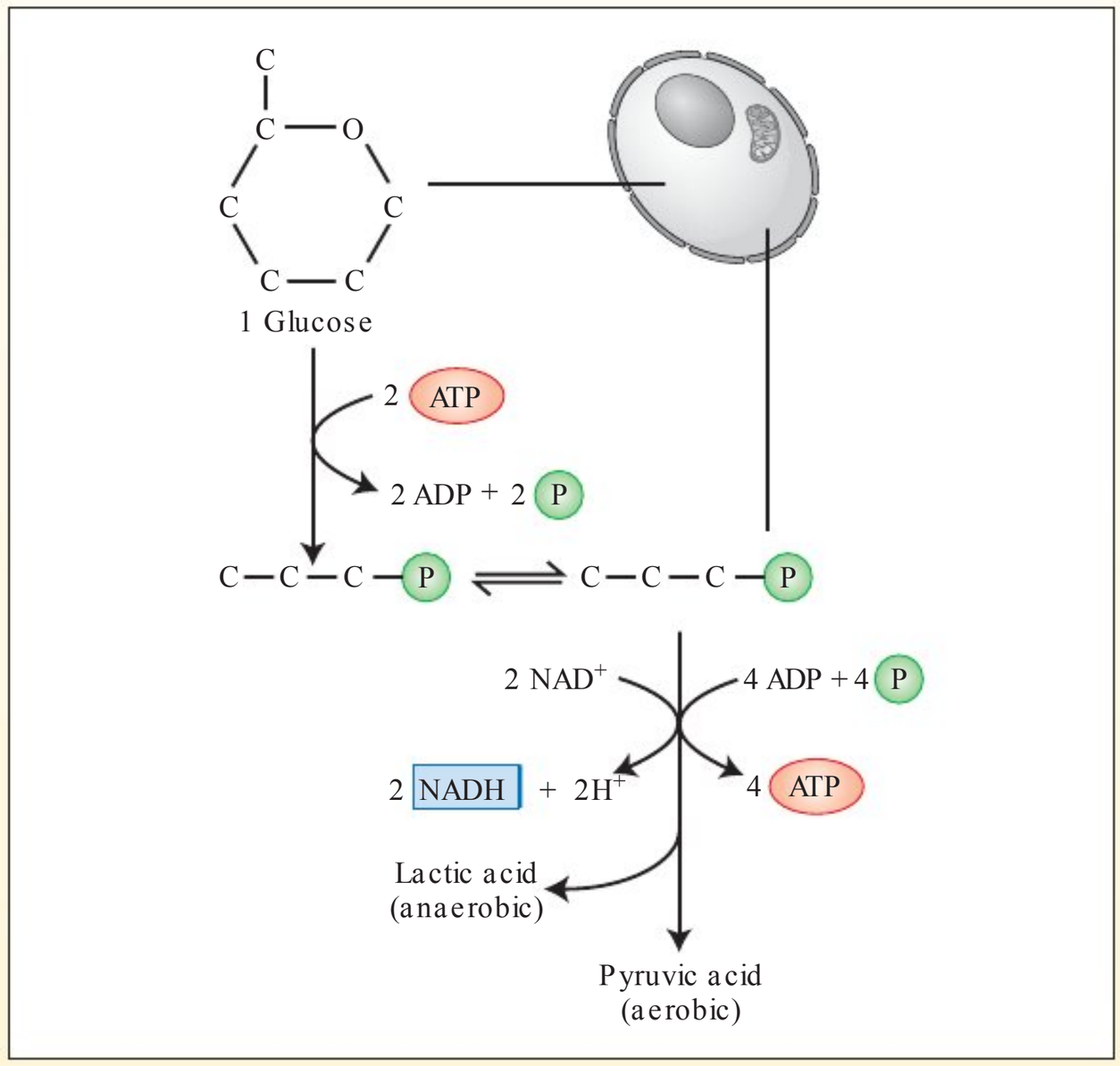
(*text continues on page 12*)

UNDERSTANDING → Cell Metabolism

Cell metabolism is the process that converts dietary fuels from carbohydrates, proteins, and fats into adenosine triphosphate (ATP), which provides energy for the cell. Adenosine triphosphate is formed through three major pathways: (1) the glycolytic pathway, (2) the citric acid cycle, and (3) the electron transport chain. In fuel metabolism, which is an oxidation–reduction reaction, the fuel donates electrons and is oxidized, and the coenzymes nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) accept electrons and are reduced.

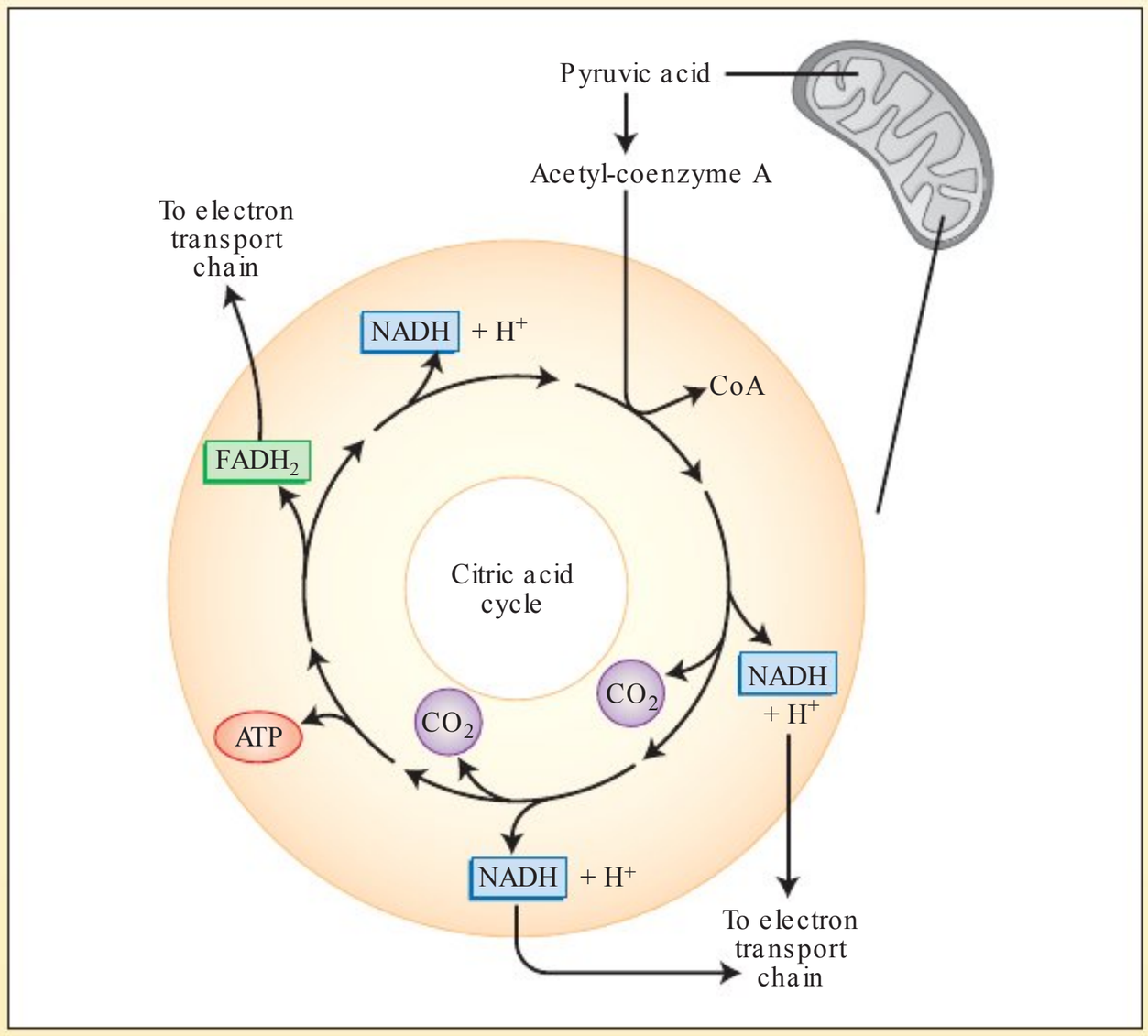
1

Glycolytic Pathway. Glycolysis, which occurs in the cytoplasm of the cell, involves the splitting of the six-carbon glucose molecule into two three-carbon molecules of pyruvic acid. Because the reaction that splits glucose requires two molecules of ATP, there is a net gain of only two molecules of ATP from each molecule of glucose that is metabolized. The process is anaerobic and does not require oxygen (O_2) or produce carbon dioxide (CO_2). When O_2 is present, pyruvic acid moves into the mitochondria, where it enters the aerobic citric acid cycle. Under anaerobic conditions, pyruvate is converted to lactic acid, allowing glycolysis to continue as a means of supplying cells with ATP when O_2 is lacking.



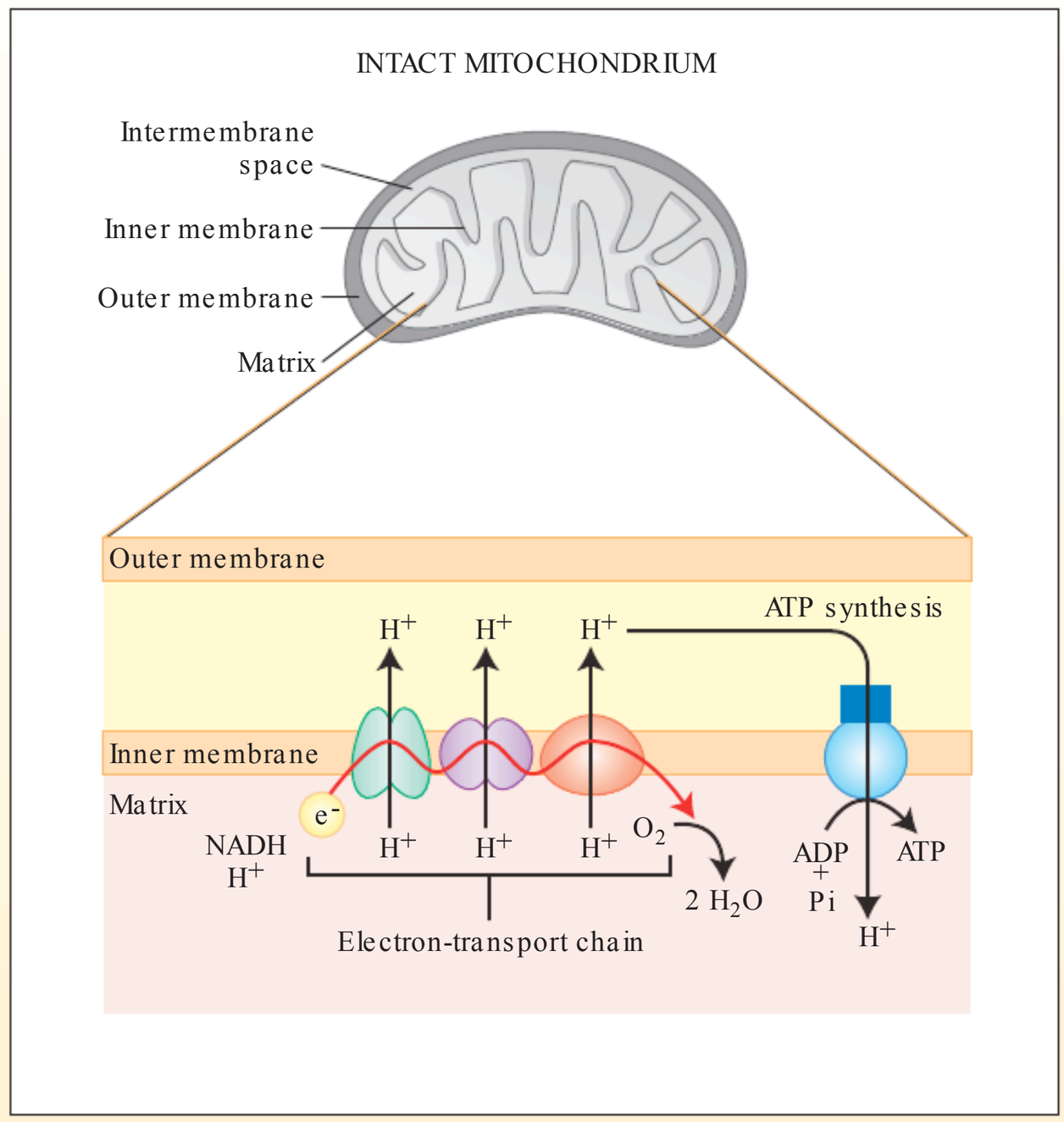
2

Citric Acid Cycle. Under aerobic conditions, both of the pyruvic acid molecules formed by the glycolytic pathway enter the mitochondria, where each combines with acetyl-coenzyme to form acetyl-coenzyme A (acetyl-CoA). The formation of acetyl-CoA begins the reactions that occur in the citric acid cycle. Some reactions release CO_2 and some transfer electrons from the hydrogen atom to NADH or FADH. In addition to pyruvic acid from the glycolysis of glucose, fatty acid and amino acid breakdown products can also enter the citric acid cycle. Fatty acids, which are the major source of fuel in the body, are oxidized by a process called β-*oxidation* to acetyl-CoA for entry into the citric acid cycle.



3

Electron Transport Chain. At the completion of the citric acid cycle, each glucose molecule has yielded only four new molecules of ATP (two from glycolysis and two from the citric acid cycle). In fact, the principal function of these earlier stages is to make the electrons (e^-) from glucose and other food substrates available for oxidation. Oxidation of the electrons carried by NADH and $FADH_2$ is accomplished through a series of enzymatically catalyzed reactions in the mitochondrial electron transport chain. During these reactions, protons (H^+) combine with O_2 to form water (H_2O), and large amounts of energy are released and used to add a high-energy phosphate bond to adenosine diphosphate (ADP), converting it to ATP. There is a net yield of 36 molecules of ATP from 1 molecule of glucose (2 from glycolysis, 2 from the citric acid cycle, and 32 from the electron transport chain). In general, the net amount of ATP formed from each gram of protein that is metabolized is less than for glucose, whereas that obtained from fat is greater (e.g., each 16-carbon fatty acid molecule yields about 129 molecules of ATP).



SUMMARY CONCEPTS

- Metabolism is the process whereby the carbohydrates, fats, and proteins from the foods we eat are broken down and subsequently converted into the energy needed for cell function. Energy is stored in the high-energy phosphate bonds of adenosine triphosphate (ATP), which serves as the energy currency for the cell.
- Two sites of energy conversion are present in cells: the anaerobic glycolytic pathway in the cytoplasm and the aerobic pathways in the mitochondria. The most efficient of these pathways is the aerobic citric acid cycle and electron transport chain in the mitochondria. This pathway, which requires oxygen, produces carbon dioxide and water as end products and results in the release of large amounts of energy that is used to convert adenosine diphosphate (ADP) to ATP. The glycolytic pathway in the cytoplasm involves the breakdown of glucose to form ATP. This pathway can function without oxygen by producing lactic acid.

(*text continued from page 9*)

Integration of Cell Function

Within a complex organism, such as a human being, different organs, tissues, and individual cell types develop specialized functions and needs. Yet each cell must contribute to the integrated life process as the body grows, differentiates, and adapts to changing conditions. Such integration requires that cells have the ability to communicate with one another, transport substances between their intracellular and extracellular environments, and generate and respond to changes in the electrical charge of membrane potentials.

Cell Signaling and Communication Mechanisms

Signaling systems consist of receptors that reside either on the cell membrane (surface receptors) or within the cells (intracellular receptors). Receptors are activated by a variety of chemical messengers including neurotransmitters, hormones, growth factors, and other chemical messengers, as well as signaling proteins called *cytokines* and *lipids*. Some lipid-soluble chemical messengers move through the membrane and bind to cytoplasmic or nuclear receptors to exert their physiologic effects. Signaling systems often rely on the intermediary activity of a separate class of membrane-bound regulatory proteins to convert extracellular signals, or first messengers, into intracellular signals, or second messengers, such as a unique form of adenosine monophosphate called *cyclic adenosine monophosphate* (cAMP). Many molecules involved in signal transduction within cells are enzymes and other proteins. Some of the enzymes are protein kinases that catalyze the phosphorylation of proteins, thereby changing their activity and function.

Cell Surface Receptors

Each cell type in the body contains numerous receptor proteins, which as a set may characterize the cell type, that enable it to respond to a complementary set of ligands (i.e., molecules with a high affinity for a receptor) or signaling molecules in a specific, preprogrammed way. These receptors, which span the cell membrane, relay information to a series of intracellular intermediates that eventually pass the signal to its final destination. There are three major classes of cell surface receptor proteins: G protein–linked receptors, enzyme-linked receptors, and ion channel–linked receptors.

G Protein–Linked Receptors. G protein–linked receptors mediate cellular responses for numerous types of first messengers through regulatory proteins called *G proteins* that bind to guanine nucleotides such as guanine diphosphate (GDP) and guanine triphosphate (GTP). With more than 1000 members, G protein–linked receptors are the largest family of cell surface receptors.

Although there are differences among the G protein–linked receptors, all share a number of features. They all have a ligand-binding extracellular receptor component,

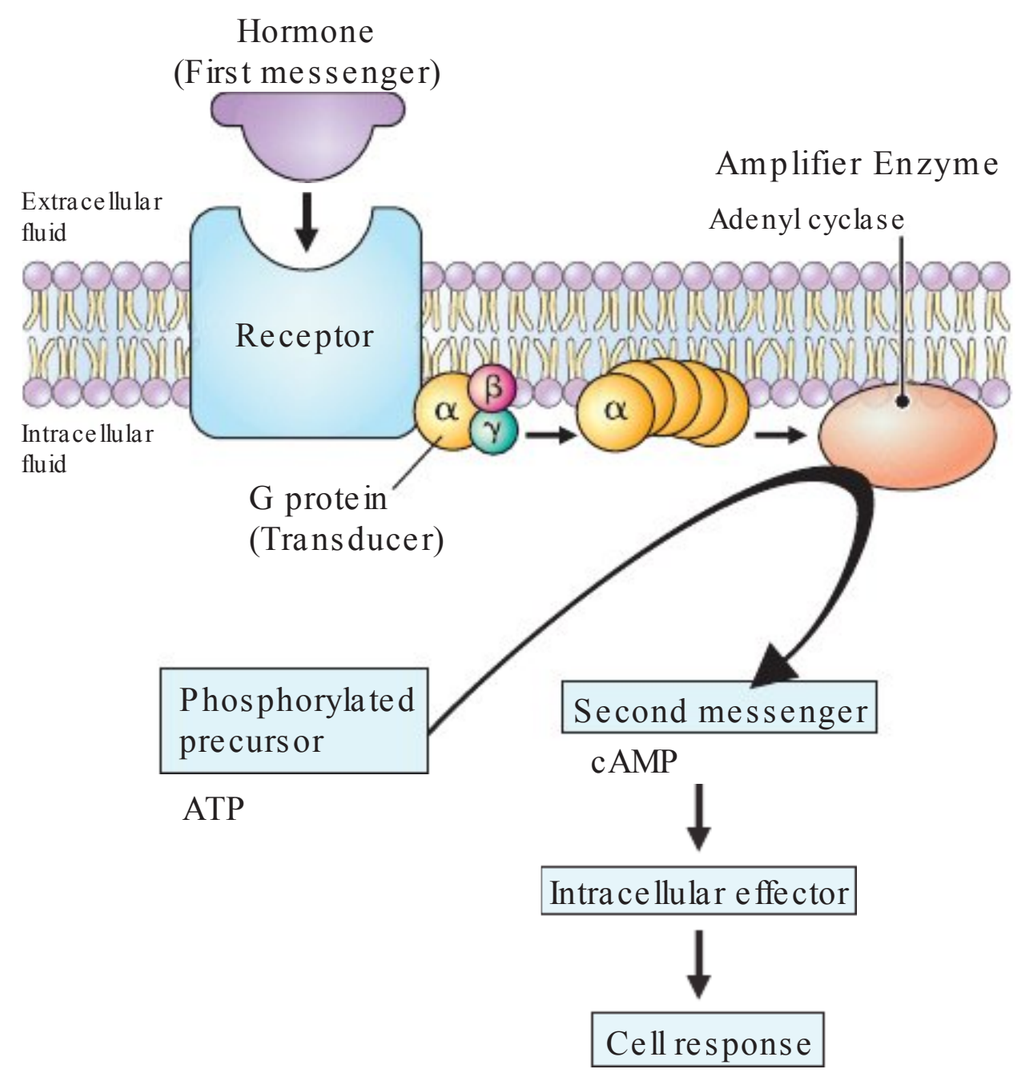


FIGURE 1-9. Activation of a G-protein-linked receptor and production of cyclic adenosine monophosphate (cAMP). Binding of a hormone (the first messenger) causes the activated receptor to interact with the inactive, guanine diphosphate (GDP)-bound G protein. This results in activation of the G protein and dissociation of the G protein α, β, and γ subunits. The activated α subunit of the G protein can then interact with and activate the membrane protein adenyl cyclase to catalyze the conversion of adenosine triphosphate (ATP) to the second messenger cAMP. The second messenger then activates an internal effector, which leads to the cell response.

which recognizes a specific ligand or first messenger. Upon ligand-binding, they all undergo conformational changes that activate the G protein found on the cytoplasmic side of the cell membrane (Fig. 1-9). All G proteins incorporate the *guanosine triphosphatase (GTPase) cycle*, which functions as a molecular switch that exists in two states: an activated (on) state and an inactivated (off) state. Receptor activation causes the α subunit to dissociate from the receptor and the β and γ subunits and transmit the signal from the first messenger to a membrane-bound intermediate called an *effector*. Often, the effector is an enzyme that converts an inactive precursor molecule into a second messenger, which diffuses into the cytoplasm and carries the signal beyond the cell membrane. One common effector is the enzyme *adenylyl cyclase*, which converts the precursor ATP to the second messenger cAMP, transferring the two phosphate groups to other proteins. This transfer changes the conformation and function of these proteins. Such changes eventually produce the cell response initiated by the first messenger, whether it is a secretion, muscle contraction or relaxation, or change in metabolism. Sometimes it is the opening of membrane channels involved in calcium or potassium influx.

Enzyme-Linked Receptors. Like G protein–linked receptors, enzyme-linked receptors are transmembrane

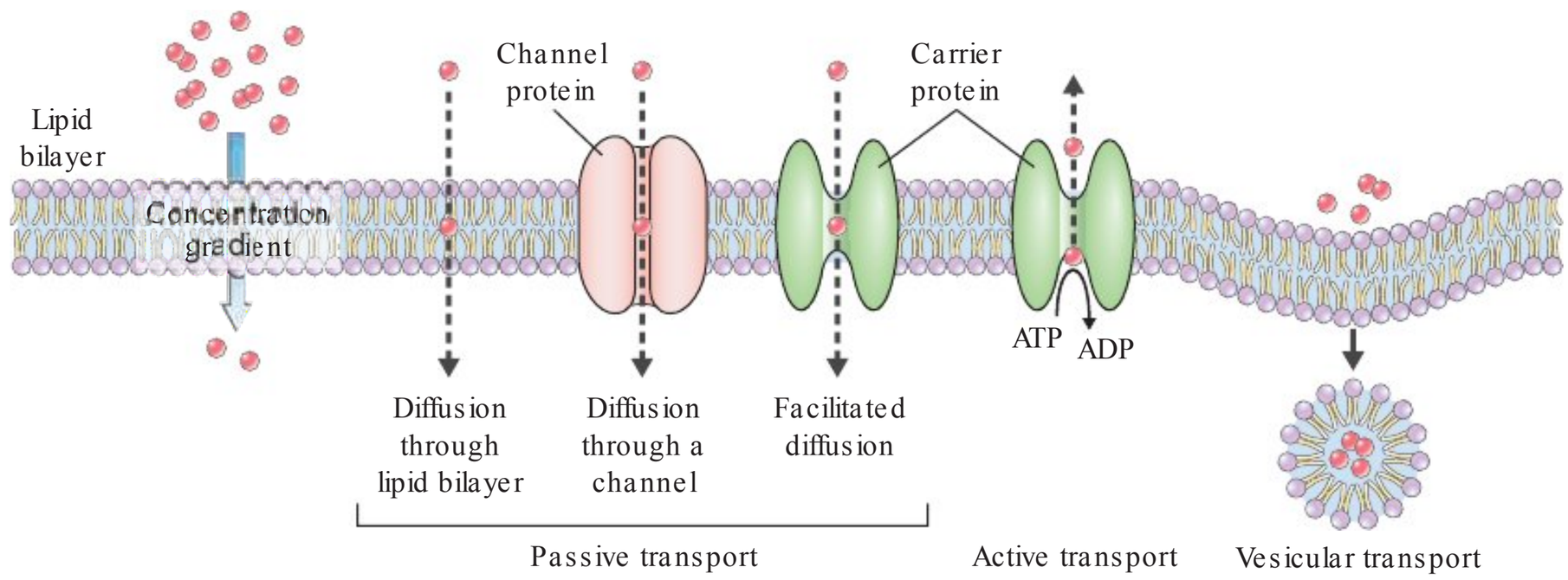


FIGURE 1-10. Mechanisms of membrane transport. Passive transport represents the net movement from a region of higher to lower concentration and active transport (energy requiring) from a region of lower to higher concentration. Vesicular transport involves the formation of membrane-enclosed vesicles or sacs that serve as transport vehicles from extracellular materials that are being moved into the cell (endocytosis) or intracellular materials that are being moved out of the cell (exocytosis). ADP, adenosine diphosphate; ATP, adenosine triphosphate.

proteins with their ligand-binding site on the outer surface of the cell membrane. Instead of having a cytosolic domain that associates with a G protein, their cytosolic domain either has intrinsic enzyme activity or associates directly with an enzyme. There are several classes of enzyme-linked receptors, including one widely used in hormonal control of cell function. The binding of the hormone to a special transmembrane receptor results in activation of the enzyme adenylyl cyclase at the intracellular portion of the receptor. This enzyme then catalyzes the formation of the second messenger cAMP, which has multiple effects on cell function. Insulin, for example, acts by binding to an enzyme-linked receptor (see Chapter 33).

Ion Channel–Linked Receptors. Ion channel–linked receptors are involved in the rapid synaptic signaling between electrically excitable cells. Many neurotransmitters mediate this type of signaling by transiently opening or closing ion channels formed by integral proteins in the cell membrane (to be discussed). This type of signaling is involved in the transmission of impulses in nerve and muscle cells.

Intracellular Receptors

Some messengers, such as thyroid hormone and steroid hormones, do not bind to membrane receptors but move directly across the lipid bilayer of the cell membrane and are transported to the cell nucleus, where they influence DNA activity (see Chapter 31). Many of these hormones bind to a receptor within the cytoplasm, and the receptor–hormone complex enters the nucleus. There it binds to DNA, initiating processes that increase the production of proteins that alter cell function.

Membrane Transport Mechanisms

The lipid layer of the cell membrane serves as a barrier against the movement of water and water-soluble substances between the intracellular and extracellular fluids, while allowing a few lipid-soluble (e.g., alcohols with lower numbers of hydrocarbons, oxygen, nitrogen) and uncharged molecules (glycerol, water) to cross the cell membrane by simple diffusion. The cell membrane also contains large numbers of protein molecules, many of which insert completely through the membrane (Fig. 1-10). Most ions and small molecules rely on these proteins for transport.

Different membrane proteins function in different ways. For example, *channel proteins* form water-lined passageways through the membrane and allow free movement of water as well as selected ions or molecules. *Membrane transport proteins* bind molecules or ions and undergo a series of conformational changes to transfer the bound solute across the membrane. Some transport proteins, called *uniporters*, simply mediate the movement of a single solute from one side of the membrane to the other, whereas others function as coupled transporters in which the transfer of one solute depends on the transfer of a second solute (Fig. 1-11). This coupled transport involves either the simultaneous transport in the same direction, performed by transporters called *symporters*, or the transport of a second solute in the opposite direction, by transporters called *antiporters*.

All channels and many transporters allow solutes to cross the membrane only passively by *passive transport* or *facilitated diffusion*. Cells also require transport proteins that actively pump certain solutes across the membrane against an electrochemical gradient, in a process called *active transport*. Active transport is directional and requires an energy source such as ATP. The cell membrane can also engulf substances, forming a membrane-bound vesicle; this vesicle is brought into the cell by *endocytosis*. The process by which cellular vesicles fuse to the cell membrane releasing contents outside of the cell is called *exocytosis*.

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 that can transverse the channel.

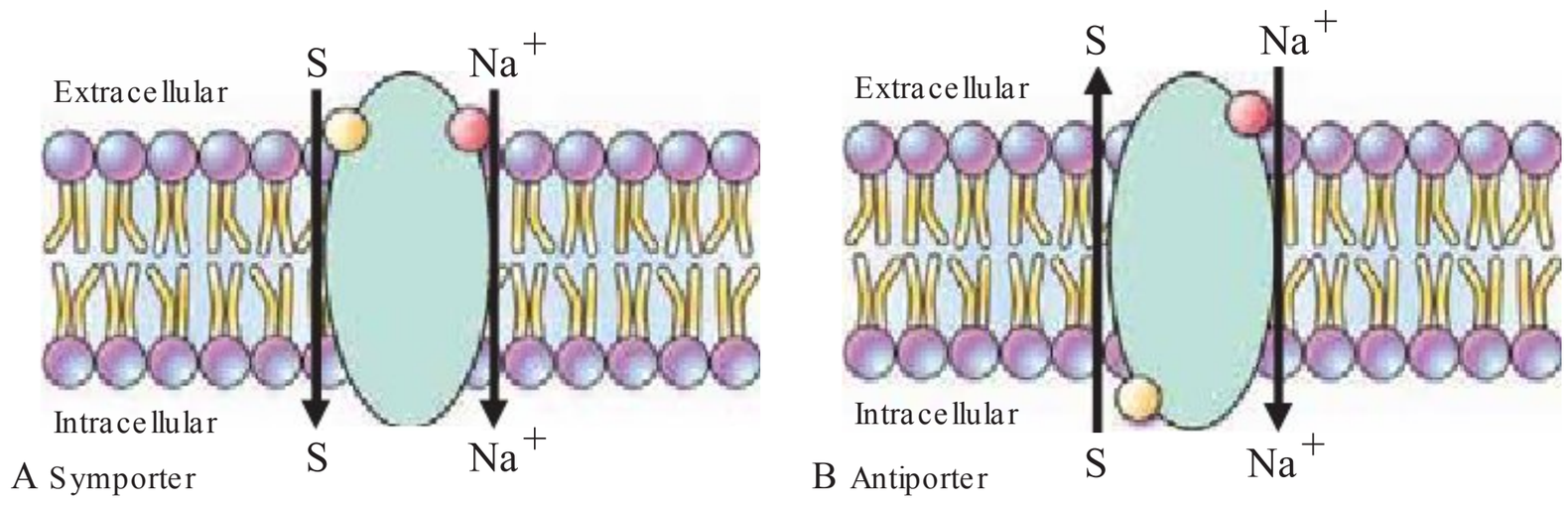


FIGURE 1-11. Secondary active transport systems. **(A)** Symport or cotransport carries the transported solute (S) in the same direction as the sodium (Na^+) ion. **(B)** Antiport or countertransport carries the solute and Na^+ in the opposite direction.

A host of genetic disorders known as *channelopathies* involve mutations in channel proteins. For example, in cystic fibrosis (see Chapter 23), the primary defect resides in an abnormal chloride channel, which results in increased sodium and water reabsorption that causes respiratory tract secretions to thicken and occlude the airways.

Diffusion

Diffusion refers to the passive process by which molecules and other particles in a solution become widely dispersed and reach a uniform concentration because of energy created by their spontaneous kinetic movements. In the process of reaching a uniform concentration, these molecules and particles move "downhill" from an area of higher to an area of lower concentration. If the molecules or particles carry a net charge, both the concentration gradient and the electrical potential difference across the membrane influence transport.

Lipid-soluble molecules, such as oxygen, carbon dioxide, alcohol, and fatty acids, become dissolved in the lipid matrix of the cell membrane and diffuse through the membrane in the same manner that diffusion occurs in water. Other substances diffuse through minute pores of the cell membrane.

Simple Diffusion. Simple diffusion means that the kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with a carrier protein. The rate of diffusion depends on how many particles are available for diffusion, the kinetic movement of the particles, and the number and size of the openings in the membrane through which the molecules or ions can move.

Facilitated Diffusion. Like simple diffusion, facilitated diffusion occurs down a concentration gradient; thus, it does not require input of metabolic energy. Unlike simple diffusion, however, facilitated diffusion requires a transport protein. Some substances, such as glucose, cannot pass unassisted through the cell membrane because they are not lipid soluble or they are too large to pass through the membrane's pores. These substances combine with special transport proteins at the membrane's outer surface, are carried across the membrane attached to the transporter, and then are released. In facilitated diffusion, a substance can move only from an area of higher concentration to one of lower concentration. The rate at which a substance moves across the membrane by facilitated diffusion depends on the difference in concentration between the two sides of the membrane. Also important are the availability of transport proteins and the rapidity with which they can bind and release the substance being transported. It is thought that insulin, which facilitates the movement of glucose into cells, acts by increasing the availability of glucose transporters in the cell membrane.

Ion Channels and Gates. Ion channels (leak channels) are integral proteins that span the width of the membrane and are normally composed of several polypeptides or protein subunits that form a gating system (Fig. 1-12). Specific stimuli cause the protein subunits to undergo conformational changes to form an open channel or gate through which the ions can move. In this way, ions do not need to cross the lipid-soluble portion of the membrane but can remain in the aqueous solution that fills the ion channel. Many of the ion channels are highly selective for transport of one or more specific ions or molecules. This selectivity results from the characteristics of the channel itself, such as its diameter, its shape, and the nature of electrical charges and chemical bonds along its inside surface.

The cell membrane contains two basic groups of ion channels: leakage channels and gated channels. Leakage channels are open even in the unstimulated state, whereas gated channels open and close in response to specific stimuli. Three main types of gated channels are present in the cell membrane: *voltage-gated channels*, which have electrically operated channels that open when the membrane potential changes beyond a certain point; *ligand-gated channels*, which are chemically operated and respond to specific receptor-bound ligands, such as the neurotransmitter acetylcholine; and *mechanically gated channels*, which open or close in response to such mechanical stimulations as vibrations, tissue stretching, or pressure.

Movement of Water Across the Cell Membrane. Water molecules move through adjacent phospholipid

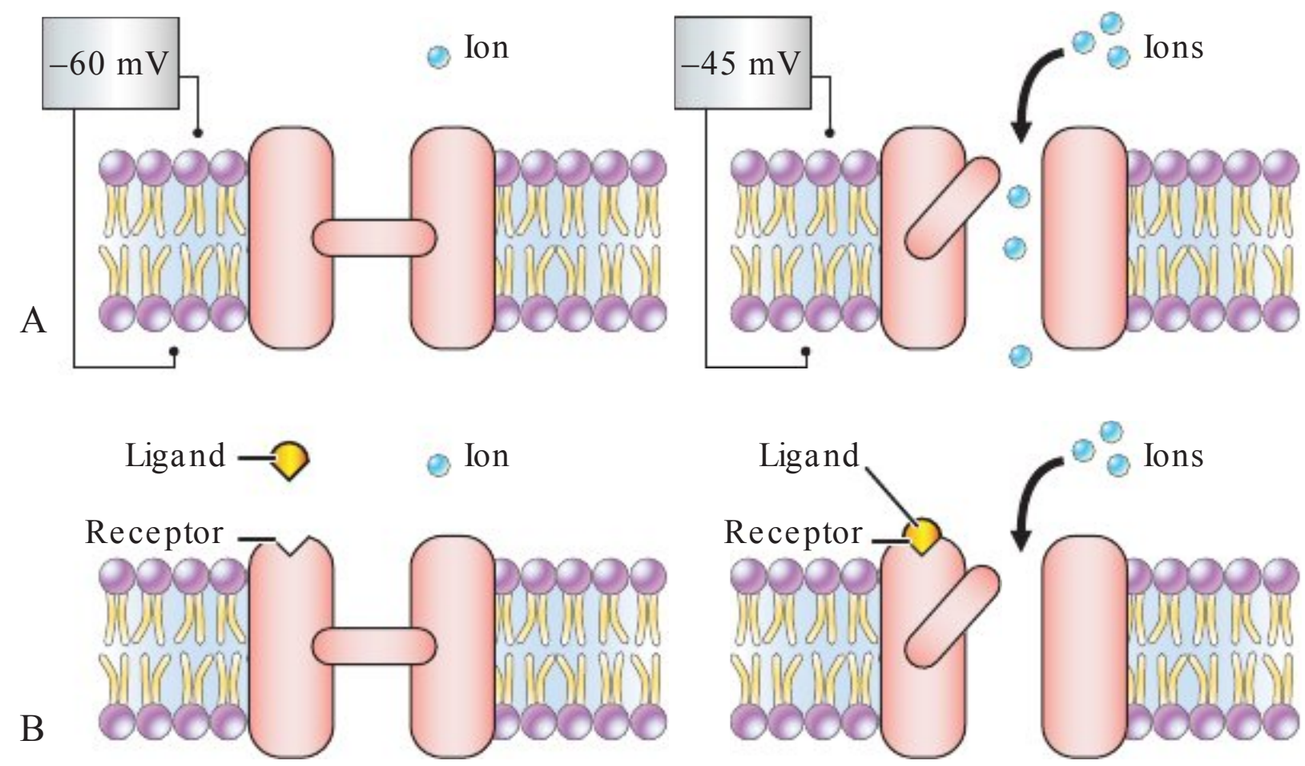


FIGURE 1-12. Gated ion channels that open in response to specific stimuli. **(A)** Voltage-gated channels are controlled by a change in the membrane potential. **(B)** Ligand-gated channels are controlled by binding of a ligand to a receptor.

molecules in the cell membrane by osmosis without actually dissolving in the region occupied by the fatty acid side of the chains. Osmosis is regulated by the concentration of nondiffusible particles on either side of the membrane, with water moving from the side with the lower concentration of particles to the side with the higher concentration. The cell membranes of most cells also contain transmembrane proteins, called *aquaporins*, that function as water channels. Aquaporins are especially abundant in cells that must transport water at particularly high rates, such as certain cells of the kidney.

Active Transport

The process of diffusion describes particle movement from an area of higher concentration to one of lower concentration, resulting in an equal distribution of permeable substances across the cell membrane. Sometimes, however, different concentrations of a substance are needed in the intracellular and extracellular fluids. For example, to function, a cell requires a higher intracellular concentration of potassium ions than is present in the extracellular fluid, while maintaining a much lower concentration of sodium ions than the extracellular fluid. In these situations, energy is required to pump the ions "uphill" or against their concentration gradient. When cells use energy to move ions against an electrical or chemical gradient, the process is called *active transport*. Two types of active transport systems exist: primary active transport and secondary active transport.

Primary Active Transport. Among the substances that are transported by primary active transport are sodium, potassium, calcium, and hydrogen ions. The active transport system studied in the greatest detail is the sodium/potassium (Na^+/K^+)-adenosine triphosphatase (ATPase) membrane pump. The Na^+/K^+–ATPase membrane pump moves sodium from inside the cell to the extracellular region, where its concentration is approximately 14 times greater than inside; the pump also returns potassium to the inside, where its concentration is approximately 35 times greater than it is outside the cell. If it were not for the activity of the Na^+/K^+–ATPase membrane pump, the osmotically active sodium particles would accumulate in the cell, causing cellular swelling because of an accompanying influx of water.

Secondary Active Transport. Secondary active transport mechanisms harness the energy derived from the primary active transport of one substance, usually sodium, for the cotransport of a second substance. For example, when sodium ions are actively transported out of a cell by primary active transport, a large concentration gradient develops (i.e., high concentration on the outside and low on the inside). This concentration gradient represents a large storehouse of energy because sodium ions are always attempting to diffuse into the cell. Similar to facilitated diffusion, secondary transport uses membrane transport proteins. These proteins have two binding sites: one for sodium and the other for the substance undergoing secondary transport. Secondary active transport systems are classified into two groups: cotransport, or symport systems, in which sodium and the solute are transported in the same direction, and countertransport, or antiport systems, in which sodium and the solute are transported in the opposite directions. An example of cotransport occurs in the intestine, where the absorption of glucose and amino acids is coupled with sodium transport.

Vesicular Transport

Vesicular transport is a mechanism in which materials are transported in membrane-bound vesicles. There are two types of vesicular transport: *endocytosis*, in which materials are moved into a cell in a vesicle formed from the cell membrane, and *exocytosis*, in which materials are moved out of a cell by fusion of a vesicle with the cell membrane.

Endocytosis is the process by which cells engulf materials from their surroundings. In the process, the material is progressively enclosed in small portions of the cell membrane, which first invaginates (folds inward) and then pinches off to become an endocytotic vesicle. If the vesicle is small (>150 nm in diameter), the process is called *pinocytosis*, and the vesicle is called a *pinocytotic vesicle*; if the vesicle is large (>250 nm in diameter), the process is called *phagocytosis*, and the vesicle is called

a *phagosome*. The process of pinocytosis, which means "cell drinking," is important in the transport of proteins and strong solutions of electrolytes. Phagocytosis, which means "cell eating," involves the engulfment and subsequent killing or degradation of microorganisms and other particulate matter. Certain cells, such as macrophages and neutrophils, are adept at engulfing and disposing of invading organisms, damaged cells, and unneeded extracellular constituents.

Exocytosis is the mechanism for the secretion of intracellular substances into the extracellular spaces. It may be considered a reverse of endocytosis in that the membrane of the secretory granule fuses with the cell membrane and allows the contents of the granule to be released into the extracellular fluid. Exocytosis is important in removing cellular debris and releasing substances, such as hormones and cytokines, synthesized in the cell.

Receptor-mediated endocytosis involves the binding of substances to a receptor on the cell surface. Many of these receptor proteins are concentrated in *clathrin-coated pits*, which are specific areas of the cell where the membrane is lined on its cytoplasmic side by a peripheral protein called *clathrin*. The interaction between the proteins in the receptor–ligand complex causes the membrane to invaginate. The edges of the membrane around the clathrin-coated pit then fuse, and a portion of the membrane pinches off as an endocytic vesicle. Almost immediately after it is formed, the vesicle loses its clathrin coat and becomes fused with an early endosome in a manner similar to that involved in non–receptor-mediated endocytosis. The uptake of cholesterol transported in the blood as low-density lipoprotein (LDL) relies on receptor-mediated removal associated with clathrin-coated pits. This pathway for cholesterol removal is disrupted in persons who inherit defective genes for encoding LDL receptors (see Chapter 18).

In addition to clathrin-coated pits and vesicles, there are a number of other mechanisms by which cells can form endocytotic vesicles. One of these pathways involves the formation of small invaginations or "little cavities" in the cell membrane, called *caveolae*, that extend inward, indenting the cell membrane and the cytoplasm. These cavities may pinch off and form free vesicles within the cytoplasm. Caveolae are considered to be sites for uptake of material into the cell, for expulsion of material from the cell, and for addition or removal of cell membrane components. In smooth muscle, caveolae project into the cytoplasm and, analogous to the T tubules in striated muscle, play an important role in regulating intracellular calcium concentration and smooth muscle tone. In addition to transport, caveolae are involved in a number of other functions such as signal transduction and may be involved in the pathogenesis of a number of diseases, including muscular dystrophy.

Generation of Membrane Potentials

Living organisms have electrical properties in which current flow involves the movement of ions in water. Electrical potentials exist across the membranes of most cells in the body. Because these potentials occur at the level of the cell membrane, they are called *membrane potentials*. In excitable tissues, such as nerve or muscle cells, changes in the membrane potential are necessary for generation and conduction of nerve impulses and muscle contraction. In other types of cells, such as glandular cells, changes in the membrane potential contribute to hormone secretion and other functions.

Electrical potentials describe the ability of separated electrical charges of opposite polarity (+ and −) to do work. In regard to cells, the oppositely charged particles are ions, and the barrier that separates them is the cell membrane. Electrical potentials are measured in volts (V) or units of electromotive force (EMF). Voltage is always measured with respect to two points in a system. For example, the voltage in a car battery (6 or 12 V) is the potential difference between the two battery terminals. In a cell it is the potential difference between the inside and outside of the cell membrane. Because the total amount of charge that can be separated by a biologic membrane is small, the potential differences are small and are therefore measured in millivolts (mV), or 1/1000 of a volt.

There are two main factors that alter membrane potentials: the difference in the concentration of ions on the inside and outside of the membrane and the permeability of the membrane to these ions. Extracellular and intracellular fluids are electrolyte solutions containing approximately 150 to 160 mmol/L of positively charged ions and an equal concentration of negatively charged ions. The diffusion of these current-carrying ions is responsible for generating and conducting membrane potentials. A *diffusion potential* describes the voltage generated by ions that diffuse across the cell membrane.

An *equilibrium potential* is one in which there is no net movement of a particular ion across a membrane because the diffusion potential and electrical forces generated by the movement of the ion are exactly balanced. The magnitude of the equilibrium potential, also known as the *Nernst potential*, is determined by the ratio of the concentration of a specific ion on the two sides of the membrane. The greater the ratio, the greater the tendency for the ion to diffuse in one direction, and therefore the greater the electrical forces required to prevent further diffusion. The Nernst equation (described in the figure on Understanding Membrane Potentials) can be used to calculate the equilibrium potential for any univalent ion at a given concentration difference, assuming that membrane is permeable to the ion. When using the equation, it is generally assumed that the electrical potential of the extracellular fluid outside the membrane remains at zero and the potential being calculated is the electrical potential inside the membrane. It is also assumed that the sign of the potential is negative (−) if a positively charged ion diffuses from the inside to the outside of the membrane and positive (+) if a positively charged ion diffuses from the outside to the inside of the membrane.

The *resting membrane potential* represents the period of time when excitable cells, such as nerve fibers, are not transmitting signals. Because resting cell membranes are

more permeable to potassium than sodium, the resting membrane reflects the diffusion of potassium ions. The Na^+/K^+-ATPase membrane pump, which removes three Na^+ from inside the cell while returning two K^+ to the inside, assists in maintaining the resting membrane potential. During an action potential, the cell membrane becomes more permeable to sodium, causing its polarity to change so that it is positive on the inside and negative on the outside (discussed in Chapter 34).

SUMMARY CONCEPTS

- Cells communicate with each other by chemical messenger systems. Chemical messengers bind to receptors on or near the cell surface. There are three classes of cell surface receptor proteins: G protein-linked, enzyme-linked, and channel-linked. G protein–linked receptors rely on a class of molecules called G proteins that function as an on–off switch to convert external signals (first messengers) into internal signals (second messengers). Enzyme-linked receptors have intrinsic enzyme activity or rely on enzymes that are closely associated with the receptor they activate. One type of enzyme-linked receptor is widely used in hormonal control of cell function and involves the activation of the enzyme adenylyl cyclase, which catalyzes the formation of cAMP, a second messenger that has multiple effects inside the cell. Activation of ion channel–linked receptors (e.g., by neurotransmitters) may trigger signaling to transiently open or close ion channels formed by integral proteins in the cell.
- Substances that enter or leave the cell must cross the cell membrane. Diffusion is a process by which substances such as ions move from areas of greater concentration to areas of lesser concentration until reaching a uniform distribution. Facilitated diffusion is a passive process, in which molecules that cannot normally pass through the cell's membranes do so with the assistance of a carrier molecule. Active transport requires the cell to expend energy in moving ions against a concentration gradient. The Na^+/K^+-ATPase membrane pump is the best-known type of active transport. Vesicular transport is a mechanism in which a cell encloses extracellular material in a membrane-bound vesicle. There are two types of vesicular transport: endocytosis, in which materials are brought into the cell by invagination of the cell membrane to form a vesicle, and exocytosis, in which materials are exported from the cell by fusion of a vesicle with the cell membrane.
- Electrical potentials, which are measured in volts, describe the ability of separated electrical charges of opposite polarity (+ and −) to do work. In regard to cells, the oppositely charged particles are ions, and the barrier that separates them is the cell membrane. There are two main factors that alter membrane potentials and excitability: the difference in concentration of ions on the inside and outside of the membrane and the permeability of the membrane to these ions. An equilibrium potential is one in which there is no net movement of a particular ion across a membrane because the diffusion and electrical forces generated by the movement of the ions are exactly balanced. The resting membrane potential (– outside and + inside) is essentially a potassium equilibrium potential that results from the selective permeability of the membrane to the potassium ion and the large difference in potassium concentration that exists between the inside and the outside of the membrane. During an action potential, the cell membrane becomes highly permeable to sodium, causing it to depolarize and reverse its polarity (− inside and + outside).

Tissues

In the preceding sections, we discussed the individual cell, its metabolic processes, and mechanisms of signaling and communication. Although cells have similarities, their structures and functions vary according to the specific needs of the body. For example, muscle cells are specialized to perform different functions from skin cells or nerve cells. Groups of cells that are closely associated in structure and have common or similar functions are called *tissues*. Four categories of tissue exist: (1) epithelial, (2) connective, (3) muscle, and (4) nervous. These tissues do not exist in isolated units but in association with each other and in variable proportions, forming different structures and organs of the body. This section of the chapter provides a brief overview of the cells in each of the four tissue types, the structures that hold these cells together, and the extracellular matrix in which they live.

Embryonic Origin of Tissue Types

After conception, the fertilized ovum undergoes a series of divisions, ultimately forming different cell types that comprise the various tissues of the body. The formation of different, more specialized types of cells and

(*text continues on page 20*)

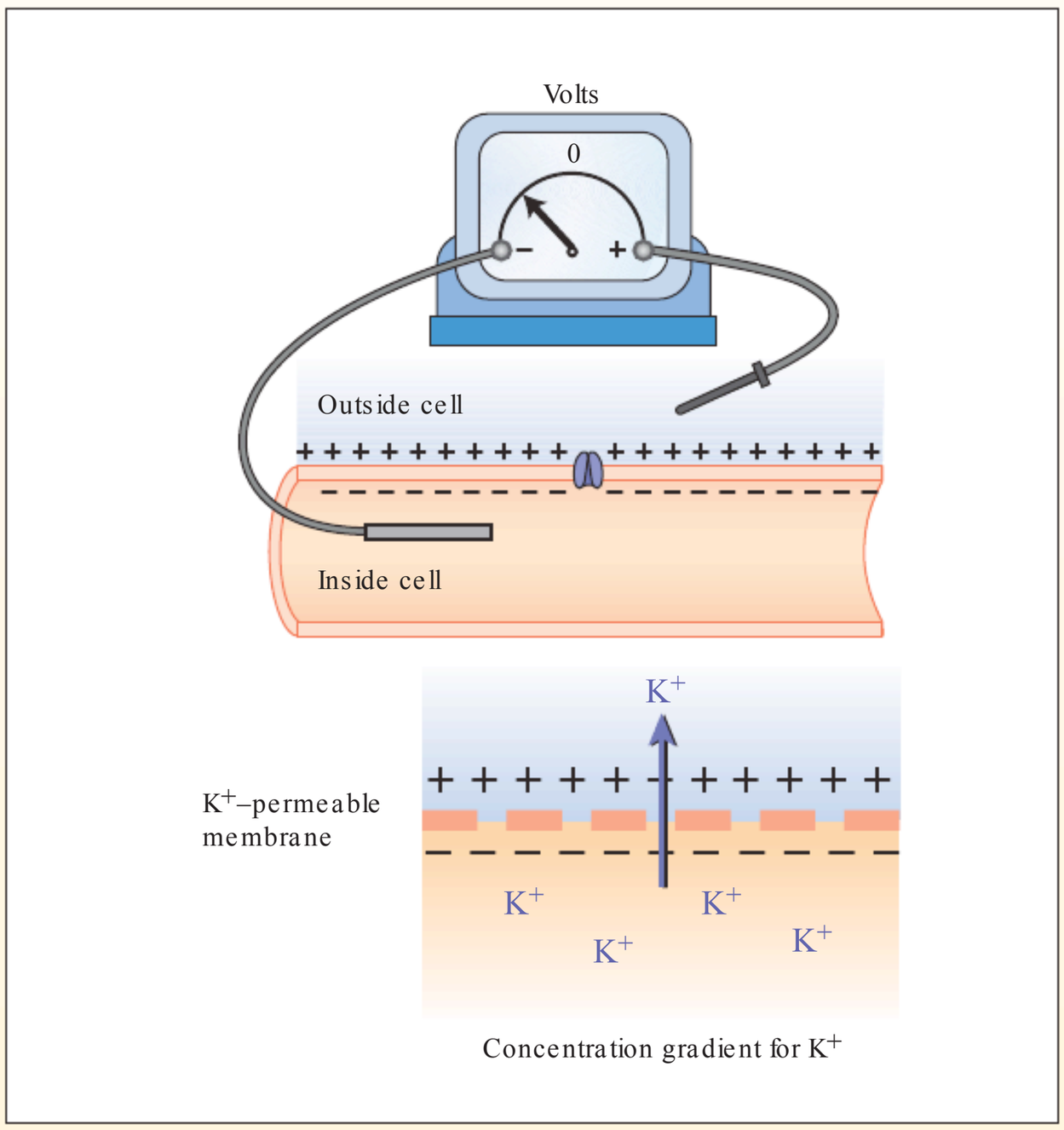
UNDERSTANDING → Membrane Potentials

Electrochemical potentials are present across the membranes of virtually all cells in the body. Some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrical impulses and transmitting these impulses along their membranes. Generation of membrane potentials relies on (1) diffusion of current-carrying ions, (2) development of an electrochemical equilibrium, and (3) establishment of a resting membrane potential and triggering an action potential.

1

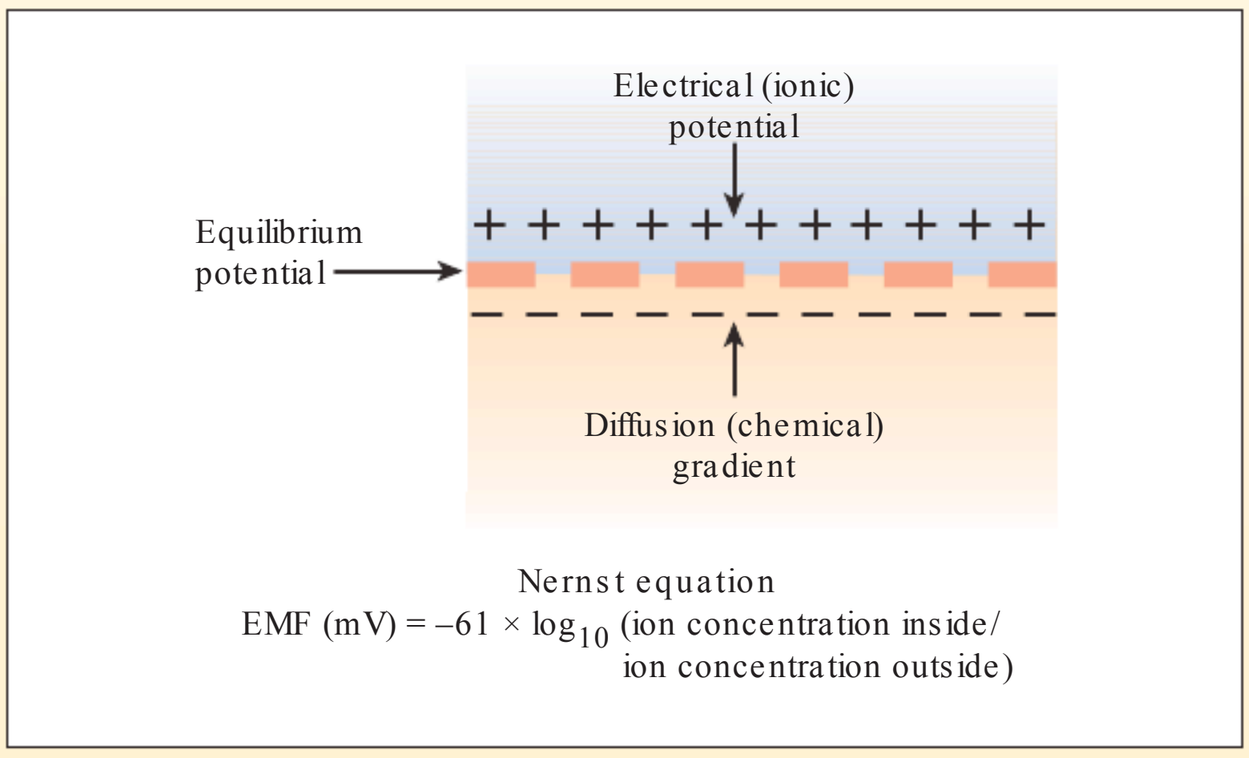
Diffusion potentials. A diffusion potential is a potential difference generated across a membrane when a current-carrying ion, such as the potassium (K^+) ion, diffuses down its concentration gradient. Two conditions are necessary for this to occur: (1) the membrane must be selectively permeable to a particular ion, and (2) the concentration of the diffusible ion must be greater on one side of the membrane than the other.

The magnitude of the diffusion potential, measured in millivolts (mV), depends on the size of the concentration gradient. The sign (+ or −) or polarity of the potential depends on the diffusing ion. It is negative on the inside when a positively charged ion such as K^+ diffuses from the inside to the outside of the membrane, carrying its charge with it.



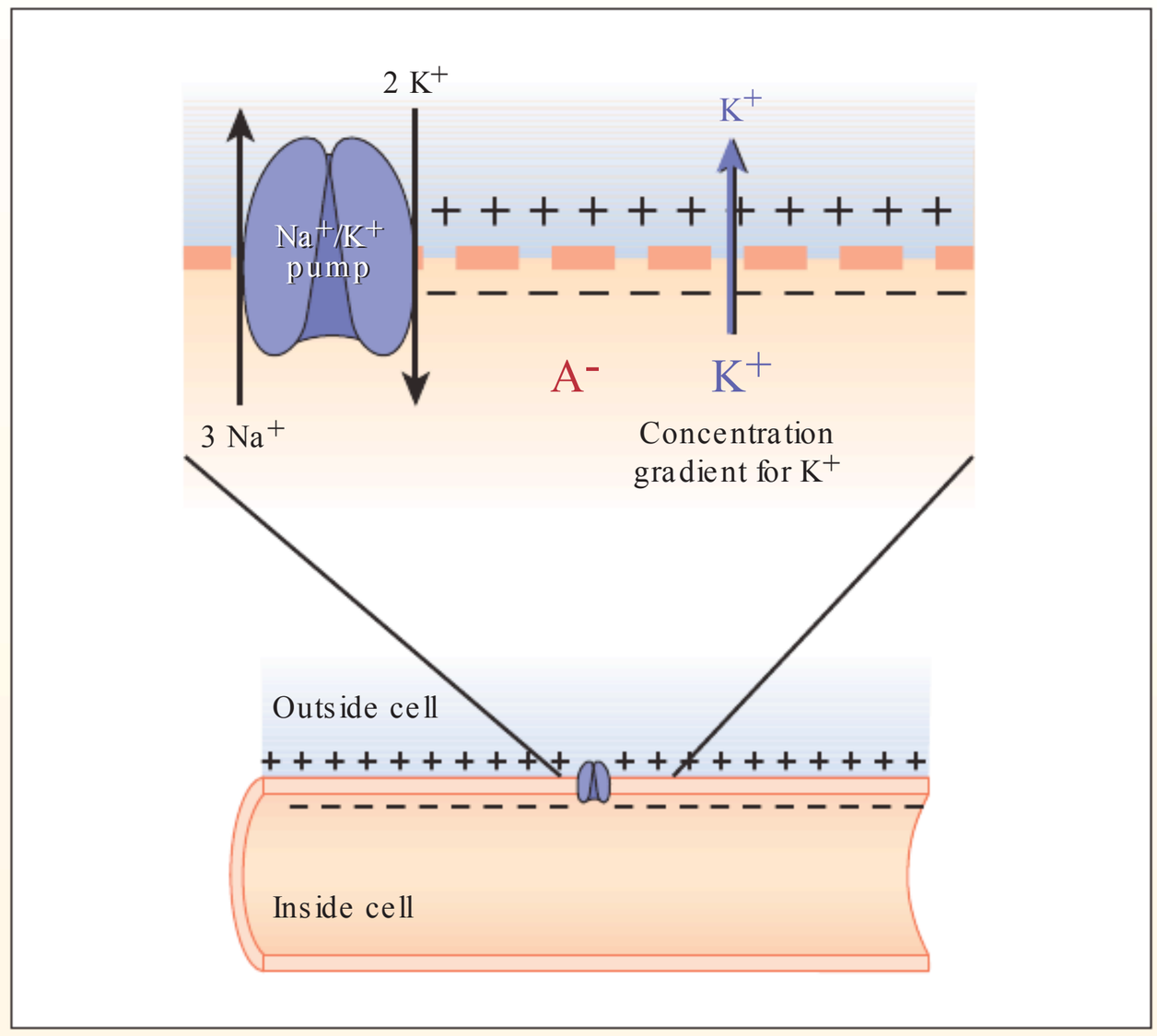
2

Equilibrium potentials. An equilibrium potential is the membrane potential that exactly balances and opposes the net diffusion of an ion down its concentration gradient. As a cation diffuses down its concentration gradient, it carries its positive charge across the membrane, thereby generating an electrical force that will eventually retard and stop its diffusion. An electrochemical equilibrium is one in which the *chemical forces* driving diffusion and the *repelling electrical forces* are exactly balanced so that no further diffusion occurs. The equilibrium potential (EMF, electromotive force) can be calculated by inserting the inside and outside ion concentrations into the Nernst Equation.



3

Resting membrane potential (RMP). The RMP, which is necessary for electrical excitability, is present when the cell is not transmitting impulses. Because the resting membrane is permeable to K^+, it is essentially an K^+ equilibrium potential. This can be explained in terms of the large K^+ concentration gradient (e.g., 140 mEq/L inside and 4 mEq/L outside), which causes the positively charged K^+ to diffuse outward, leaving the nondiffusible, negatively charged intracellular anions (A^-) behind. This causes the membrane to become polarized, with negative charges aligned along the inside and positive charges along the outside. The Na^+/K^+ membrane pump, which removes three Na^+ from inside while returning only two K^+ to the inside, contributes to the maintenance of the RMP.



4

Action potentials. Action potentials involve rapid changes in the membrane potential. Each action potential begins with a sudden change from the negative RMP to a positive threshold potential, causing an opening of the membrane channels for Na^+ (or other ions of the action potential). Opening of the Na^+ channels allows large amounts of the positively charged Na^+ ions to diffuse to the interior of the cell, causing the membrane potential to undergo depolarization or a rapid change to positive on the inside and negative on the outside. This is rapidly followed by closing of Na^+ channels and opening of the K^+ channels, which leads to a rapid efflux of K^+ from the cell and reestablishment of the RMP.

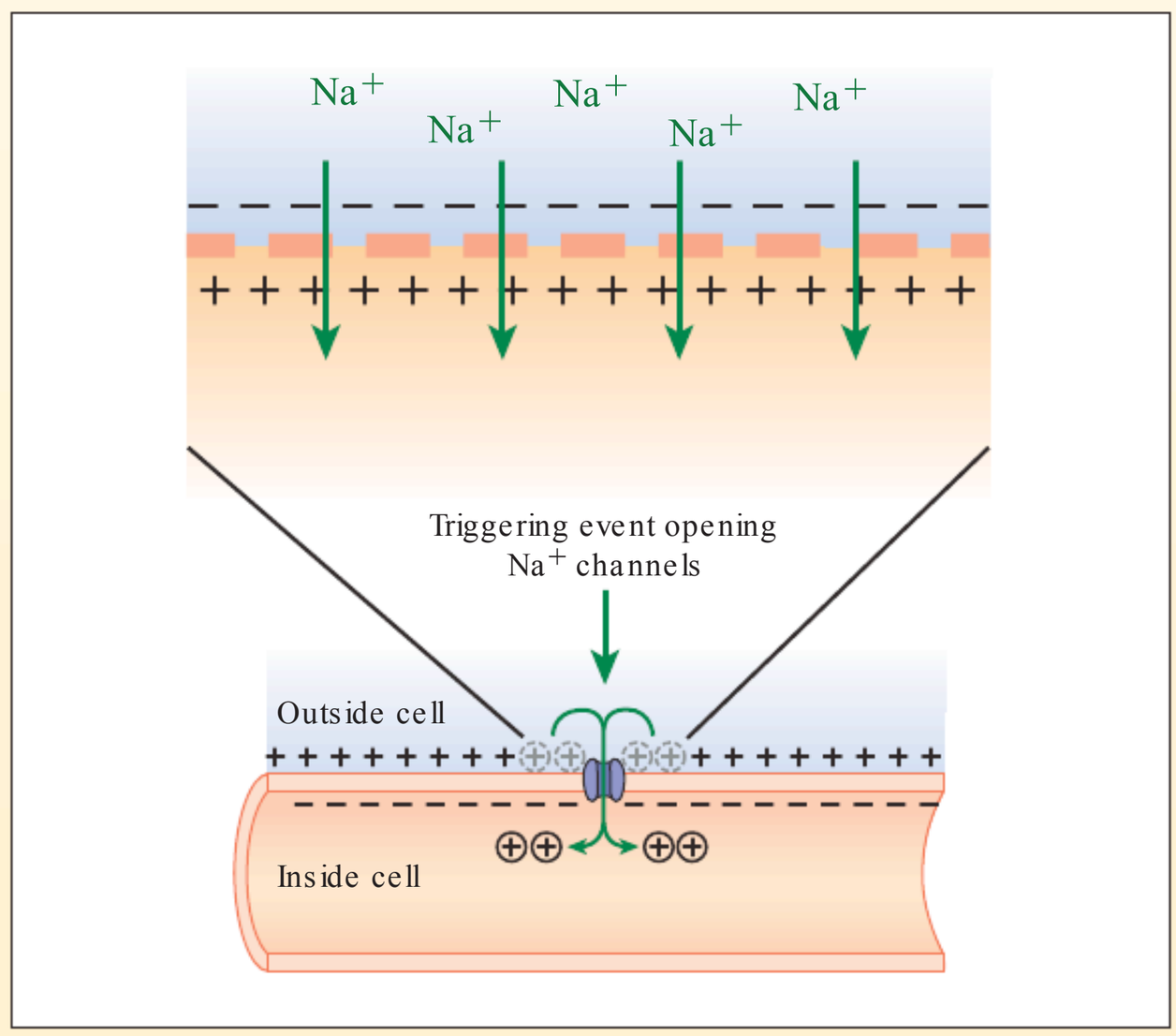


TABLE 1-1 Classification of Tissue Types

Tissue Type	Location
Epithelial Tissue	
Covering and lining of body surfaces	
Simple epithelium	
Squamous	Lining of blood vessels, body cavities, alveoli of lungs
Cuboidal	Collecting tubules of kidney; covering of ovaries
Columnar	Lining of intestine and gallbladder
Stratified epithelium	
Squamous keratinized	Skin
Squamous nonkeratinized	Mucous membranes of mouth, esophagus, and vagina
Cuboidal	Ducts of sweat glands
Columnar	Large ducts of salivary and mammary glands; also found in conjunctiva
Transitional	Bladder, ureters, renal pelvis
Pseudostratified	Tracheal and respiratory passages
Glandular	
Endocrine	Pituitary gland, thyroid gland, adrenal and other glands
Exocrine	Sweat glands and glands in gastrointestinal tract
Neuroepithelium	Olfactory mucosa, retina, tongue
Reproductive epithelium	Seminiferous tubules of testis; cortical portion of ovary
Connective Tissue	
Embryonic connective tissue	
Mesenchymal	Embryonic mesoderm
Mucous	Umbilical cord (Wharton jelly)
Adult connective tissue	
Loose or areolar	Subcutaneous areas
Dense regular	Tendons and ligaments
Dense irregular	Dermis of skin
Adipose	Fat pads, subcutaneous layers
Reticular	Framework of lymphoid organs, bone marrow, liver
Specialized connective tissue	
Bone	Long bones, flat bones
Cartilage	Tracheal rings, external ear, articular surfaces
Hematopoietic	Blood cells, myeloid tissue (bone marrow)
Muscle Tissue	
Skeletal	Skeletal muscles
Cardiac	Heart muscles
Smooth	Gastrointestinal tract, blood vessels, bronchi, bladder, and others
Nervous Tissue	
Neurons	Central and peripheral neurons and nerve fibers
Supporting cells	Glial and ependymal cells in central nervous system; Schwann and satellite cells in peripheral nervous system

(*text continued from page 17*)

tissues is called *cell differentiation*, a process that is controlled by mechanisms that switch genes on and off (see Chapter 4).

All of the approximately 200 different cells of the body can be classified into the four basic or primary tissue types: epithelial, connective, muscle, and nervous (Table 1-1). These basic tissue types are often described by their embryonic origin. The embryo is essentially a three-layered tubular structure (Fig. 1-13). The outer layer of the tube is called the *ectoderm*; the middle layer, the *mesoderm*; and the inner layer, the *endoderm*. All of the mature tissue types originate from these three cellular layers. Epithelium has its origin in all three embryonic layers, connective tissue and muscle develop mainly from the mesoderm, and nervous tissue develops from the ectoderm.

Epithelial Tissue

Epithelial tissue forms sheets that cover the body's outer surface, line the internal surfaces, and form glandular tissue. Underneath all types of epithelial tissue is a fibrous extracellular layer, called the *basement membrane*, which serves to attach the epithelial cells to adjacent connective tissue and may serve other functions, such as providing a barrier against cancer cell invasion and contributing to the filtration function of the glomerulus.

The cells that make up epithelium have three general characteristics: (1) they have three distinct surfaces: a free surface or apical surface, a lateral surface, and a basal surface; (2) they are closely apposed and joined by cell-to-cell adhesion molecules, which form specialized cell junctions; and (3) their basal surface is attached

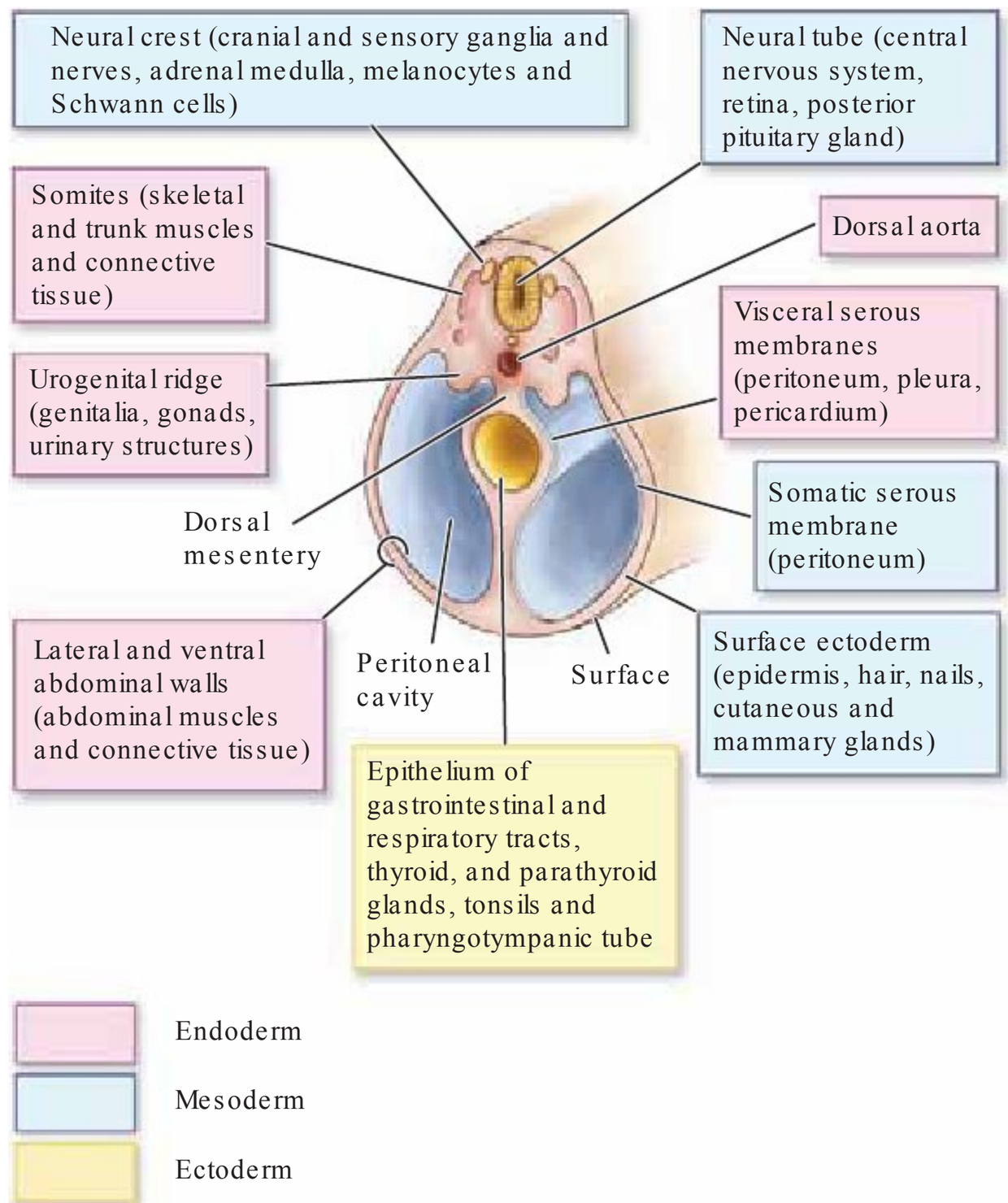


FIGURE 1-13. Cross-section of human embryo illustrating the development of the somatic and visceral structures.

to the underlying basement membrane (Fig. 1-14). The characteristics and geometric arrangement of the cells in the epithelium contribute to their function. In an epithelium formed from a single layer of epithelial cells, the free or apical surface is directed toward the exterior surface or lumen of an enclosed cavity or tube, the lateral surface communicates with adjacent cells and is characterized by specialized attachment areas, and the basal surface rests on the basement membrane anchoring the cell to the surrounding connective tissue.

Epithelial tissues are classified according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudostratified. Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. The terms *squamous* (thin and flat), *cuboidal* (cube shaped), and *columnar* (resembling a column) refer to the cells' shape (Fig. 1-15).

Simple Epithelium

Simple epithelium contains a single layer of cells, all of which rest on the basement membrane. Simple squamous epithelium is adapted for filtration; it is found lining the blood vessels, lymph nodes, and alveoli of the lungs. The single layer of squamous epithelium lining the heart and blood vessels is known as the *endothelium*. A similar type of layer, called the *mesothelium*, forms the serous membranes that line the pleural, pericardial, and peritoneal cavities and covers the organs of these cavities. A *simple cuboidal epithelium* is found on the surface of the ovary and in the thyroid. *Simple columnar epithelium* lines the intestine. One form of a simple columnar epithelium has hair-like projections called *cilia*, often with specialized mucus-secreting cells called *goblet cells*. This form of simple columnar epithelium lines the airways of the respiratory tract.

Stratified and Pseudostratified Epithelium

Stratified epithelium contains more than one layer of cells, with only the deepest layer resting on the basement membrane. It is designed to protect the body surface. *Stratified squamous keratinized epithelium* makes up the epidermis of the skin. *Keratin* is a tough, fibrous protein that polymerizes to form intermediate filaments that are abundant in the outer cells of skin. A stratified squamous keratinized epithelium is made up of many layers. The layers closest to the underlying tissues are cuboidal or columnar. The cells become more irregular and thinner as they move closer to the surface. Surface cells become totally filled with keratin and die, are sloughed off, and then replaced by the deeper cells. A stratified squamous nonkeratinized epithelium is found on moist surfaces such as the mouth and tongue. Stratified cuboidal and

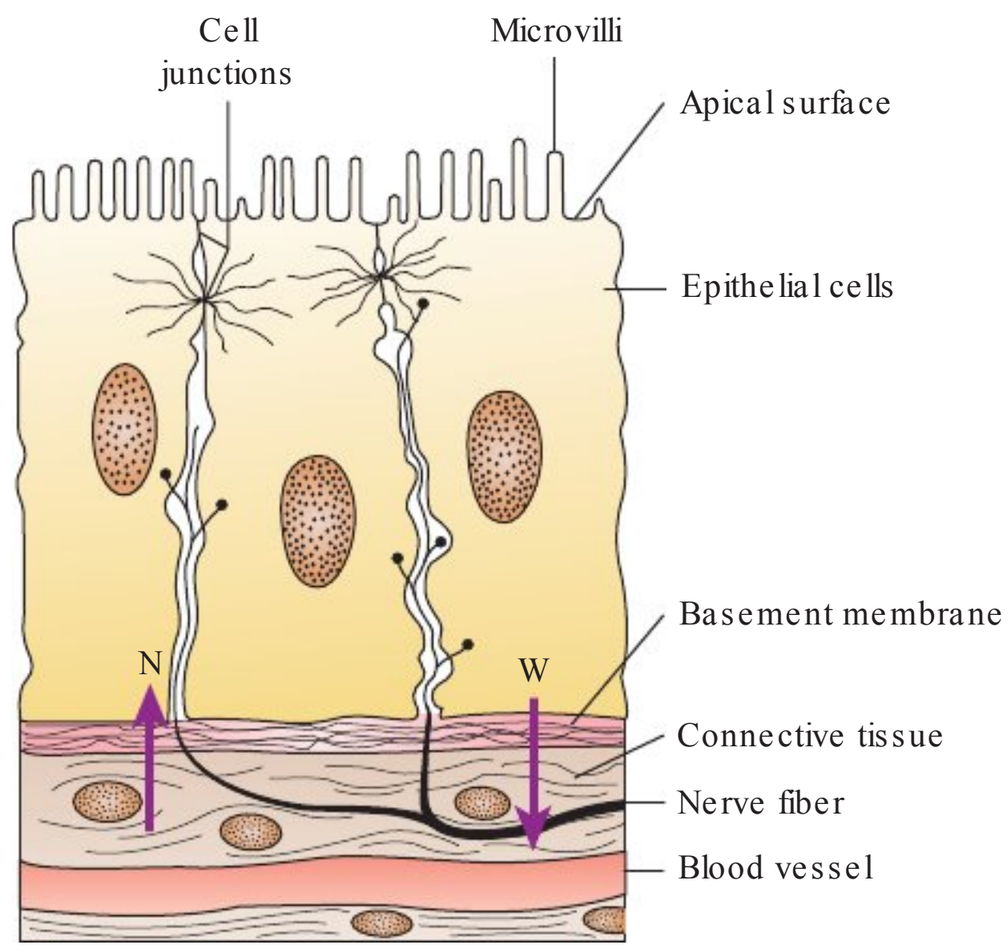


FIGURE 1-14. Typical arrangement of epithelial cells in relation to underlying tissues and blood supply. Epithelial tissue has no blood supply of its own but relies on the blood vessels in the underlying connective tissue for nutrition (N) and elimination of wastes (W).

columnar epithelia are found in the ducts of salivary glands and the larger ducts of the mammary glands. In smokers, the normal columnar ciliated epithelial cells of the trachea and bronchi are often replaced with stratified squamous epithelial cells that are better able to withstand the irritating effects of cigarette smoke.

Pseudostratified epithelium is a type of epithelium in which all of the cells are in contact with the underlying intercellular matrix, but some do not extend to the surface. A pseudostratified ciliated columnar epithelium with goblet cells forms the lining of most of the upper respiratory tract. All of the tall cells reaching the surface of this type of epithelium are either ciliated cells or mucus-producing goblet cells. The basal cells that do not reach the surface serve as stem cells for ciliated and goblet cells.

Transitional epithelium is a stratified epithelium characterized by cells that can change shape and become thinner when the tissue is stretched. Such tissue can be stretched without pulling the superficial cells apart. Transitional epithelium is well adapted for the lining of organs that are constantly changing their volume, such as the urinary bladder.

Glandular Epithelium

Glandular epithelial tissue is formed by cells specialized to produce a fluid secretion. This process is usually accompanied by the intracellular synthesis of macromolecules. The chemical nature of these macromolecules is variable. The macromolecules typically are stored in the cells in small membrane-bound vesicles called *secretory granules*. For example, glandular epithelia can synthesize, store, and secrete proteins (e.g., insulin), lipids (e.g., adrenocortical hormones, secretions of the sebaceous glands), and complexes of carbohydrates and proteins (e.g., saliva). Less common are secretions that require minimal synthetic activity, such as those produced by the sweat glands.

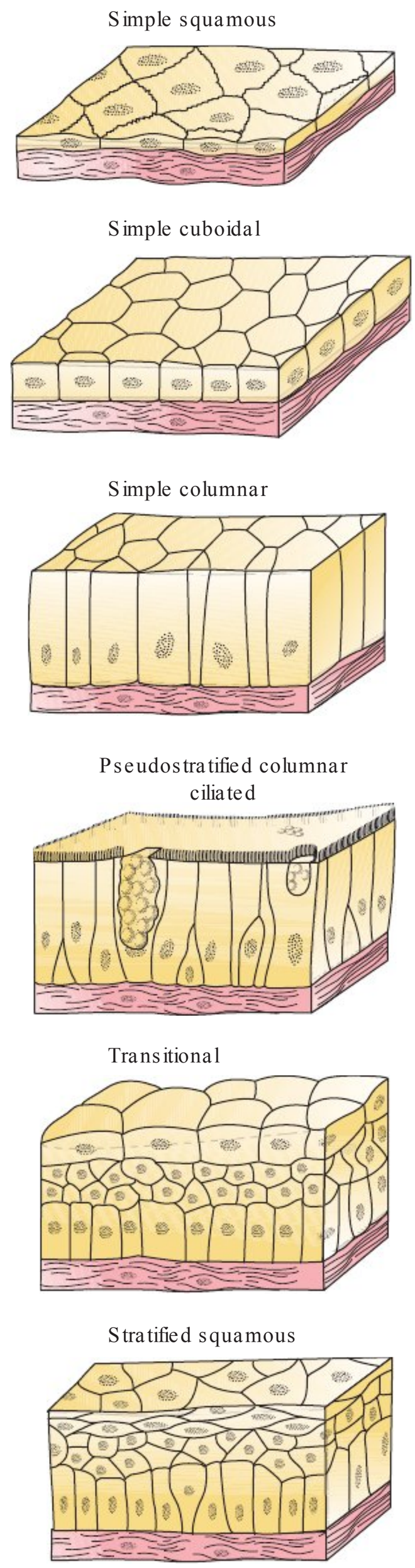


FIGURE 1-15. Representation of the various epithelial tissue types.

All glandular cells arise from surface epithelia by means of cell proliferation and invasion of the underlying connective tissue. Epithelial glands can be divided into two groups: exocrine and endocrine glands. Exocrine glands, such as the sweat glands and lactating mammary glands, retain their connection with the surface epithelium from which they originated. This connection takes the form of epithelium-lined tubular ducts through which the secretions pass to reach the surface. Endocrine glands are epithelial structures that have had their connection with the surface obliterated during development. These glands are ductless and produce secretions (i.e., hormones) that move directly into the bloodstream.

Epithelial Cell Renewal

Cells making up the epithelial tissues generally exhibit a high rate of turnover, which is related to their location and function. The rate of cell turnover is characteristic of specific epithelium. For example, the epithelial cells of the small intestine are renewed every 4 to 6 days by regenerative cells in the lower portion of the intestinal glands (crypts). Similarly, the cells of the stratified squamous epithelium of the skin are constantly being renewed at the basal layer by cell division.

Connective Tissue

Connective or supportive tissue is the most abundant tissue in the body. As its name suggests, it connects and binds or supports the various tissues. Connective tissue is unique in that its cells produce the extracellular matrix that supports and holds tissues together. The proximity of the extracellular matrix to blood vessels allows it to function as an exchange medium through which nutrients and metabolic wastes pass.

The functions of the various connective tissues are reflected by the types of cells and fibers present in the tissue and the characteristics of the extracellular matrix (Fig. 1-16). The capsules that surround organs of the body are composed of connective tissue. Bone, adipose tissue, and cartilage are specialized types of connective tissue that function to support the soft tissues of the body and store fat. One type of cell, the fibroblast, is responsible for synthesis of collagen, elastic, reticular fibers, and ground substance of the extracellular matrix. Other cells, such as lymphocytes, plasma cells, macrophages, and eosinophils, are associated with body defense systems.

Adult connective tissue can be divided into two types: connective tissue proper, which is the focus of the discussion in this chapter, and specialized connective tissue (cartilage, bone, and blood cells), which is discussed in other chapters. There are four recognized types of connective tissue proper: loose (areolar), adipose, reticular, and dense connective tissue.

Loose Connective Tissue

Loose connective tissue, also known as areolar tissue, is soft and pliable. It fills spaces between muscle sheaths, forms a layer that encases blood and lymphatic vessels, and provides support for epithelial tissues and the means

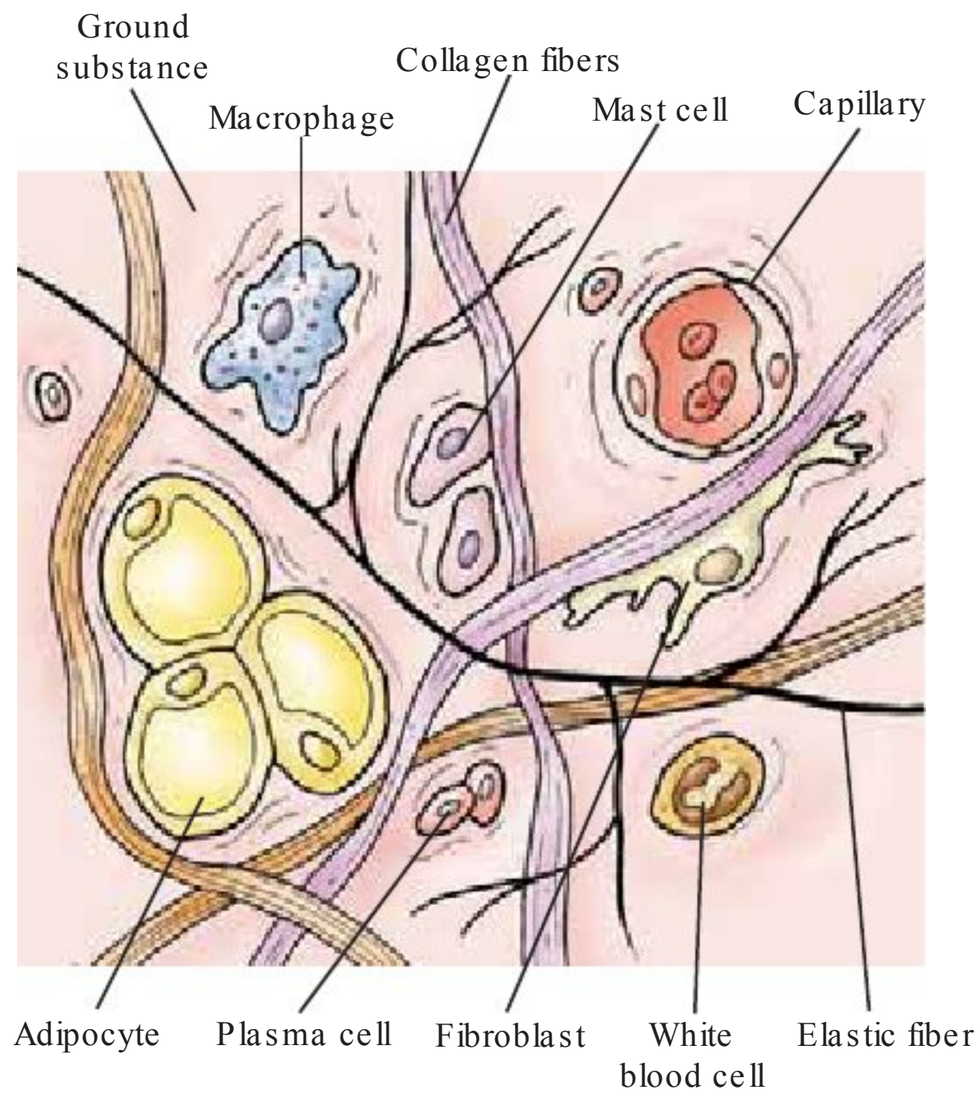


FIGURE 1-16. Diagrammatic representation of cells that may be seen in loose connective tissue. The cells lie in an intercellular matrix that is bathed in tissue fluid that originates in the capillaries.

by which these tissues are nourished. Loose connective tissue is characterized by an abundance of ground substance and tissue fluid housing the fixed connective tissue cells: fibroblasts, mast cells, adipose or fat cells, macrophages, and leukocytes. Fibroblasts are the most abundant of these cells. They produce all three fiber types—collagen, elastic, and reticular fibers—found in loose connective tissue, and synthesize the ground substance that fills the intercellular tissue spaces.

Adipose Tissue

Adipose tissue is a special form of connective tissue in which adipocytes predominate. Adipocytes do not generate an extracellular matrix but maintain a large intracellular space. These cells store large quantities of triglycerides and are the largest repository of energy in the body. Adipose tissue helps fill spaces between tissues and to keep organs in place. The subcutaneous fat helps to shape the body. Because fat is a poor conductor of heat, adipose tissue serves as thermal insulation for the body. Adipose tissue exists in two forms: unilocular and multilocular. Unilocular (white) adipose tissue is composed of cells in which the fat is contained in a single, large droplet in the cytoplasm. Multilocular (brown) adipose tissue is composed of cells that contain multiple droplets of fat and numerous mitochondria.

Reticular and Dense Connective Tissue

Reticular and dense connective tissue is characterized by a network of fibers interspersed with macrophages and fibroblasts that synthesize collagen fibers. *Reticular fibers* provide the framework for capillaries, nerves, and muscle

cells. They also constitute the main supporting elements for the blood-forming tissues and the liver.

Dense connective tissue exists in two forms: dense irregular and dense regular. Dense irregular connective tissue consists of the same components found in loose connective tissue but exhibits a predominance of collagen fibers and fewer cells. This type of tissue can be found in the dermis of the skin (i.e., reticular layer), the fibrous capsules of many organs, and the fibrous sheaths of cartilage (i.e., perichondrium) and bone (i.e., periosteum). It also forms the fascia that invests muscles and organs. Dense regular connective tissues are rich in collagen fibers and form the tendons and aponeuroses that join muscles to bone or other muscles and the ligaments that join bone to bone.

Muscle Tissue

Muscle tissue, whose primary function is contraction, is responsible for movement of the body and its parts and for changes in the size and shape of internal organs. Muscle tissue contains two types of fibers that are responsible for contraction: thin actin and thick myosin filaments.

There are three types of muscle tissues: skeletal, cardiac, and smooth. *Skeletal* and *cardiac muscles* are striated muscles, in which the actin and myosin filaments are arranged in large parallel arrays in bundles, giving the muscle fibers a striped or striated appearance when observed with a microscope. *Smooth muscle* lacks striations and is found in the iris of the eye; the walls of blood vessels; hollow organs, such as the stomach and urinary bladder; and hollow tubes, such as the ureters and common bile duct that connect internal organs.

Although the three types of muscle tissues differ significantly in structure, contractile properties, and control mechanisms, they have many similarities. In the following section, the structural properties of skeletal muscle are presented as the prototype of striated muscle tissue. Smooth muscle and the ways in which it differs from skeletal muscle are also discussed. Cardiac muscle is described in Chapter 17.

Skeletal Muscle

Skeletal muscle is the most abundant tissue in the body, accounting for 40% to 45% of the total body weight. Most skeletal muscles are attached to bones, and their contractions are responsible for movements of the skeleton.

Skeletal Muscle Structure. Skeletal muscle fibers are packaged into skeletal muscles that attach to and cover the body skeleton. Each skeletal muscle is a discrete organ made up of hundreds or thousands of muscle fibers. Although muscle fibers predominate, substantial amounts of connective tissue, blood vessels, and nerve fibers are present. In an intact muscle, several different layers of connective tissue hold the individual muscle fibers together. Skeletal muscles such as the biceps brachii are surrounded by a dense irregular connective tissue covering called the *epimysium* (Fig. 1-17A). Each muscle is subdivided into smaller bundles called *fascicles*, which are surrounded by a connective tissue covering called the *perimysium*. The number of fascicles and their size vary among muscles. Fascicles consist of many elongated structures called *muscle fibers*, each of which is surrounded by connective tissue called the *endomysium*.

Skeletal muscles are syncytial or multinucleated structures, meaning there are no true cell boundaries within a skeletal muscle fiber. The cytoplasm or sarcoplasm of the muscle fiber is contained within the sarcolemma, which

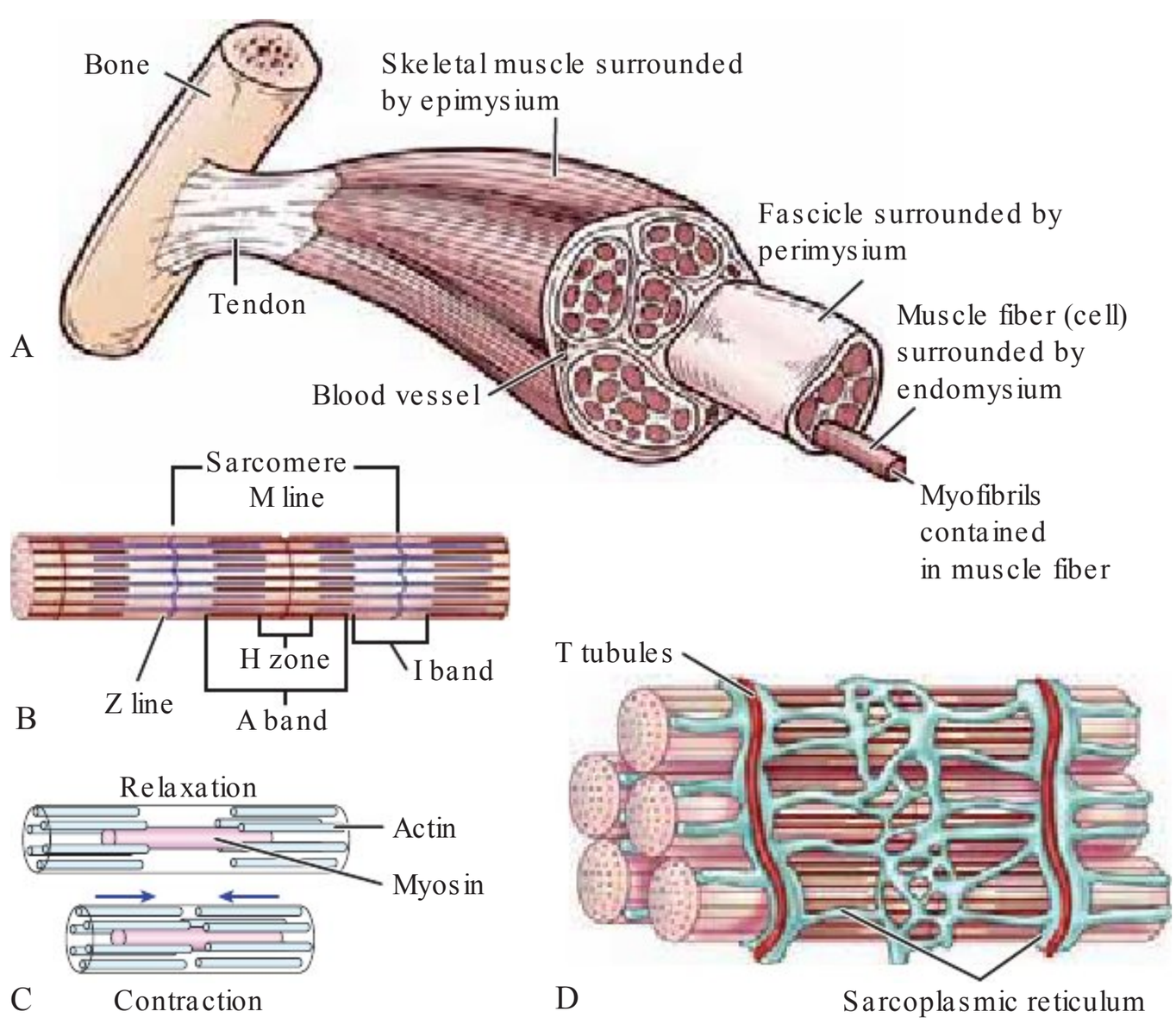


FIGURE 1-17. **(A)** Connective tissue components of a skeletal muscle. **(B)** Striations of the myofibril showing the overlap of contractile proteins and the A and I bands, the H zone, and the Z and M lines. **(C)** The relaxed and contracted states of the myofibril showing the position of actin filaments (blue) between the myosin filaments (pink) in the relaxed muscle (top) and pulling of the Z membranes toward each other (bottom) as the muscle contracts. **(D)** The sarcoplasmic reticulum with T tubules.

represents the cell membrane. Embedded throughout the sarcoplasm are the contractile elements actin and myosin, which are arranged in parallel bundles (i.e., *myofibrils*). Each myofibril consists of regularly repeating units called *sarcomeres* along its length.

Sarcomeres, which are the structural and functional units of striated muscle, extend from one Z line to another Z line (Fig. 1-17B). The central portion of the sarcomere contains the dark band (A band) consisting mainly of myosin filaments, with some overlap with actin filaments. Straddling the Z line, the lighter I band contains only actin filaments; therefore, it takes two sarcomeres to complete an I band. An H zone is found in the middle of the A band and represents the region where only myosin filaments are found. In the center of the H zone is a thin, dark band, the M band or M line, produced by linkages between the myosin filaments. Z lines consist of short elements that interconnect and provide the thin actin filaments from two adjoining sarcomeres with an anchoring point. Muscle contraction involves the actin filaments sliding inward among the myosin filaments (Fig. 1-17C). In the relaxed state, the ends of the actin filaments extend from two successive Z lines, barely overlapping one another. In the contracted state, these actin filaments have been pulled inward among the myosin filaments so their ends overlap one another.

The *sarcoplasmic reticulum*, which is comparable to the smooth ER, is composed of longitudinal tubules that run parallel to the muscle fiber and surround each myofibril (Fig. 1-17D). This network ends in enlarged, saclike regions called the *lateral sacs* or *terminal cisternae*. These sacs store calcium that is released during muscle contraction. A second system of tubules consists of the *transverse* or *T tubules*, which are extensions of the cell membrane and run perpendicular to the muscle fiber. The hollow portion or lumen of the T tubule is continuous with the extracellular fluid compartment. Action potentials, which are rapidly conducted over the surface of the muscle fiber, are in turn propagated by the T tubules into the sarcoplasmic reticulum. As the action potential moves through the lateral sacs, the sacs release calcium, initiating muscle contraction. The membrane of the sarcoplasmic reticulum also has an active transport mechanism for pumping calcium ions back into the reticulum. This prevents interactions between calcium ions and the actin and myosin myofilaments after cessation of a muscle contraction.

Skeletal Muscle Contraction. Muscle contraction involves the sliding of the thick myosin and thin actin filaments over each other to produce shortening of the muscle fiber, while the actual length of the individual thick and thin filaments remains unchanged. The thick myosin filaments consist of a thin tail, which provides the structural backbone for the filament, and a globular head that forms cross-bridges with the thin actin filaments (Fig. 1-18A). Myosin molecules are bundled together side by side in the thick filaments such that one half have their heads toward one end of the filament and their tails toward the other end, and the other half are arranged in the opposite manner. Each globular myosin head contains a site able to bind to a complementary site on the actin molecule. Besides the binding site for actin, each myosin head has a separate active site that catalyzes the breakdown of ATP to provide the energy needed to activate the myosin head so it can form a cross-bridge with actin. After contraction, myosin also

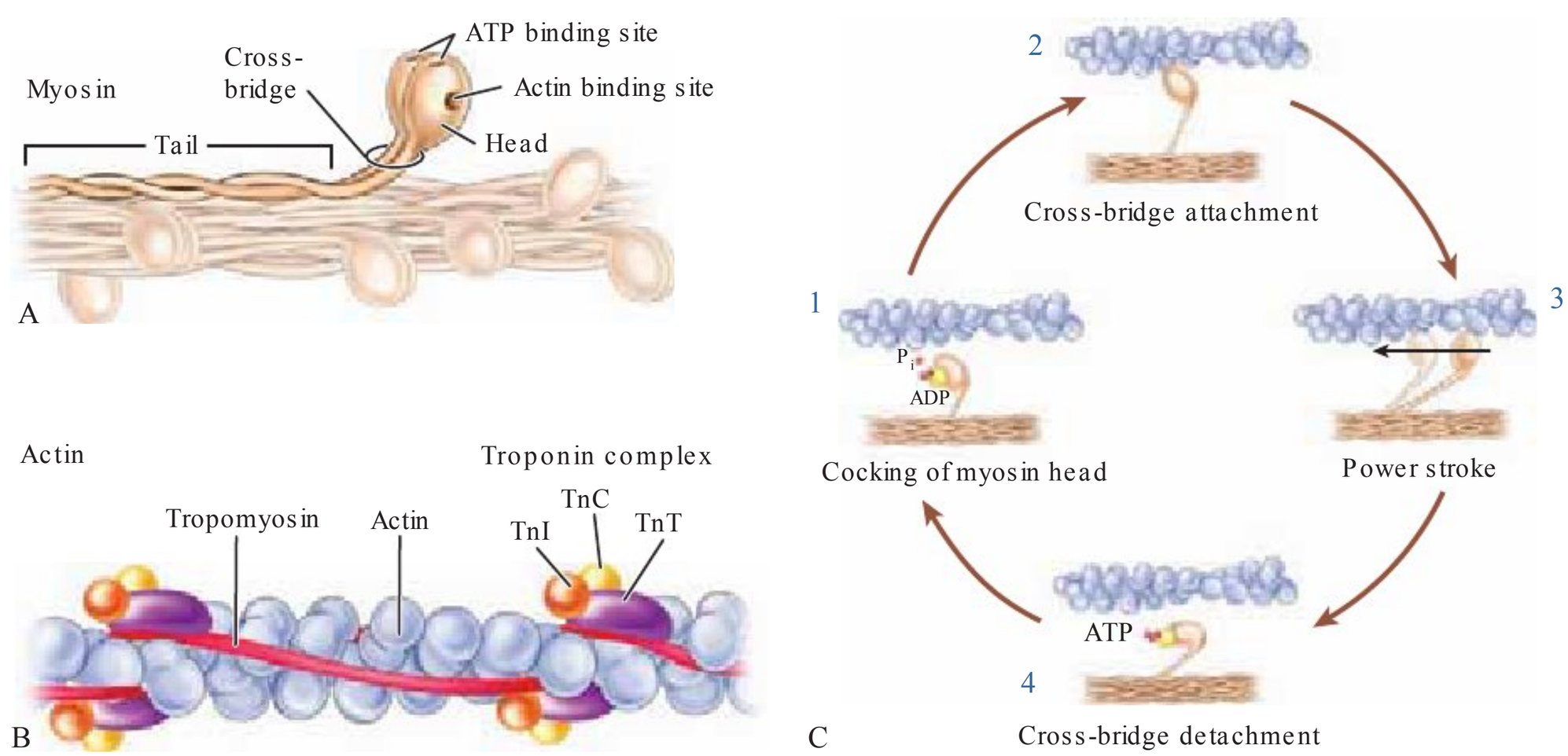


FIGURE 1-18. Molecular structure of the thicker myosin filament **(A)** and the thinner actin filament **(B)** of striated muscle. The thin filament is a double-stranded helix of actin molecules with tropomyosin and troponin molecules lying along the grooves of the actin strands. **(C)** Sequence of events involved in sliding of adjacent actin and myosin filaments: (1) cocking of the myosin head, which occurs as adenosine triphosphate (ATP) is split to adenosine diphosphate (ADP); (2) cross-bridge attachment; (3) power stroke during which the myosin head bends as it moves the actin forward; and (4) cross-bridge detachment, which occurs as a new ATP attaches to the myosin head.

binds ATP, thus breaking the linkage between actin and myosin.

The thin filaments are composed mainly of actin, a globular protein lined up in two rows that coil around each other to form a long helical strand (Fig. 1-18B). Associated with each actin filament are two regulatory proteins, tropomyosin and troponin. *Tropomyosin*, which lies in grooves of the actin strand, provides the site for attachment of the globular heads of the myosin filament. In the noncontracted state, *troponin* covers the tropomyosin-binding sites and prevents formation of cross-bridges between the actin and myosin. During an action potential, calcium ions released from the sarcoplasmic reticulum diffuse to the adjacent myofibrils, where they bind to troponin. The binding of calcium to troponin uncovers the tropomyosin-binding sites such that the myosin heads can attach and form cross-bridges.

Muscle contraction begins with activation of the cross-bridges from the myosin filaments and uncovering of the tropomyosin-binding sites on the actin filament (Fig. 1-18C). When activated by ATP, the heads of the myosin filaments swivel in a fixed arc, much like the oars of a boat, as they become attached to the actin filament. During contraction, each myosin head undergoes its own cycle of movement, forming a bridge attachment and releasing it, then moving to another site where the same sequence of movement occurs. This pulls the thin and thick filaments past each other. Energy from ATP is used to break the actin and myosin cross-bridges, stopping the muscle contraction. After the linkage between actin and myosin, the concentration of calcium around the myofibrils decreases as calcium is actively transported into the sarcoplasmic reticulum by a membrane pump that uses energy derived from ATP.

Smooth Muscle

Smooth muscle is often called *involuntary muscle* because its activity arises spontaneously or through the activity of the autonomic nervous system. Smooth muscle is usually arranged in sheets or bundles and its contractions are slower and more sustained than skeletal or cardiac muscle contractions.

Smooth muscle cells are spindle shaped and smaller than skeletal muscle fibers. Each smooth muscle cell has one centrally positioned nucleus. Z bands and M lines are not present in smooth muscle fibers, and the cross-striations are absent because the bundles of filaments are not parallel but criss-cross obliquely through the cell. Instead, the actin filaments are attached to structures called *dense bodies*. Some dense bodies are attached to the cell membrane, and others are dispersed in the cell and linked together by structural proteins (Fig. 1-19).

The lack of Z lines and regular overlapping of contractile elements provide a greater range of tension development. This is important in hollow organs that undergo changes in volume, with consequent changes in the length of the smooth muscle fibers in their walls. Even with the distention of a hollow organ, the smooth muscle fiber retains some ability to develop tension, whereas such distention would stretch skeletal muscle beyond the area where the thick and thin filaments overlap.

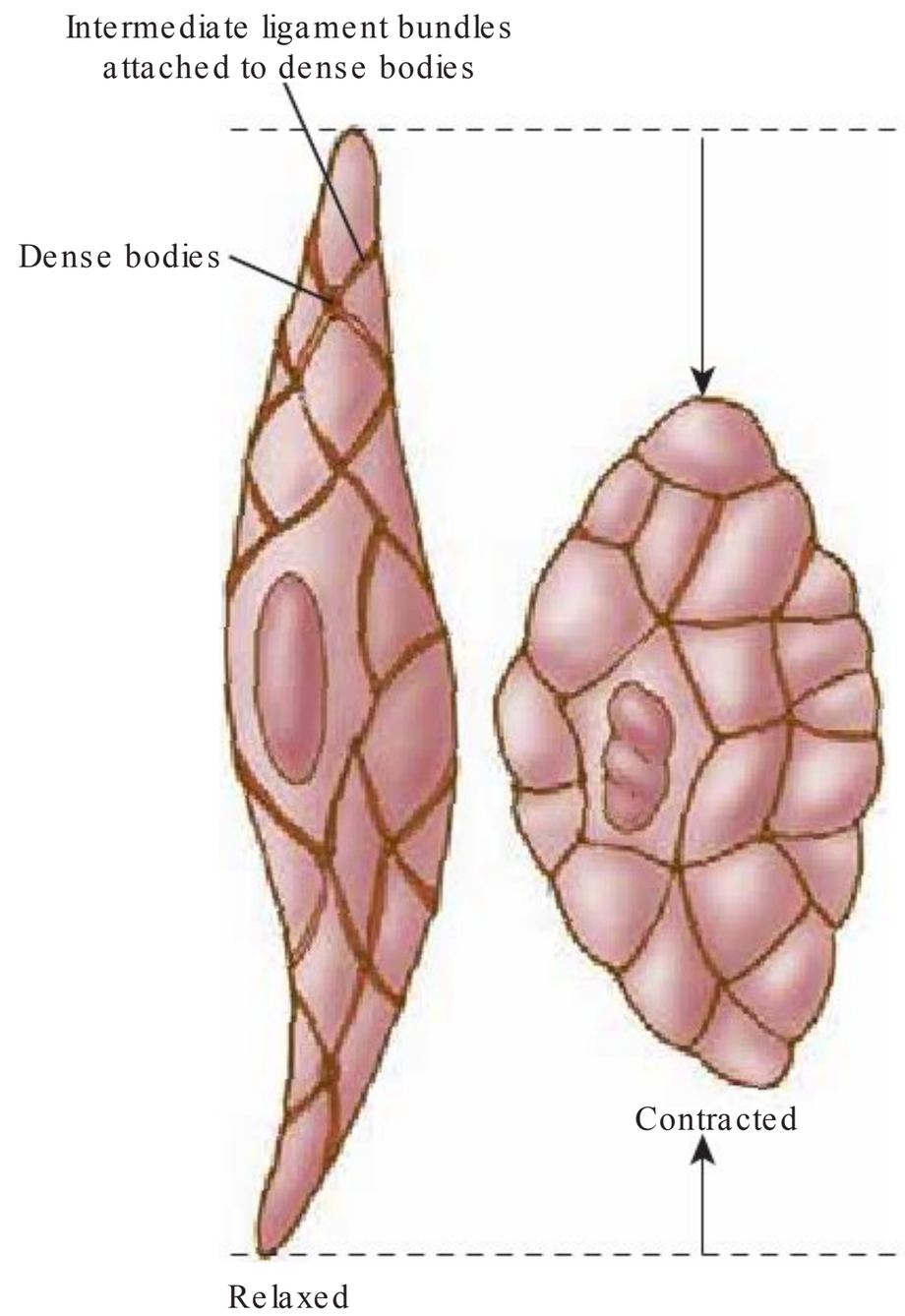


FIGURE 1-19. Structure of smooth muscle showing the dense bodies. In smooth muscle, the force of contraction is transmitted to the cell membrane by bundles of intermediate fibers.

As with cardiac and skeletal muscle, smooth muscle contraction is initiated by an increase in intracellular calcium. However, smooth muscle differs from skeletal muscle in the way its cross-bridges are formed. The sarcoplasmic reticulum of smooth muscle is less developed than in skeletal muscle, and no transverse tubules are present. Smooth muscle relies on the entrance of extracellular calcium for muscle contraction. This dependence on movement of extracellular calcium across the cell membrane during muscle contraction is the basis for the action of calcium-blocking drugs used in the treatment of cardiovascular disease.

Smooth muscle also lacks the calcium-binding regulatory protein troponin, which is found in skeletal and cardiac muscle. Instead, it relies on another calcium-regulated mechanism involving the cytoplasmic protein calmodulin and an enzyme called myosin light chain kinase. Increased calcium ions form a calcium–calmodulin complex that binds to and activates myosin light chain kinase, which in turn phosphorylates myosin to initiate contraction.

Nervous Tissue

Nervous tissue is distributed throughout the body as an integrated communication system. Nerve cells, which develop from the embryonic ectoderm, are highly differentiated and have long been considered incapable of regeneration in postnatal life. However, it is now known that parts of the brain, such as the hippocampus, contain

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areas where neurogenesis occurs from neural stem cells/progenitor cells throughout life. Embryonic development of the nervous system and the structure and functions of the nervous system are discussed more fully in Chapter 34.

Structurally, nervous tissue consists of two cell types: nerve cells or neurons and supporting cells or neuroglia. Most nerve cells consist of three parts: the soma or cell body, dendrites, and the axon. The cytoplasm-filled dendrites, which are multiple elongated processes, receive and carry stimuli from the environment, sensory epithelial cells, and other neurons to the cell. The axon, which is a single cytoplasm-filled process, is specialized for generating and conducting nerve impulses away from the cell body to other nerve cells, muscle cells, and glandular cells.

Neurons can be classified as afferent and efferent neurons according to their function. Afferent or sensory neurons carry information toward the central nervous system; they are involved in the reception of sensory information from the external environment and from within the body. Efferent or motor neurons carry information away from the central nervous system (CNS); they are needed for control of muscle fibers and endocrine and exocrine glands.

Communication between neurons and effector organs, such as muscle cells, occurs at specialized structures called *synapses*. At the synapse, chemical messengers (i.e., neurotransmitters) alter the membrane potential to conduct impulses from one nerve to another or from a neuron to an effector cell. In addition, electrical synapses exist in which nerve cells are linked through gap junctions that permit the passage of ions from one cell to another.

Neuroglia (*glia* means "glue") are the cells that support neurons, form myelin, and have trophic and phagocytic functions. Four types of neuroglia are found in the CNS: astrocytes, oligodendrocytes, microglia, and ependymal cells. Astrocytes are the most abundant of the neuroglia. They have many long processes that surround blood vessels in the CNS. They provide structural support for the neurons, and their extensions form a sealed barrier that protects the CNS. In last decade, investigations have established important roles for astrocytes in the response of the brain to injury, calcium ion-based excitation, CNS metabolism, neural stem cell source, blood–brain barrier maintenance, and numerous diseases and pathological conditions. The oligodendrocytes provide myelination of neuronal processes in the CNS. The microglia are phagocytic cells that represent the mononuclear phagocytic system in the nervous system. Ependymal cells line the cavities of the brain and spinal cord and are in contact with the cerebrospinal fluid. In the peripheral nervous system, supporting cells consist of the Schwann and satellite cells. The Schwann cells provide myelination of the axons and dendrites, and the satellite cells enclose and protect the dorsal root ganglia and autonomic ganglion cells.

Extracellular Tissue Components

The discussion thus far has focused on the cellular components of the different tissue types. Within tissues, cells are held together by cell junctions, and adhesion molecules form intercellular contacts.

Cell Junctions

The junctions between tissue cells are important in governing the shape of the body, transmitting mechanical stresses from one cell to another, and creating pathways for communication. Cell junctions occur at many points in cell-to-cell contact, but they are particularly plentiful and important in epithelial tissue. These specialized junctions enable cells to form barriers to the movement of water, solutes, and cells from one body compartment to the next. Three basic types of intercellular junctions are observed: tight junctions, adhering junctions, and gap junctions (Fig. 1-20).

Tight or *occluding junctions* (i.e., zonula occludens), which are found in epithelial tissue, seal the surface membranes of adjacent cells together. This type of intercellular junction prevents fluids and materials such as macromolecules present in the intestinal contents from entering the intercellular space.

Adhering junctions represent sites of strong adhesion between cells. The primary role of adhering junctions may be that of preventing cell separation. Adhering junctions are not restricted to epithelial tissue; they provide adherence between adjacent cardiac muscle cells as well. Adhering junctions are found as continuous, beltlike adhesive junctions (i.e., zonula adherens) or scattered, spotlike adhesive junctions, called *desmosomes* (i.e., macula adherens). A special feature of the adhesion belt junction is that it provides an anchoring site to the cell membrane for actin filaments. In epithelial desmosomes, bundles of keratin intermediate filaments (i.e., tonofilaments) are anchored to the junction on the cytoplasmic area of the cell membrane. A primary disease of desmosomes is pemphigus, which is caused by antibody binding to the desmosome proteins and the resulting separation of neighboring cells. Affected persons have skin and mucous membrane blistering. *Hemidesmosomes*, which resemble a half desmosome, are another type of junction. They are found at the base of epithelial cells and help attach the epithelial cell to the underlying connective tissue.

Gap or *nexus junctions* involve the close adherence of adjoining cell membranes with the formation of channels that connect the cytoplasm of the two cells. Because they are low-resistance channels, gap junctions are important in cell-to-cell conduction of electrical signals (e.g., between cells in sheets of smooth muscle or between adjacent cardiac muscle cells, where they function as electrical synapses). Gap junctions also enable ions and small molecules to pass directly from one cell to another.

Extracellular Matrix

Tissues are not made up solely of cells. A large part of their volume is made up of an extracellular matrix. This matrix is composed of a variety of proteins and polysaccharides (i.e., polymers made up of many sugar monomers). These proteins and polysaccharides are secreted locally and are organized into a supporting meshwork in close association with the cells that produced them. The amount and composition of the matrix vary with the different tissues and their function. In bone, for example, the matrix is more plentiful than the cells that surround it; in the brain, the cells are much more abundant and the matrix is only a minor constituent.

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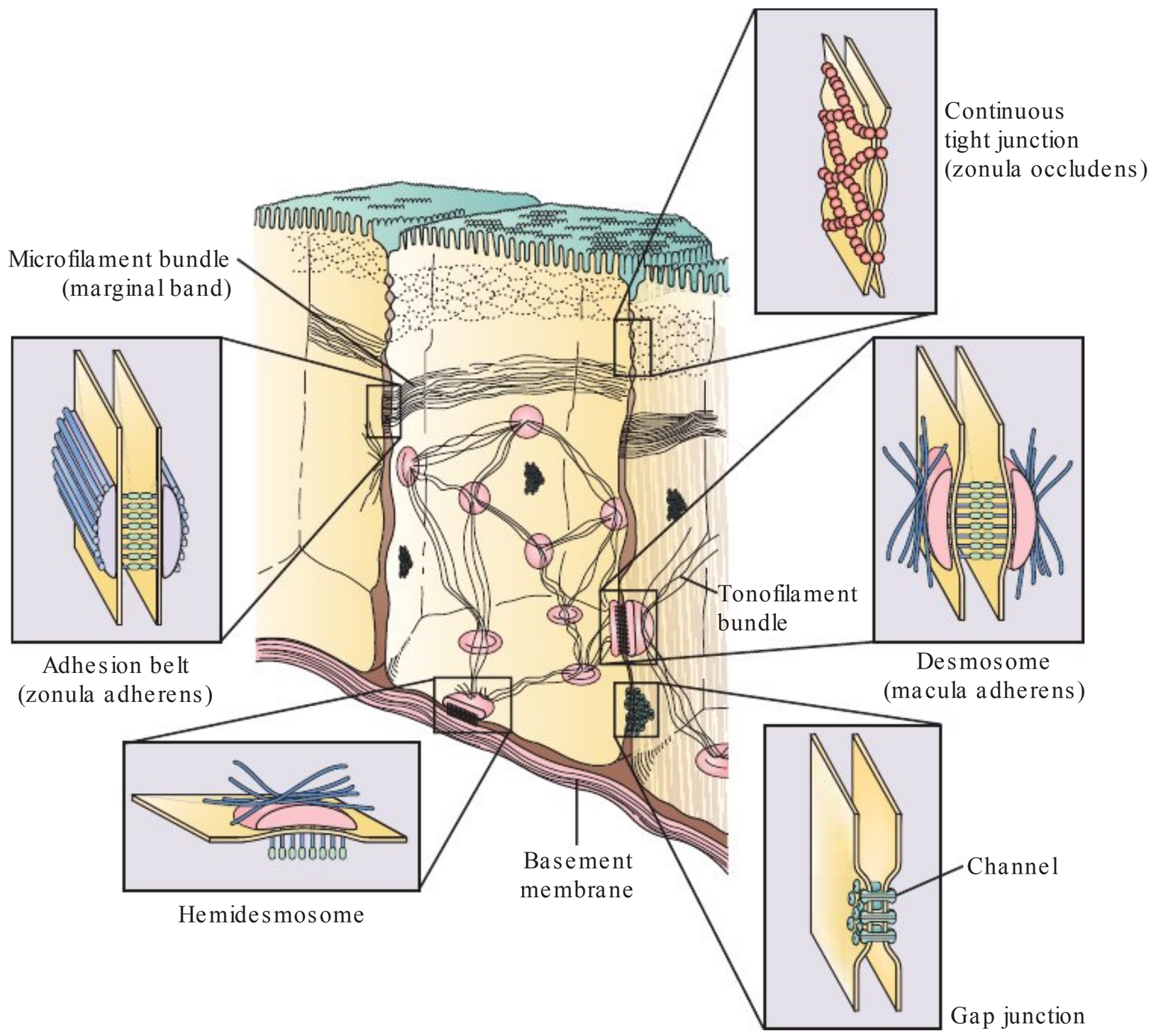

FIGURE 1-20. Three types of intercellular junctions found in epithelial tissue: the continuous tight junction (zonula occludens); the adhering junction, which includes the adhesion belt (zonula adherens), desmosomes (macula adherens), and hemidesmosomes; and the gap junction.

Two main classes of extracellular macromolecules make up the extracellular matrix. The first is an amorphous gel-like material called *ground substance*. Ground substance is composed of polysaccharide chains of proteins called *glycosaminoglycans* (GAGs), which are usually found linked to protein as proteoglycans. The second type consists of the fibrous proteins (i.e., collagen and elastin) and the fibrous adhesive proteins (i.e., fibronectin and laminin) that are found in the basement membrane. Members of each of these two classes of extracellular macromolecules come in a variety of shapes and sizes.

Ground Substance. The proteoglycan and GAG molecules form a highly hydrated, gel-like substance, or tissue gel, in which the fibrous proteins are embedded. The polysaccharide gel resists compressive forces; the collagen fibers strengthen and help organize the matrix; the rubberlike elastin adds resilience; and the adhesive proteins help cells attach to the appropriate part of the matrix. Polysaccharides in the tissue gel are highly hydrophilic, and they form gels even at low concentrations. They also produce a negative charge that attracts cations such as sodium, which are osmotically active, causing large amounts of water to be sucked into the matrix. This creates a swelling pressure, or turgor, that enables the matrix to withstand extensive compressive forces. For example, the cartilage matrix that lines the knee joint can support pressures of hundreds of atmospheres by this mechanism.

Fibrous Proteins. Three types of fibers are found in the extracellular space: collagen, elastin, and reticular fibers. *Collagen* is the most common protein in the body. It is a tough, nonliving, white fiber that serves as the structural framework for skin, ligaments, tendons, and many other structures. *Elastin* acts like a rubber band; it can be stretched and then returns to its original form. Elastin fibers are abundant in structures subjected to frequent stretching, such as the aorta and some ligaments. *Reticular fibers* are extremely thin fibers that create a flexible network in organs subjected to changes in form or volume, such as the spleen, liver, uterus, or intestinal muscle layer.

Cell Adhesion Molecules

Important classes of extracellular macromolecules are the cell adhesion molecules (CAMs). Cell adhesion molecules can be cell-to-cell or cell-to-matrix adhesion molecules. There are four major classes of CAMs: cadherins, selectins, integrins, and the immunoglobulin (Ig) superfamily of proteins. These proteins are located on the cell surface where they function as receptors, or they can be stored in the cytoplasm. As receptors, CAMs can bind to similar or

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different molecules in other cells, providing for interaction between the same cell types or different cell types.

Cadherins. Cadherins are the major CAMs responsible for calcium-dependent cell-to-cell adhesion junctions. The word *cadherin* is derived from the term "calcium-dependent adhesion protein." There are over 90 members of the cadherin superfamily. The first three cadherins that were discovered were named according to the main tissues in which they were found: the E-cadherins, which are present in many types of epithelial cells; the N-cadherins, which are present in nerve and muscle cells; and the P-cadherins, which are found on cells in the placenta and epidermis. All are found in various other tissues; N-cadherin, for example, is expressed in fibroblasts, and E-cadherin is expressed in parts of the brain.

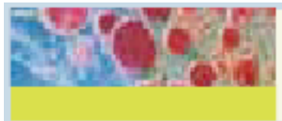
Most cadherins function as transmembrane adhesive proteins that indirectly link the actin cytoskeletons of cells they join together, an arrangement that occurs in adhering junctions. Cadherins also form desmosomes that interact with intermediate filaments of the cytoskeleton, rather than the actin filaments. Cell-to-cell interactions mediated by cadherins play a major role in regulating cell motility, proliferation, and differentiation.

Selectins. Selectins are cell surface carbohydrate-binding proteins (lectins) that mediate a variety of transient, cell-to-cell adhesion interactions in the bloodstream. They are found on activated endothelial cells of blood vessels, on leukocytes, and on platelets. Selectins, together with integrins and immunoglobulins, participate in leukocyte movement through the endothelial lining of blood vessels during inflammation.

Integrins. Integrins usually assist in attaching epithelial cells to the underlying basement membrane. Extracellularly, they are attached to fibronectin and laminin, the two major components of the basement membrane. Like the cadherins, their intracellular portion is linked to actin. One group of integrins is associated with hemidesmosomes, whereas others are associated with the surface of white blood cells, macrophages, and platelets. Integrins usually have a weak affinity for their ligands unless they are associated with cellular focal contacts and hemidesmosomes. This allows some movement between cells except where a firm attachment is required to attach epithelial cells to the underlying connective tissue.

Certain integrins play an important role in allowing white blood cells to pass through the vessel wall, a process called *transmigration*. Persons affected with leukocyte adhesion deficiency are unable to synthesize appropriate integrin molecules. As a result, they experience repeated bacterial infections because their white blood cells are not able to transmigrate through vessel walls.

Immunoglobulin Superfamily. The Ig superfamily consists of a group of one or more immunoglobulin-like adhesion proteins that are similar structurally to those of antibody molecules. They have many functions outside the immune system that are unrelated to immune defenses. The best-studied example of Ig superfamily proteins are the neural cell adhesion molecules (N-CAMs), which are expressed in a variety of cells, including most nerve cells. During early development, N-CAMs play an important role in connecting the neurons of the developing nervous system.



SUMMARY CONCEPTS

- Body cells are organized into four basic tissue types: epithelial, connective, muscle, and nervous. The epithelium covers and lines the body surfaces and forms the functional components of glandular structures. Epithelial tissue is classified into three types according to the shape of the cells and the number of layers that are present: simple, stratified, and pseudostratified.
- Connective tissue supports and connects body structures; it forms the bones and cartilage, the joint structures, the dermis of the skin, the sheaths of blood vessels and nerves, adipose tissue, lymphatic tissues, and blood. Fibroblasts are the most abundant connective tissue cells. They are responsible for the synthesis of collagen, elastic, and reticular fibers and the gel-like ground substance that fills the intercellular spaces.
- Muscle tissue is a specialized tissue designed for contractility. Three types of muscle tissue exist: skeletal, cardiac, and smooth. Actin and myosin filaments interact to produce muscle shortening, a process activated by the presence of calcium. In skeletal muscle, calcium is released from the sarcoplasmic reticulum in response to an action potential. Smooth muscle is often called involuntary muscle because it contracts spontaneously or through the activity of the autonomic nervous system. It differs from skeletal muscle in that its sarcoplasmic reticulum is less defined and it depends on the entry of extracellular calcium ions for muscle contraction.
- Nervous tissue is designed for communication purposes and includes the neurons, the supporting neural structures, and the ependymal cells that line the ventricles of the brain and the spinal canal.
- Within tissues, cells are held together by cell junctions, which are especially plentiful in epithelial tissues. There are three basic types of cell junctions: tight junctions, adhering or adhesive-type junctions, and gap junctions. The ability of cells to adhere together (cell to cell) or to components of the extracellular matrix (cell to matrix) is mediated by cell adhesion molecules (cadherins, selectins, integrins, and the immunoglobulin superfamily of proteins).

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REVIEW EXERCISES

1. Persons who drink sufficient amounts of alcohol display rapid changes in central nervous system function, including both motor and behavioral changes, and the odor of alcohol can be detected on their breath.

A. Use the concepts related to the lipid bilayer structure of the cell membrane to explain these observations.

2. Tattoos consist of pigments that have been injected into the skin.

A. Explain what happens to the dye once it has been injected and why it does not eventually wash away.

3. Insulin is synthesized in the beta cells of the pancreas as a prohormone and then secreted as an active hormone.

A. Using your knowledge of the function of DNA, the RNAs, the endoplasmic reticulum, and the Golgi complex, propose a pathway for the synthesis of insulin.

4. Mitochondrial disorders, whether due to mutations in mitochondrial or nuclear genes, often produce muscle weakness, sometimes with severe involvement of the muscles that move the eyes, other neurologic symptoms, lactic acidosis, and cardiomyopathy.

A. Mitochondrial disorders that are responsible for these manifestations are often classified as mitochondrial encephalomyopathies. Propose an explanation for the propensity to develop encephalopathies and myopathies with mitochondrial disorders rather than disorders of other body systems such as the kidney or digestive tract.

B. Relate the function of the mitochondria in terms of oxidative metabolism to the development of lactic acidosis.

5. The absorption of glucose from the intestine involves a cotransport mechanism in which the active primary transport of sodium is used to provide for the secondary transport of glucose.

A. Hypothesize how this information might be used to design an oral rehydration solution for someone who is suffering from diarrhea.

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Porth Essentials Resources

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- Study Guide for Essentials of Pathophysiology
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Cellular Responses to Persistent Stress
Adaptations of Growth and Differentiation
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia
Intracellular Accumulations
Pathologic Calcifications
Dystrophic Calcification
Metastatic Calcification
Cell Injury, Death, and Senescence
Causes of Cell Injury
Injury from Physical Agents
Radiation Injury
Chemical Injury
Injury from Biologic Agents
Injury from Nutritional Imbalances
Mechanisms of Cell Injury
Free Radical Injury
Hypoxic Cell Injury
Impaired Calcium Homeostasis
Reversible Cell Injury and Cell Death
Reversible Cell Injury
Programmed Cell Death
Necrosis
Cellular Aging
Replicative Senescence
Genetic Influences
Accumulation of Environmental and Genetic Damage
Syndromes of Premature Aging

Chapter 2

Cellular Responses to Stress, Injury, and Aging

In their simplest form, all diseases exert their effects on the smallest living unit of the body—the cell. When confronted with stresses that endanger its normal structure and function, the cell undergoes adaptive changes that permit survival and maintenance of function. It is only when the stress is overwhelming or adaptation is ineffective that injury, maladaptive changes, and cell death occur. Biologic aging produces its own changes in cell structure and function.

Cellular Responses to Persistent Stress

Cells adapt to changes in the internal environment just as the total organism adapts to changes in the external environment. Cells may adapt by undergoing changes in size, number, and type. These changes, occurring singly or in combination, may lead to atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia (Fig. 2-1). Cellular stresses also include intracellular accumulations and storage of products in abnormal amounts.[1,2]

Adaptations of Growth and Differentiation

Numerous molecular mechanisms mediate cellular adaptation, including factors in the cellular microenvironment and the cells themselves. These mechanisms largely depend on extracellular signals and cues, which in turn activate intracellular signaling mechanisms transmitted by chemical messengers that alter gene expression. Once the primary stimulus for adaptation is removed, the cause of changing gene expression patterns is removed and the cell may revert back to its previous state. Whether adaptive cellular changes are normal or abnormal depends in part on whether the response was mediated by an appropriate stimulus. Normal adaptive responses occur in response to need and an appropriate

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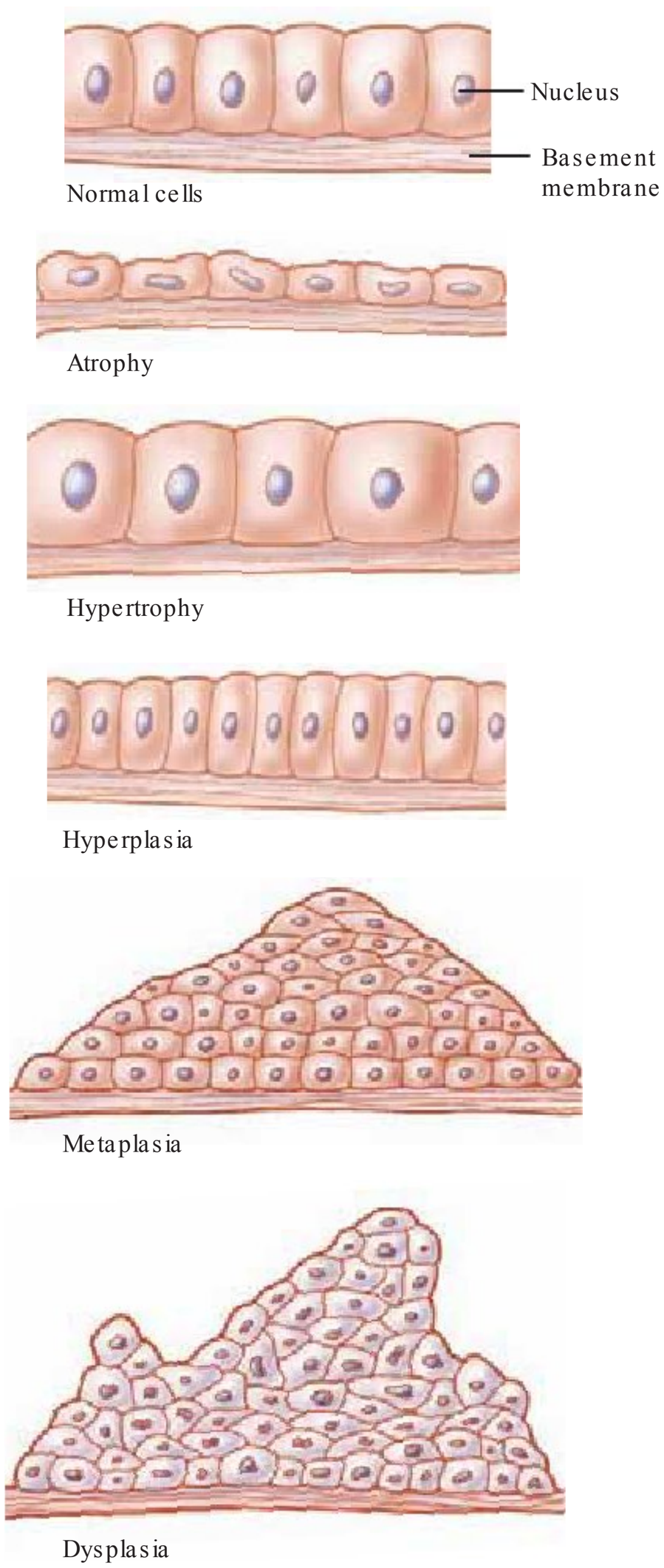

FIGURE 2-1. Adaptive cell and tissue responses involving a change in cell size (hypertrophy and atrophy), number (hyperplasia), cell type (metaplasia), or size, shape, and organization (dysplasia). (From Anatomical Chart Company. Atlas of Pathophysiology. Springhouse, PA: Springhouse; 2002:4.)

stimulus. After the need has been removed, the adaptive response ceases.

Atrophy

When confronted with a decrease in work demands or adverse environmental conditions, most cells are able to revert to a smaller size and a lower and more efficient level of functioning that is compatible with survival.[1,2] This decrease in cell size is called *atrophy*. Cells that are atrophied reduce oxygen consumption and other cellular functions by decreasing the number and size of their organelles and other structures. There are fewer mitochondria, myofilaments, and endoplasmic reticulum structures. When a sufficient number of cells are involved, the entire tissue atrophies.

Cell size, particularly in muscle tissue, is related to workload. As the workload of a cell declines, oxygen consumption and protein synthesis decrease. Furthermore, proper muscle mass is maintained by sufficient levels of insulin/insulin-like growth factor-1 (IGF-1). When insulin/IGF-1 levels are low or catabolic signals are present, muscle atrophy occurs by a variety of mechanisms. One such mechanism is increased proteolysis by the ubiquitin-proteasome system, in which intracellular proteins destined for destruction are covalently bonded to a small protein called *ubiquitin* and then degraded by small cytoplasmic organelles called *proteasomes* (see Chapter 1). Other mechanisms, such as reduced synthetic (anabolic) processes and apoptosis (programmed cell death), are also involved (to be discussed).[3]

The general causes of atrophy can be grouped into five categories: (1) disuse, (2) denervation, (3) loss of endocrine stimulation, (4) inadequate nutrition, and (5) ischemia or decreased blood flow. Disuse atrophy occurs when there is a reduction in skeletal muscle use. An extreme example of disuse atrophy is seen in the muscles of extremities that have been encased in casts. Because atrophy is adaptive and reversible, muscle size is restored after the cast is removed and muscle use is resumed. Denervation atrophy is a form of disuse atrophy that occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation produces a form of disuse atrophy. In women, the loss of estrogen stimulation during menopause results in atrophic changes in the reproductive organs. With malnutrition and decreased blood flow, cells decrease their size and energy requirements as a means of survival.

Hypertrophy

Hypertrophy represents an increase in cell size, and with it an increase in the amount of functioning tissue mass. It results from an increased workload imposed on an organ or body part and is commonly seen in cardiac and skeletal muscle tissue, which cannot adapt to an increase in workload through mitotic division and formation of more cells. Hypertrophy involves an increase in the functional components of the cell that allows it to achieve equilibrium between demand and functional capacity. For example, as muscle cells hypertrophy, additional actin and myosin filaments, cell enzymes, and adenosine triphosphate (ATP) are synthesized.

Hypertrophy may occur as the result of normal physiologic or abnormal pathologic conditions. The increase in muscle mass associated with exercise is an example of physiologic hypertrophy. Pathologic hypertrophy occurs as the result of disease conditions and may be adaptive or compensatory. Examples of adaptive hypertrophy are

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the thickening of the urinary bladder from long-continued obstruction of urinary outflow and myocardial hypertrophy from valvular heart disease or hypertension. Compensatory hypertrophy is the enlargement of a remaining organ or tissue after a portion has been surgically removed or rendered inactive. For instance, if one kidney is removed, the remaining kidney enlarges to compensate for the loss.

The initiating signals for hypertrophy appear to be complex and related to ATP depletion, mechanical forces such as stretching of the muscle fibers, activation of cell degradation products, and hormonal factors. In the case of the heart, initiating signals can be divided into two broad categories: (1) biomechanical and stretch-sensitive mechanisms and (2) neurohumoral mechanisms associated with the release of hormones, growth factors, cytokines, and chemokines.[4] Internal stretch-sensitive receptors for the biochemical signals and an array of membrane-bound receptors for the specific neurohumoral ligands, such as IGF-1 and epidermal growth factor (EGF), activate specific signal transduction pathways. These pathways control myocardial growth by altering gene expression to increase protein synthesis and reduce protein degradation, thereby causing hypertrophic enlargement of the heart. A limit is eventually reached beyond which further enlargement of the tissue mass is no longer able to compensate for the increased work demands. The limiting factors for continued hypertrophy might be related to limitations in blood flow. In hypertension, for example, the increased workload required to pump blood against an elevated arterial pressure results in a progressive increase in left ventricular muscle mass and need for coronary blood flow (Fig. 2-2).

There continues to be interest in the signaling pathways that control the arrangement of contractile elements in myocardial hypertrophy. Research suggests that certain signal molecules can alter gene expression controlling the size and assembly of the contractile proteins in hypertrophied myocardial cells. For example, the hypertrophied myocardial cells of well-trained athletes have proportional increases in width and length. This is in contrast to the hypertrophy that develops in dilated cardiomyopathy, in which the hypertrophied cells have a relatively greater increase in length than width. In pressure overload, as occurs with hypertension, the hypertrophied cells have greater width than length.[5] It is anticipated that further elucidation of the signal pathways that determine the adaptive and nonadaptive features of cardiac hypertrophy will lead to new targets for treatment.

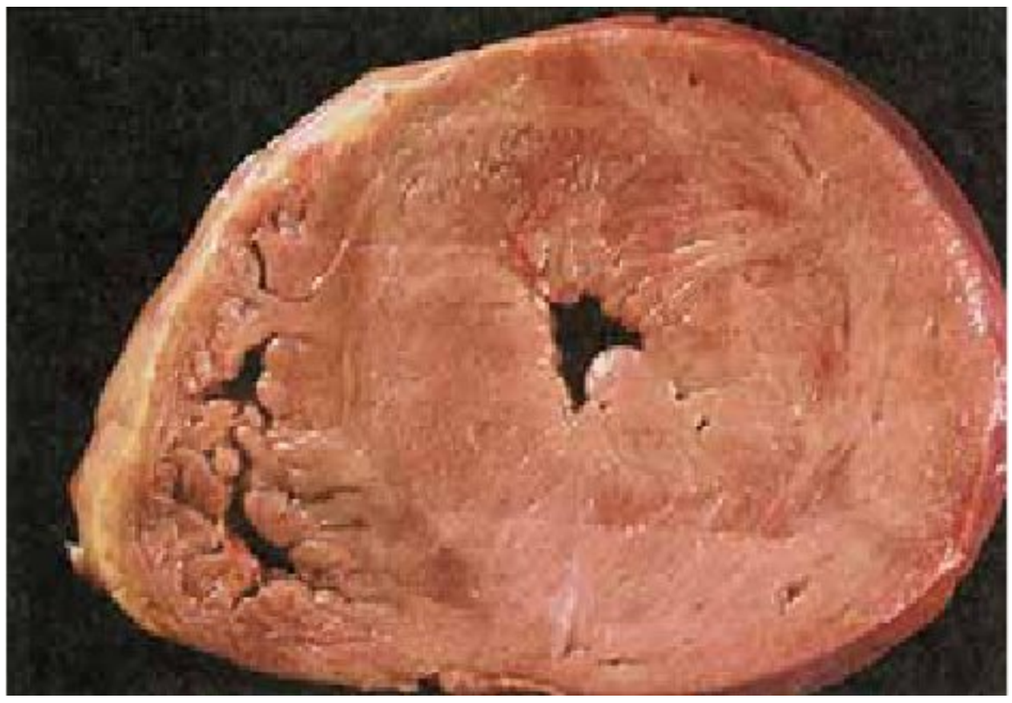

FIGURE 2-2. Myocardial hypertrophy. Cross-section of the heart in a patient with long-standing hypertension. (From Strayer DS, Rubin E. Cell adaptation, cell injury and cell death. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2012:4.)

Hyperplasia

Hyperplasia refers to an increase in the number of cells in an organ or tissue. It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue.[1,2] Certain cells, such as neurons, rarely divide and therefore have little (if any) capacity for hyperplastic growth. There is evidence that hyperplasia involves activation of genes controlling cell proliferation and the presence of intracellular messengers that control cell replication and growth. As with other normal adaptive cellular responses, hyperplasia is a controlled process that occurs in response to an appropriate stimulus and ceases after the stimulus has been removed.

The stimuli that induce hyperplasia may be physiologic or nonphysiologic. There are two common types of physiologic hyperplasia: hormonal and compensatory. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that results from estrogen stimulation. The regeneration of the liver that occurs after partial hepatectomy (i.e., partial removal of the liver) is an example of compensatory hyperplasia. Hyperplasia is also an important response of connective tissue in wound healing, during which proliferating fibroblasts and blood vessels contribute to wound repair. Although hypertrophy and hyperplasia are two distinct processes, they may occur together and are often triggered by the same mechanism.[1] For example, the pregnant uterus undergoes both hypertrophy and hyperplasia as a result of estrogen stimulation.

Most forms of nonphysiologic hyperplasia are due to excessive hormonal stimulation or the effects of growth factors on target tissues.[2] Excessive estrogen production can cause endometrial hyperplasia and abnormal menstrual bleeding (see Chapter 40). Benign prostatic hyperplasia, which is a common disorder of men older than 50 years of age, is thought to be related to the action of androgens (see Chapter 39). Skin warts are an example of hyperplasia caused by growth factors produced by certain viruses, such as the papillomaviruses.

Metaplasia

Metaplasia represents a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.[1,2] These changes are thought

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to involve the reprogramming of undifferentiated stem cells that are present in the tissue undergoing the metaplastic changes.

Metaplasia usually occurs in response to chronic irritation and inflammation and allows for substitution of cells that are better able to survive under circumstances in which a more fragile cell type might succumb. However, the conversion of cell type never oversteps the boundaries of the primary tissue type (e.g., one type of epithelial cell may be converted to another type of epithelial cell, but not to a connective tissue cell). An example of metaplasia is the adaptive substitution of stratified squamous epithelial cells for the ciliated columnar epithelial cells in the trachea and large airways of a habitual cigarette smoker. Although the squamous epithelium is better able to survive in these situations, the protective function that the ciliated epithelium provides for the respiratory tract is lost. Also, continued exposure to the influences that cause metaplasia may predispose to cancerous transformation of the metaplastic epithelium.

Dysplasia

Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and organization. Minor degrees of dysplasia are associated with chronic irritation or inflammation.[1] The pattern is most frequently encountered in areas of metaplastic squamous epithelium of the respiratory tract and uterine cervix. Although dysplasia is abnormal, it is adaptive in that it is potentially reversible after the irritating cause has been removed. Dysplasia is strongly implicated as a precursor of cancer. In cancers of the respiratory tract and the uterine cervix, dysplastic changes have been found adjacent to the foci of cancerous transformation. Through the use of the Papanicolaou (Pap) test, it has been documented that cancer of the uterine cervix develops in a series of incremental epithelial changes ranging from severe dysplasia to invasive cancer (discussed in Chapter 40). However, dysplasia is an adaptive process and as such does not necessarily lead to cancer. In many cases, the dysplastic cells revert to their former structure and function.

Intracellular Accumulations

Intracellular accumulations represent the buildup of substances that cells cannot immediately use or eliminate. The substances may accumulate in the cytoplasm (frequently in the lysosomes) or in the nucleus. In some cases the accumulation may be an abnormal substance that the cell has produced, and in other cases the cell may be storing exogenous materials or products of pathologic processes occurring elsewhere in the body. These substances can be grouped into three categories: (1) normal body substances, such as lipids, proteins, carbohydrates, melanin, and bilirubin, that are present in abnormally large amounts; (2) abnormal endogenous products, such as those resulting from inborn errors of metabolism; and (3) exogenous products, such as environmental agents and pigments that cannot be broken down by the cell.[2] These substances may accumulate transiently or permanently, and they may be harmless or, in some cases, toxic.

Under some conditions cells may accumulate abnormal amounts of various substances, some of which may be harmless while others may be associated with varying degrees of injury. Frequently, normal substances accumulate because they are synthesized at a rate that exceeds their metabolism or removal. An example of this type of process is a condition called fatty liver, which is due to intracellular accumulation of triglycerides. Liver cells normally contain some fat, which is either oxidized and used for energy or converted to triglycerides. This fat is derived from free fatty acids released from adipose tissue. Abnormal accumulation occurs when the delivery of free fatty acids to the liver is increased, as in starvation and diabetes mellitus, or when the intrahepatic metabolism of lipids is disturbed, as in alcoholism.

Intracellular accumulation can result from genetic disorders that disrupt the enzymatic degradation of selected substances or their transport to other sites. A normal enzyme may be replaced with an abnormal one, resulting in the formation of a substance that cannot be used or eliminated from the cell, or an enzyme may be missing, so that an intermediate product accumulates in the cell. For example, there are at least 10 genetic disorders that affect glycogen metabolism, most of which lead to the accumulation of intracellular glycogen stores. In the most common form of this disorder, von Gierke disease, large amounts of glycogen accumulate in the liver and kidneys because of a deficiency of the enzyme glucose-6-phosphatase. Without this enzyme, glycogen cannot be broken down to form glucose. The disorder leads not only to an accumulation of glycogen but also to a reduction in blood glucose levels. In Tay-Sachs disease, another genetic disorder, abnormal lipids accumulate in the brain and other tissues, causing motor and mental deterioration beginning at approximately 6 months of age, followed by death at 2 to 3 years of age (see Chapter 6).

Pigments are colored substances that may accumulate in cells. They can be endogenous (i.e., arising from within the body) or exogenous (i.e., arising from outside the body). Icterus, also called *jaundice*, is characterized by a yellow discoloration of tissue due to the retention of bilirubin, an endogenous bile pigment. This condition may occur because of increased bilirubin production from red blood cell destruction, obstruction of bile passage into the intestine, or diseases that affect the liver's ability to remove bilirubin from the blood. Lipofuscin is a yellow-brown pigment that results from the accumulation of the indigestible residues produced during normal turnover of cell structures (Fig. 2-3). The accumulation of lipofuscin increases with age and is sometimes referred to as the *wear-and-tear pigment*. It is more common in heart, nerve, and liver cells than other

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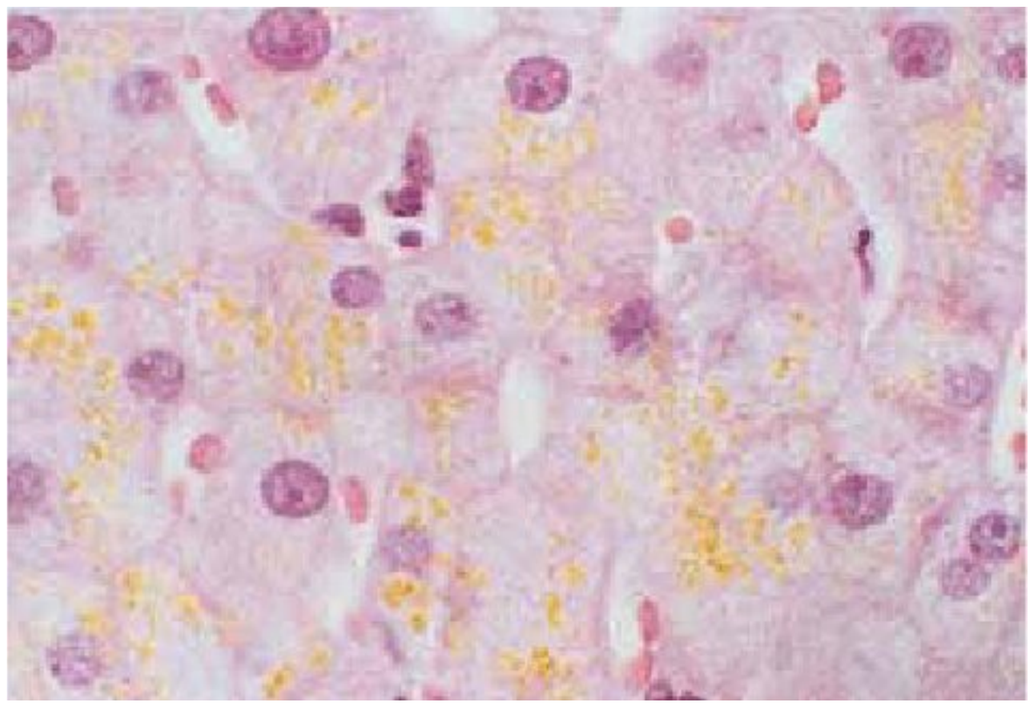

FIGURE 2-3. Accumulation of intracellular lipofuscin. A photomicrograph of the liver of an 80-year-old man shows golden cytoplasmic granules, which represent lysosomal storage of lipofuscin. (From Strayer DS, Rubin E. Cell adaptation, cell injury and cell death. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2012:21.)

FIGURE 2-4. Calcific aortic stenosis. Large deposits of calcium salts are evident in the cusps and free margins of the thickened aortic valve as viewed from above. (From Strayer DS, Rubin E. Cell adaptation, cell injury and cell death. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2012:13.)

tissues and is seen more often in conditions associated with atrophy of an organ.

One of the most common exogenous pigments is carbon in the form of coal dust. In coal miners or persons exposed to heavily polluted environments, the accumulation of carbon dust blackens the lung tissue and may cause serious lung disease. The formation of a blue lead line along the margins of the gum is one of the diagnostic features of lead poisoning. Tattoos are the result of insoluble pigments introduced into the skin, where they are engulfed by macrophages and persist for a lifetime.

The significance of intracellular accumulations depends on the cause and severity of the condition. Many accumulations, such as lipofuscin and mild fatty changes, have no effect on cell function. Some conditions, such as the hyperbilirubinemia that causes jaundice, are reversible. Other disorders, such as glycogen storage diseases, produce accumulations that result in organ dysfunction and other alterations in physiologic function.

Pathologic Calcifications

Pathologic calcification involves the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. It is known as *dystrophic calcification* when it occurs in dead or dying tissue and as *metastatic calcification* when it occurs in normal tissue.[1,2]

Dystrophic Calcification

Dystrophic calcification represents the macroscopic deposition of calcium salts in injured tissue. It is often visible to the naked eye as deposits that range from gritty sand-like grains to firm, hard, rock-like material. The pathogenesis of dystrophic calcification involves the intracellular or extracellular formation of crystalline calcium phosphate. The components of the calcium deposits are derived from the bodies of dead or dying cells as well as from the circulation and interstitial fluid.

Dystrophic calcification is commonly seen in atheromatous lesions of advanced atherosclerosis, areas of injury in the aorta and large blood vessels, and damaged heart valves. While the presence of calcification may only indicate the presence of previous cell injury, as in healed tuberculosis lesions, it is also a frequent cause of organ dysfunction. For example, calcification of the aortic valve is a frequent cause of aortic stenosis in the elderly (Fig. 2-4).

Metastatic Calcification

In contrast to dystrophic calcification, which occurs in injured tissues, metastatic calcification occurs in normal tissues as the result of increased serum calcium levels (hypercalcemia). Almost any condition that increases the serum calcium level can lead to calcification in inappropriate sites such as the lung, renal tubules, and blood vessels. The major causes of hypercalcemia are hyperparathyroidism, either primary or secondary to phosphate retention in renal failure; increased release of calcium from bone as in immobilization, Paget disease, or cancer with metastatic bone lesions; and vitamin D intoxication.

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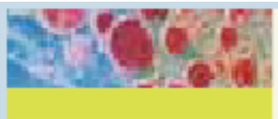

SUMMARY CONCEPTS

- Cells adapt to changes in their environment and in their work demands by changing their size, number, and characteristics. These adaptive changes are consistent with the needs of the cell and occur in response to an appropriate stimulus. The changes are usually reversed after the stimulus has been withdrawn.
- When confronted with a decrease in work demands or adverse environmental conditions, cells atrophy, or reduce in size. When confronted with an increase in work demands they undergo hypertrophy, an increase in size. An increase in the number of cells in an organ or tissue is called hyperplasia.
- Metaplasia occurs in response to chronic irritation and represents the substitution of cells of a type that are better able to survive under circumstances in which a more fragile cell type might succumb. Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and appearance. It is often a precursor of cancer.
- Under some circumstances, cells may accumulate abnormal amounts of various substances. If the accumulation reflects a correctable systemic disorder, such as the hyperbilirubinemia that causes jaundice, the accumulation is reversible. If the disorder cannot be corrected, as often occurs in many inborn errors of metabolism, the cells become overloaded, causing cell injury and death.
- Pathologic calcification involves the abnormal tissue deposition of calcium salts. Dystrophic calcification occurs in dead or dying tissue, whereas metastatic calcification occurs in normal tissues as the result of elevated serum calcium levels.

Cell Injury, Death, and Senescence

Cells can be injured in many ways. The extent to which any injurious agent can cause reversible or irreversible cell injury and death depends in large measure on the intensity and duration of the injury and the type of cell that is involved, as well as variables such as blood supply, nutritional status, and regenerative capacity. Cell injury and death are ongoing processes, and in the healthy state, they are balanced by cell renewal.

Causes of Cell Injury

Cell damage can occur in many ways. For purposes of discussion, the ways by which cells are injured have been grouped into five categories: (1) injury from physical agents, (2) radiation injury, (3) chemical injury, (4) injury from biologic agents, and (5) injury from nutritional imbalances.

Injury from Physical Agents

Physical agents responsible for cell and tissue injury include mechanical forces, extremes of temperature, and electrical forces. They are common causes of injuries due to environmental exposure, occupational and transportation accidents, and physical violence and assault.

Mechanical Forces. Injury or trauma due to mechanical forces occurs as the result of body impact with another object. The body or the mass can be in motion or, as sometimes happens, both can be in motion at the time of impact. These types of injuries split and tear tissue, fracture bones, injure blood vessels, and disrupt blood flow.

Extremes of Temperature. Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems. Exposure to low-intensity heat (43°C to 46°C), such as occurs with partial-thickness burns and severe heat stroke, causes cell injury by inducing vascular injury, accelerating cell metabolism, inactivating temperature-sensitive enzymes, and disrupting the cell membrane. With more intense heat, coagulation of blood and tissue proteins occurs. Exposure to cold increases blood viscosity and induces vasoconstriction by direct action on blood vessels and through reflex activity of the sympathetic nervous system. The resultant decrease in blood flow may lead to hypoxic tissue injury, depending on the degree and duration of cold exposure. Injury from freezing probably results from a combination of ice crystal formation and vasoconstriction. The decreased blood flow leads to capillary stasis and arteriolar and capillary thrombosis. Edema results from increased capillary permeability.

Electrical Forces. Injuries due to electrical forces can affect the body through extensive tissue injury and disruption of neural and cardiac impulses. The effect of electricity on the body is mainly determined by its voltage, the type of current (i.e., direct or alternating), its amperage, the resistance of the intervening tissue, the pathway of the current, and the duration of exposure.[6]

Lightning and high-voltage wires that carry several thousand volts produce the most severe damage.[2] Alternating current (AC) is usually more dangerous than direct current (DC) because it causes violent muscle contractions, preventing the person from releasing the electrical source and sometimes resulting in fractures and dislocations. In electrical injuries, the body acts as

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a conductor of the electrical current. The current enters the body from an electrical source, such as an exposed wire, and passes through the body and exits to another conductor, such as the moisture on the ground or a piece of metal the person is holding. The pathway that a current takes is critical because the electrical energy disrupts impulses in excitable tissues. Current flow through the brain may interrupt impulses from respiratory centers in the brain stem, and current flow through the chest may cause fatal cardiac arrhythmias.

The resistance to the flow of current in electrical circuits transforms electrical energy into heat. This is why the elements in electrical heating devices are made of highly resistive metals. Much of the tissue damage produced by electrical injuries is caused by heat production in tissues that have the highest electrical resistance.[2,7] Resistance to electrical current varies from the greatest to the least in bone, fat, tendons, skin, muscles, blood, and nerves. The most severe tissue injury usually occurs at the skin sites where the current enters and leaves the body (Fig. 2-5). After electricity has penetrated the skin, it rapidly passes through the body along the lines of least resistance—through body fluids and nerves. Degeneration of vessel walls may occur, and thrombi may form as current flows along the blood vessels. This can cause extensive muscle and deep tissue injury. Thick, dry skin is more resistant to the flow of electricity than thin, wet skin. It is generally believed that the greater the skin resistance, the greater is the amount of local skin burn; and the less the resistance, the greater are the deep and systemic effects.

Radiation Injury

Electromagnetic radiation comprises a wide spectrum of wave-propagated energy, ranging from ionizing gamma rays to radiofrequency waves. A photon is a particle of radiation energy. Radiation energy with frequencies above the ultraviolet (UV) range is called *ionizing radiation* because the photons have enough energy to knock electrons off atoms and molecules. *Nonionizing radiation* refers to radiation energy at frequencies below those of visible light. *Ultraviolet radiation* represents the portion of the spectrum of electromagnetic radiation just above the visible range.

FIGURE 2-5. Electrical burn of the skin. The victim was electrocuted after attempting to stop a fall from a ladder by grasping a high-voltage line. (From Strayer DS, Rubin E. Environmental and nutritional pathology. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2012:313.)

Ionizing Radiation. Ionizing radiation affects cells by causing ionization of molecules and atoms in the cell, by directly hitting the target molecules in the cell, or by producing free radicals (highly reactive chemical species) that destabilize molecules in critical cell components.[2,7] It can immediately kill cells, interrupt cell replication, or cause a variety of genetic mutations, which may or may not be lethal. Most radiation injury is caused by localized irradiation that is used in the treatment of cancer (see Chapter 7). Except for unusual circumstances such as the use of high-dose irradiation that precedes bone marrow transplantation, exposure to whole-body irradiation is rare.

The injurious effects of ionizing radiation vary with the dose, dose rate (a single large dose can cause greater injury than divided or fractionated doses), and the differential sensitivity of the exposed tissue to radiation injury. Because of the effect on deoxyribonucleic acid (DNA) synthesis and interference with mitosis, rapidly dividing cells of the bone marrow and intestine are much more vulnerable to radiation injury than tissues such as bone and skeletal muscle. Over time, occupational and accidental exposure to ionizing radiation can result in increased risk for the development of various types of cancers, including skin cancers, leukemia, osteogenic sarcomas, and lung cancer.

Many of the clinical manifestations of radiation injury result from acute cell injury, dose-dependent changes in the blood vessels that supply the irradiated tissues, and fibrotic tissue replacement. The cell's initial response to radiation injury involves swelling, disruption of the mitochondria and other organelles, alterations in the cell membrane, and marked changes in the nucleus. The endothelial cells in blood vessels are particularly sensitive to irradiation. During the immediate post-irradiation period, only vessel dilatation is apparent (e.g., the initial erythema of the skin after radiation therapy). Later or with higher levels of radiation, destructive changes occur in small blood vessels such as the capillaries and venules. Acute reversible necrosis is represented by such disorders as radiation cystitis, dermatitis, and diarrhea from enteritis. More persistent damage can be attributed to acute necrosis of tissue cells that are not capable of regeneration, or because of chronic ischemia. Chronic effects of radiation damage are characterized by fibrosis and scarring of tissues and organs in the irradiated area (e.g., interstitial fibrosis of the heart and lungs after irradiation of the chest). Because the radiation delivered in radiation therapy inevitably travels through the skin, radiation dermatitis is common. There may be necrosis of the skin, impaired wound healing, and chronic radiation dermatitis.

Ultraviolet Radiation. Ultraviolet radiation contains increasingly energetic rays that are powerful enough to disrupt intracellular bonds, cause sunburn, and increase the risk of skin cancers (see Chapter 46). The degree of risk depends on the type of UV rays, the intensity of exposure, and the amount of protective melanin pigment in the skin. Skin damage induced by UV radiation is thought to be caused by reactive oxygen species and by damage to melanin-producing processes in the skin. Ultraviolet radiation also damages DNA, resulting in the formation of pyrimidine dimers (i.e., the insertion of two identical pyrimidine bases into replicating DNA instead of one). Other forms of DNA damage include the production of single-stranded breaks and formation of DNA–protein cross-links. Normally, errors that occur during DNA replication are repaired by enzymes that remove the faulty section of DNA and repair the damage. The importance of DNA repair in protecting against UV radiation injury is evidenced by the vulnerability of persons who lack the enzymes needed to repair UV-induced DNA damage. In a genetic disorder called *xeroderma pigmentosum*, an enzyme needed to repair sunlight-induced DNA damage is lacking. This autosomal recessive disorder is characterized by extreme photosensitivity and a 2000-fold increased risk of skin cancer in sun-exposed skin.[2]

Nonionizing Radiation. Nonionizing radiation includes infrared light, ultrasound, microwaves, and laser energy.[1] Unlike ionizing radiation, which can directly break chemical bonds, nonionizing radiation exerts its effects by causing vibration and rotation of atoms and molecules. All of this vibrational and rotational energy is eventually converted to thermal energy. Low-frequency nonionizing radiation is used widely in radar, television, industrial operations (e.g., heating, welding, melting of metals, processing of wood and plastic), household appliances (e.g., microwave ovens), and medical applications (e.g., diathermy). Isolated cases of skin burns and thermal injury to deeper tissues have occurred in industrial settings and from improperly used household microwave ovens. Injury from these sources is mainly thermal and, because of the deep penetration of infrared or microwave rays, tends to involve dermal and subcutaneous tissue injury.

Chemical Injury

Chemicals capable of damaging cells are everywhere around us. Pollutants in the air, water, and soil, such as carbon monoxide, pesticides, and trace metals including lead, are capable of tissue injury, as are certain chemicals in foods.

Chemical agents can injure the cell membrane and other cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of the cell. Corrosive substances such as strong acids and bases destroy cells as the substances come into contact with the body. Other chemicals may injure cells in the process of metabolism or elimination. For example, carbon tetrachloride (CCl_4), a chemical used in manufacturing, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical that is extremely toxic to liver cells.

Drugs. Many drugs—alcohol, prescription drugs, over-the-counter drugs, and street drugs—are capable of directly or indirectly damaging tissues. Ethyl alcohol can harm the gastric mucosa, liver (see Chapter 30), developing fetus (see Chapter 6), and other organs. Antineoplastic (anticancer) and immunosuppressant drugs can directly injure cells. Other drugs produce metabolic end products that are toxic to cells. Acetaminophen, a commonly used over-the-counter analgesic drug, is detoxified in the liver, where small amounts of the drug are converted to a highly toxic metabolite. This metabolite is detoxified by a metabolic pathway that uses a substance (i.e., glutathione) normally present in the liver. When large amounts of the drug are ingested, this pathway becomes overwhelmed and toxic metabolites accumulate, causing massive liver necrosis.

Lead Toxicity. Lead is a particularly toxic metal. Small amounts accumulate to reach toxic levels. There are innumerable sources of lead in the environment, including flaking paint, lead-contaminated dust and soil, pottery glazes, traditional remedies, cosmetics, and wild game contaminated by lead shot. Adults often encounter lead through occupational exposure. Lead and other metal smelters, miners, welders, storage battery workers, and pottery makers are particularly at risk.[2,7] Children are exposed to lead through ingestion of peeling lead paint, by breathing dust from lead paint (e.g., during remodeling), playing in contaminated soil, or playing with toys or items made or decorated with lead.[8,9] Factors that increase the risk of lead toxicity include preschool age, low socioeconomic status, and living in housing built before 1960.[9]

Lead is absorbed through the gastrointestinal tract or the lungs into the blood. A deficiency in calcium, iron, or zinc increases lead absorption. In children, most lead is absorbed through the lungs. Although infants and children may have the same or a lower intake of lead as compared to adults, their absorption is greater. Also, the more permeable blood–brain barrier of infants and children makes them highly susceptible to brain damage.[2,7,9] Lead crosses the placenta, exposing the fetus to levels of lead that are comparable with those of the mother. Most of the absorbed lead (80% to 85%) is stored in bone (and teeth of young children), 5% to 10% remains in the blood, and the remainder accumulates in soft tissues.[2] Although the half-life of lead is hours to days, bone serves as a repository from which blood levels are maintained. In a sense, bone protects other tissues, but the slow turnover maintains blood levels for months to years.

The toxicity of lead is related to its multiple biochemical effects.[2,7] It has the ability to inactivate enzymes, compete with calcium for incorporation into bone, and interfere with nerve transmission and brain development. The major targets of lead toxicity are the red blood cells, the gastrointestinal tract, the kidneys, and the nervous system. Anemia is a cardinal sign of lead toxicity.

Lead competes with the enzymes required for hemoglobin synthesis and with the membrane-associated enzymes that prevent hemolysis of red blood cells. The life span of the red cell is decreased. The gastrointestinal tract is the main source of symptoms in the adult. This is characterized by "lead colic," a severe and poorly localized form of acute abdominal pain. A lead line formed by precipitated lead sulfite may appear along the gingival margins. The lead line is seldom seen in children. The kidneys are the major route for excretion of lead. Lead can cause diffuse kidney damage, eventually leading to renal failure. Even without overt signs of kidney damage, lead toxicity leads to hypertension.

In the nervous system, lead toxicity is characterized by demyelination of cerebral and cerebellar white matter and death of brain cells. When this occurs in early childhood, it can affect neurobehavioral development and result in lower IQ levels and poorer classroom performance.[9] Demyelination of peripheral nerves may occur in adults. The most serious manifestation of lead poisoning is acute encephalopathy. It is manifested by persistent vomiting, ataxia, seizures, papilledema, impaired consciousness, and coma. Acute encephalopathy may manifest suddenly, or it may be preceded by other signs of lead toxicity such as behavioral changes or abdominal complaints.

The threshold level at which lead causes subclinical and clinical disturbances has been redefined a number of times over the past 50 years. At one time, a blood level of 25 μg/dL was considered safe. Recent research suggests that even levels below 10 μg/dL are associated with declines in children's IQ at 3 to 5 years of age.[10,11]

Approximately 99% of children are identified by screening procedures, which are recommended for high-risk populations based on the likelihood of lead exposure. A screening value greater than 10 μg/dL requires repeat testing for a diagnosis and to determine the need for treatment. Treatment involves removal of the lead source and, in cases of severe toxicity, administration of a chelating agent. A public health team should evaluate the source of lead because meticulous removal is needed.

Mercury Toxicity. Mercury has been used for industrial and medical purposes for hundreds of years. Mercury is toxic, and the hazards of mercury-associated occupational and accidental exposures are well known. In recent times, the primary concern of the general public about the potential hazards of mercury has focused on exposure from eating certain fish, amalgams used in dentistry, and vaccines.[12] Mercury is present in four primary forms: mercury vapor, inorganic divalent mercury, methyl mercury, and ethyl mercury.[12] Depending on the form of mercury exposure, toxicity involving the central nervous system and kidney can occur.

In the case of dental fillings, the concern involves mercury vapor being released into the mouth. However, the amount of mercury vapor released from fillings is very small. There is no clear evidence supporting health risk from this type of exposure, and removal of amalgams may temporarily increase blood levels of mercury.[12] The main source of methyl mercury exposure is from consumption of long-lived fish, such as tuna and swordfish. Fish concentrate mercury from sediment in the water. Because the developing brain is more susceptible to mercury-induced damage, it is recommended that young children and pregnant and nursing women avoid consumption of fish known to contain high mercury content. Thimerosal is an ethyl mercury–containing preservative that helps prevent microbial growth in vaccines. Concern about potential adverse effects have led to the creation of single-dose vials that eliminate the need for thimerosal.[12] In the United States and Canada, most vaccines are either free of thimerosal or contain only trace amounts.

Injury from Biologic Agents

Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects (see Chapter 14). These agents range from submicroscopic viruses to the larger parasites. Biologic agents injure cells by diverse mechanisms. Viruses enter the cell and incorporate its genetic material into their cellular DNA, which then enables synthesis of new viruses. Certain bacteria produce exotoxins that may interfere with cellular protein synthesis. Other bacteria, such as the gram-negative bacilli, release endotoxins that cause cell injury and increased capillary permeability.

Injury from Nutritional Imbalances

Nutritional excesses and nutritional deficiencies predispose cells to injury. Obesity and diets high in saturated fats are thought to predispose persons to atherosclerosis. The body requires more than 60 organic and inorganic substances in amounts ranging from micrograms to grams. These nutrients include minerals, vitamins, certain fatty acids, and specific amino acids. Dietary deficiencies can occur because of a selective deficiency of a single nutrient. Iron-deficiency anemia, scurvy, beriberi, and pellagra are examples of injury caused by a lack of specific vitamins or minerals. The protein and calorie deficiencies that occur with starvation cause widespread tissue damage.

Mechanisms of Cell Injury

The mechanisms by which injurious agents cause cell injury and death are complex. Some agents, such as heat, produce direct cell injury; other factors, such as genetic derangements, produce their effects indirectly through metabolic disturbances and altered immune responses. There seem to be at least three major mechanisms whereby most injurious agents exert their effects: free radical formation, hypoxia and ATP depletion, and disruption of intracellular calcium homeostasis (Fig. 2-6).

Free Radical Injury

Cell injury in many circumstances involves the production of reactive chemical species known as free radicals.[1,2,13–15] These circumstances include ischemia-reperfusion injury,

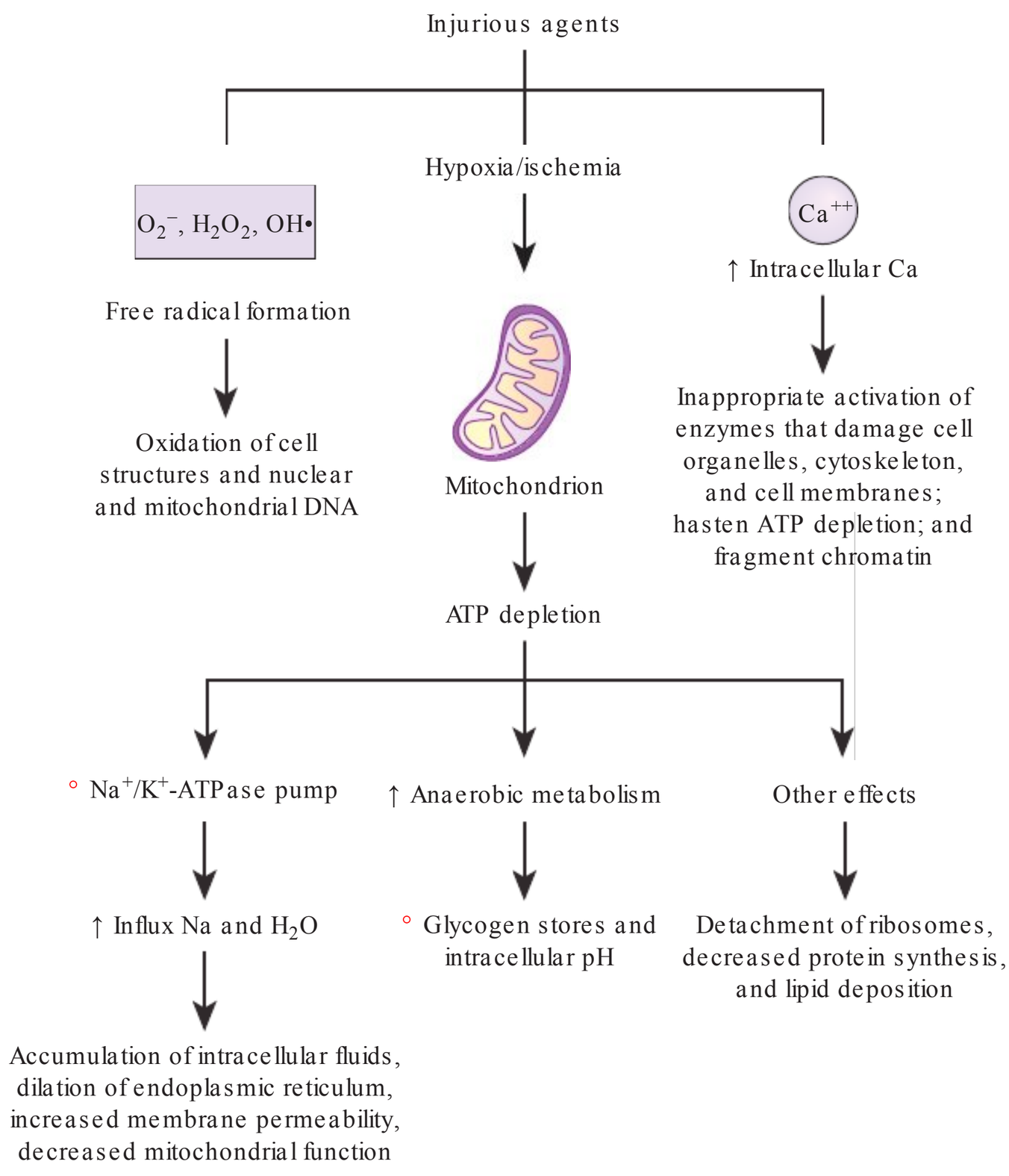

FIGURE 2-6. Mechanisms of cell injury. ATP, adenosine triphosphate.

chemical and radiation injury, toxicity from oxygen and other gases, cellular aging, responses to microbial infections, and tissue injury caused by inflammation.

Free radicals are highly reactive chemical species with an unpaired electron in the outer orbit (valence shell) of the molecule. In the literature, the unpaired electron is denoted by a dot, for example, NO·. The unpaired electron causes free radicals to be unstable and highly reactive, so that they react nonspecifically with molecules in the vicinity. Moreover, free radicals can establish chain reactions consisting of many events that generate new free radicals. In cells and tissues, free radicals react with proteins, lipids, and carbohydrates, thereby damaging cell membranes, inactivating enzymes, and damaging nucleic acids that make up DNA.

Many free radicals that are harmful in human physiology are derived from oxygen. These *reactive oxygen species* (ROS) include free radicals, such as superoxide anion (O_2^-) and hydroxyl radical (OH·), as well as reactive oxygen-containing species that are not free radicals, such as hydrogen peroxide (H_2O_2). Reactive oxygen species are normal products of mitochondrial respiration and energy metabolism, and are typically removed by cellular antioxidative systems. Exogenous causes, including ionizing and UV radiation, can also cause ROS production in the body. *Oxidative stress* is a condition that occurs when the generation of ROS exceeds the ability of the body to neutralize and eliminate ROS. Oxidative stress can lead to oxidation of cell components, activation of signal transduction pathways, DNA damage, and changes in gene expression. In addition to focusing on nuclear DNA as a target of oxidative injury, current studies are focusing on mitochondrial DNA as a target of oxidation and subsequent cause of mitochondrial dysfunction.[16]

Although ROS and oxidative stress are clearly associated with cell and tissue damage, recent evidence suggests that ROS are not always acting in a random and damaging manner. Current studies find that ROS are also important signaling molecules that are used in healthy cells to regulate normal functions such as vascular smooth muscle tone and vascular endothelial growth factor (VEGF) signaling, and even function as a preconditioning factor to protect cells from injury.[17]

Antioxidants are natural and synthetic molecules that inhibit the reactions of ROS with biologic structures or that prevent the uncontrolled formation of ROS. Antioxidants include enzymatic and nonenzymatic compounds. Enzymes known to function as antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase, and thioreductase. Superoxide dismutase forms hydrogen peroxide from superoxide. Catalase,

present in peroxisomes, catalyzes the reaction that forms water from hydrogen peroxide. Nonenzymatic antioxidants include carotenes (e.g., vitamin A), tocopherols (e.g., vitamin E), ascorbate (vitamin C), glutathione, and flavonoids, as well as micronutrients such as selenium and zinc.[18] Nonenzymatic antioxidants often directly react with oxidants to "disarm" them. For example, vitamin C directly scavenges superoxide and hydroxyl radicals.[19]

Oxidative damage has been implicated in many diseases. Mutations in the gene for SOD are associated with amyotrophic lateral sclerosis (ALS; so-called *Lou Gehrig disease*).[20] Oxidative stress is thought to have an important role in the development of cancer.[21] Reestablishment of blood flow following loss of perfusion, as occurs during heart attack and stroke, is associated with oxidative injury to vital organs. The endothelial dysfunction that contributes to the development, progression, and prognosis of cardiovascular diseases is thought to be caused in part by oxidative stress.[22] In addition, oxidative stress has been associated with age-related functional declines.[23]

Hypoxic Cell Injury

Hypoxia deprives the cell of oxygen and interrupts oxidative metabolism and the generation of ATP. The actual time necessary to produce irreversible cell damage depends on the degree of oxygen deprivation and the metabolic needs of the cell. Some cells, such as those in the heart, brain, and kidney, require large amounts of oxygen to provide the energy to perform their functions. Brain cells, for example, begin to undergo permanent damage after 4 to 6 minutes of oxygen deprivation. A thin margin of time exists between reversible and irreversible cell damage. A classic study found that the epithelial cells of the proximal tubule of the kidney in the rat could survive 20 but not 30 minutes of ischemia.[24] Recent work has identified a group of proteins called *hypoxia-inducible factors* (HIFs). During hypoxic conditions, HIFs cause the expression of genes that stimulate red blood cell formation, manufacture glycolytic enzymes that produce ATP in the absence of oxygen, and increase angiogenesis[25] (i.e., the formation of new blood vessels).

Hypoxia can result from an inadequate amount of oxygen in the air, respiratory disease, ischemia (i.e., decreased blood flow due to vasoconstriction or vascular obstruction), anemia, edema, or inability of the cells to use oxygen. Ischemia is characterized by impaired oxygen delivery and impaired removal of metabolic end products such as lactic acid. In contrast to pure hypoxia, which depends on the oxygen content of the blood and affects all cells in the body, ischemia commonly depends on blood flow through limited numbers of blood vessels and produces local tissue injury. In some cases of edema, the distance for diffusion of oxygen may become a limiting factor in the delivery of oxygen. In hypermetabolic states, the cells may require more oxygen than can be supplied by normal respiratory function and oxygen transport. Hypoxia also serves as the ultimate cause of cell death in other injuries. For example, physical factors such as a cold temperature can cause severe constriction and impair blood flow.

Hypoxia causes a power failure in the cell, with widespread effects on the cell's structural and functional components. As oxygen tension in the cell falls, oxidative metabolism ceases, and the cell reverts to anaerobic metabolism, using its limited glycogen stores in an attempt to maintain vital cell functions. Cellular pH falls as lactic acid accumulates in the cell. This reduction in pH can have adverse effects on intracellular structures and biochemical reactions. Low pH can alter cell membranes and cause chromatin clumping and cell volume changes.

An important effect of reduced ATP is acute cell swelling caused by failure of the energy-dependent sodium/potassium (Na^+/K^+)-adenosine triphosphatase (ATPase) membrane pump, which extrudes sodium from and returns potassium to the cell. With impaired function of this pump, intracellular potassium levels decrease, and sodium and water accumulate in the cell. The movement of water and ions into the cell is associated with dilation of the endoplasmic reticulum, increased membrane permeability, and decreased mitochondrial function.[2] To a point, the cellular changes due to hypoxia are reversible if oxygenation is restored. However, if the oxygen supply is not restored there is continued loss of enzymes, proteins, and ribonucleic acid through the hyperpermeable cell membrane. Injury to the lysosomal membranes results in the leakage of destructive lysosomal enzymes into the cytoplasm and enzymatic digestion of cell components. Leakage of intracellular enzymes through the permeable cell membrane into the extracellular fluid provides an important clinical indicator of cell injury and death. These enzymes enter the blood and can be measured by laboratory tests.

Impaired Calcium Homeostasis

Calcium functions as an important second messenger and cytosolic signal for many cell responses. Various calcium-binding proteins, such as troponin and calmodulin, act as transducers for cytosolic calcium signaling. Calcium/calmodulin–dependent kinases indirectly mediate the effects of calcium on responses such as smooth muscle contraction and glycogen breakdown. Normally, intracellular calcium ion levels are kept extremely low compared with extracellular levels. These low intracellular levels are maintained by energy-dependent membrane-associated calcium/magnesium (Ca^{++}/Mg^{++})-ATPase exchange systems[2] and sequestration of calcium ions within organelles such as the mitochondria and smooth endoplasmic reticulum. Ischemia and certain toxins lead to an increase in cytosolic calcium because of the increased influx across the cell membrane and the release of calcium from intracellular stores. The increased calcium level may inappropriately activate a number of enzymes with potentially damaging effects. These enzymes include phospholipases that can damage the cell membrane, proteases that damage the cytoskeleton and membrane proteins, ATPases that break down ATP and hasten its depletion, and endonucleases that fragment chromatin. Although it is known that injured cells accumulate calcium, it is unknown whether this is the ultimate cause of irreversible cell injury.

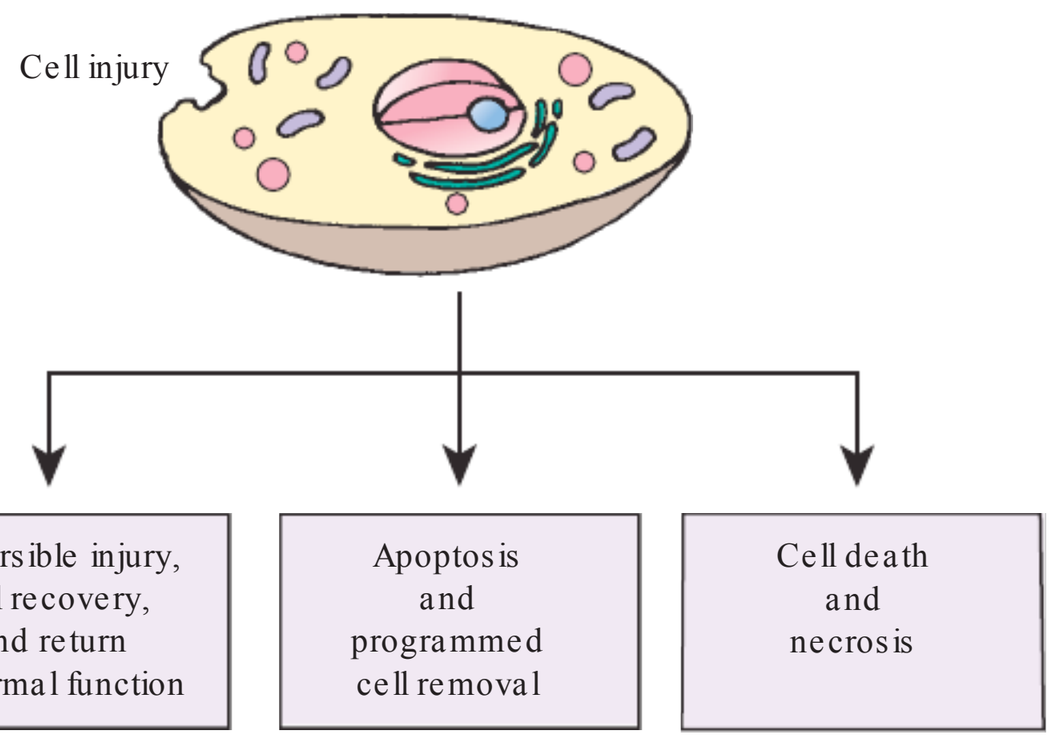

FIGURE 2-7. Outcomes of cell injury: reversible cell injury, apoptosis and programmed cell removal, cell death, and necrosis.

Reversible Cell Injury and Cell Death

The mechanisms of cell injury can produce sublethal and reversible cellular damage or lead to irreversible injury with cell destruction or death (Fig. 2-7). Cell destruction and removal usually involve one of two mechanisms: apoptosis, which is designed to remove injured or worn-out cells, or cell death or necrosis, which occurs in irreversibly damaged cells.

Reversible Cell Injury

Reversible cell injury, although impairing cell function, does not result in cell death. Two patterns of reversible cell injury can be observed under the microscope: cellular swelling and fatty change. Cellular swelling occurs with impairment of the energy-dependent Na^+/K^+-ATPase membrane pump, usually as the result of hypoxic cell injury.

Fatty changes are linked to intracellular accumulation of fat. When fatty changes occur, small vacuoles of fat disperse throughout the cytoplasm. The process is usually more ominous than cellular swelling, and although it is reversible, it usually indicates severe injury. These fatty changes may occur because normal cells are presented with an increased fat load or because injured cells are unable to metabolize the fat properly. In obese persons, fatty infiltrates often occur within and between the cells of the liver and heart because of an increased fat load. Pathways for fat metabolism may be impaired during cell injury, and fat may accumulate in the cell as production exceeds use and export. The liver, where most fats are synthesized and metabolized, is particularly susceptible to fatty change, but fatty changes may also occur in the kidney, the heart, and other organs.

Programmed Cell Death

In most normal nontumor cells, the number of cells in tissues is regulated by balancing cell proliferation and cell death. Cell death occurs by necrosis or a form of programmed cell death called *apoptosis*.

Apoptosis, from the Greek *apo* for "apart" and *ptosis* for "fallen," means "fallen apart." Apoptosis is a highly selective process that eliminates injured and aged cells, thereby controlling tissue regeneration.[26] Cells undergoing apoptosis have characteristic morphologic features, as well as biochemical changes. As shown in Figure 2-8, shrinking and condensation of the nucleus and cytoplasm occur. The chromatin aggregates at the nuclear envelope, and DNA fragmentation occurs. Then, the cell becomes fragmented into multiple apoptotic bodies in a manner that maintains the integrity of the plasma membrane and does not initiate inflammation. Changes in the plasma membrane induce phagocytosis of the apoptotic bodies by macrophages and other cells, thereby completing the degradation process.

Apoptosis is thought to be responsible for several normal physiologic processes, including the programmed destruction of cells during embryonic development, hormone-dependent involution of tissues, death of immune cells, cell death by cytotoxic T cells, and cell death in proliferating cell populations. During embryogenesis, in the development of a number of organs such as the heart, which begins as a pulsating tube and is gradually modified to become a four-chambered pump, apoptotic cell death allows for the next stage of organ development.

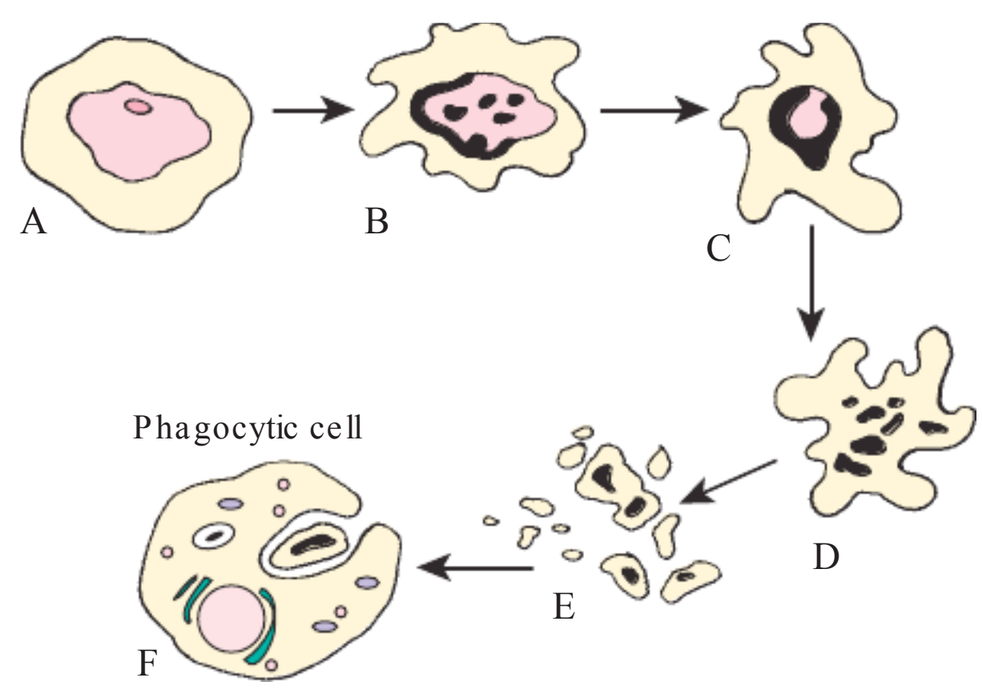

FIGURE 2-8. Apoptotic cell removal. **(A)** Shrinking of the cell structures. **(B, C)** Condensation and fragmentation of the nuclear chromatin. **(D, E)** Separation of nuclear fragments and cytoplasmic organelles into apoptotic bodies. **(F)** Engulfment of apoptotic fragments by phagocytic cell.

It also separates the webbed fingers and toes of the developing embryo. Apoptotic cell death occurs in the hormone-dependent involution of endometrial cells during the menstrual cycle and in the regression of breast tissue after weaning from breast-feeding. The control of immune cell numbers and destruction of autoreactive T cells in the thymus have been credited to apoptosis. Cytotoxic T cells and natural killer cells are thought to destroy target cells by inducing apoptotic cell death.

Apoptosis is linked to many pathologic processes and diseases. For example, interference with apoptosis is known to be a mechanism that contributes to carcinogenesis.[27] Apoptosis is also known to be involved in the cell death associated with viral infections, such as hepatitis B and C.[27,28] Apoptosis may also be implicated in neurodegenerative disorders such as ALS, Alzheimer disease, and Parkinson disease. However, the exact mechanisms involved in these diseases remains under investigation.

Two basic pathways for apoptosis have been described (Fig. 2-9). These are the extrinsic pathway, which is death receptor dependent, and the intrinsic pathway, which is death receptor independent. The execution phase of both pathways is carried out by proteolytic enzymes called *caspases* (cysteine proteases that cleave aspartate residues), which are present in the cell as *procaspases* and are activated by cleavage of an inhibitory portion of their polypeptide chain.[2,29]

The *extrinsic pathway* involves extracellular signaling proteins that bind to cell surface molecules called *death receptors* and trigger apoptosis. The prototype death receptors are tumor necrosis factor (TNF) receptor and the Fas ligand receptor.[29] Fas ligand may be expressed on the surface of certain cells, such as cytotoxic T cells, or appear in a soluble form. When Fas ligand binds to its receptor, proteins congregate at the cytoplasmic end of the Fas receptor to form a death-initiating complex. The complex then converts procaspase-8 to caspase-8. Caspase-8, in turn, activates a cascade of caspases that execute the process of apoptosis. The end result includes activation of endonucleases that cause fragmentation of DNA and cell death. In addition to TNF and Fas ligand, primary signaling molecules known to activate the extrinsic pathway include TNF-related apoptosis-inducing ligand (TRAIL); the cytokine interleukin-1 (IL-1); and lipopolysaccharide (LPS), the endotoxin found in the outer cell membrane of gram-negative bacteria.

The *intrinsic pathway,* or *mitochondrion-induced pathway,* of apoptosis is activated by conditions such as DNA damage, ROS, hypoxia, decreased ATP levels, cellular senescence, and activation of the p53 protein by DNA damage. The intrinsic pathway is tightly regulated to ensure that cells kill themselves only when appropriate. A major class of intracellular regulators of apoptosis is the Bcl-2 family of proteins. Some of these proteins insert into the mitochondrial membrane opening channels through which proteins escape into the cytoplasm.[29] A crucial protein released from the mitochondria is cytochrome c, a component of the mitochondrial electron transport chain (see Chapter 1). When released into the cytoplasm, cytochrome c binds to a procaspase-activating protein that activates caspases,

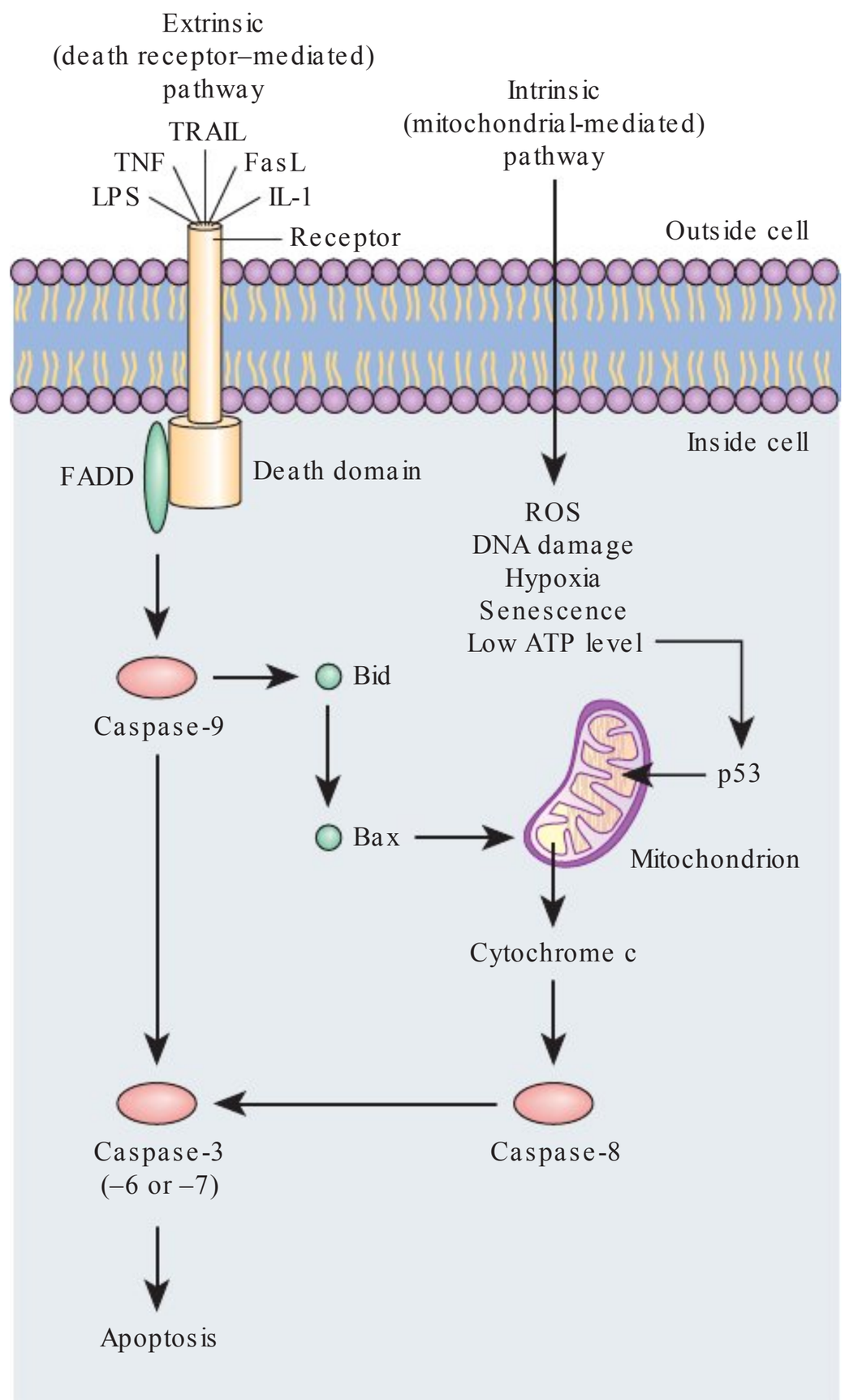

FIGURE 2-9. Pathways for apoptosis. The extrinsic pathway is activated by signals such as TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL) that, upon binding to the Fas receptor, form a death-inducing complex by joining the Fas-associated death domain (FADD) to the death domain of the Fas receptor. The intrinsic pathway is activated by signals, such as reactive oxygen species (ROS) and DNA damage, which induce the release of cytochrome c from mitochondria into the cytoplasm. Both pathways activate caspases to execute apoptosis, with activation of the pro-apoptotic proteins Bid and Bax by caspase-8 serving to bridge the two systems. ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; IL-1, interleukin-1; LPS, lipopolysaccharide; TNF, tumor necrosis factor.

including caspase-3. Caspase-3 activation is a common step to both the extrinsic and intrinsic pathways. Activation of caspase-8 in the extrinsic pathway can also lead to activation of pro-apoptotic proteins, such as Bid and Bax, thereby bridging the two pathways for apoptosis.[2,29] While some members of the Bcl-2 family are pro-apoptotic, others are anti-apoptotic and inhibit apoptosis by binding to pro-apoptotic proteins, either on the mitochondrial membranes or in the cytoplasm.

Inhibitors of apoptosis are thought to contribute to cancer and autoimmune diseases.[29–31] The Bcl-2 gene

was first identified in B-cell lymphoma, in which a chromosomal translocation causes excessive production of Bcl-2, giving the gene its name.[29] Excessive levels of Bcl2 in the lymphocytes that carry the translocation promote the development of cancer by inhibiting apoptosis. Similarly, mutation of the genes encoding the tumor-suppressor protein p53 so that it no longer suppresses apoptosis or cell cycle arrest in response to DNA damage is implicated in a number of other cancers (see Chapter 7). The therapeutic actions of certain drugs may induce or facilitate apoptosis. Apoptosis continues to be an active area of investigation to better understand and treat a variety of diseases.

Necrosis

Necrosis refers to cell death in an organ or tissue that is still part of a living person.[32] Necrosis differs from apoptosis in that it involves unregulated enzymatic digestion of cell components, loss of cell membrane integrity with uncontrolled release of the products of cell death into the extracellular space, and initiation of the inflammatory response.[32] In contrast to apoptosis, which functions in removing cells so new cells can replace them, necrosis often interferes with cell replacement and tissue regeneration.

With necrosis, there are marked changes in the appearance of the cytoplasmic contents and the nucleus. These changes often are not visible, even under a microscope, for hours after cell death. The dissolution of the necrotic cell or tissue can follow several paths. *Liquefaction necrosis* occurs when some of the cells die but their catalytic enzymes are not destroyed. An example of liquefaction necrosis is the softening of the center of an abscess with discharge of its contents. During *coagulation necrosis*, acidosis develops and denatures the enzymatic and structural proteins of the cell. This type of necrosis is characteristic of hypoxic injury and is seen in infarcted areas. *Infarction* (i.e., tissue death) occurs when an artery supplying an organ or part of the body becomes occluded and no other source of blood supply exists. As a rule, the shape of the infarction is conical and corresponds to the distribution of the artery and its branches. An artery may be occluded by an embolus, a thrombus, disease of the arterial wall, or pressure from outside the vessel.

Caseous necrosis is a distinctive form of coagulation necrosis in which the dead cells persist indefinitely as soft, cheese-like debris.[1] It is most commonly found in the center of tuberculosis granulomas, or tubercles, and is thought to result from immune mechanisms (see Chapter 22).

The term *gangrene* is applied when a considerable mass of tissue undergoes necrosis. Gangrene may be classified as dry or moist. In dry gangrene, the part becomes dry and shrinks, the skin wrinkles, and its color changes to dark brown or black. The spread of dry gangrene is slow, and its symptoms are not as marked as those of wet gangrene. The irritation caused by the dead tissue produces a line of inflammatory reaction (i.e., line of demarcation) between the dead tissue of the gangrenous area and the healthy tissue (Fig. 2-10). Dry gangrene usually results from interference with arterial blood supply to a part without interference with venous return and is a form of coagulation necrosis.

FIGURE 2-10. Gangrenous toes. (Biomedical Communications Group, Southern Illinois University School of Medicine, Springfield, IL.)

In moist or wet gangrene, the area is cold, swollen, and pulseless. The skin is moist, black, and under tension. Blebs form on the surface, liquefaction occurs, and a foul odor is caused by bacterial action. There is no line of demarcation between the normal and diseased tissues, and the spread of tissue damage is rapid. Systemic symptoms are usually severe, and death may occur unless the condition can be arrested. Moist or wet gangrene primarily results from interference with venous return from the part. Bacterial invasion plays an important role in the development of wet gangrene and is responsible for many of its prominent symptoms. Dry gangrene is confined almost exclusively to the extremities, but moist gangrene may affect the internal organs or the extremities. If bacteria invade the necrotic tissue, dry gangrene may be converted to wet gangrene.

Gas gangrene is a special type of gangrene that results from infection of devitalized tissues by one of several *Clostridium* bacteria, most commonly *Clostridium perfringens*. These anaerobic and spore-forming organisms are widespread in nature, particularly in soil; gas gangrene is prone to occur in trauma and compound fractures in which dirt and debris are embedded. Some species have been isolated in the stomach, gallbladder, intestine, vagina, and skin of healthy persons. The bacteria produce toxins that dissolve cell membranes, causing death of muscle cells, massive spreading edema, hemolysis of red blood cells, hemolytic anemia, hemoglobinuria, and renal failure.[33] Characteristic of this disorder are the bubbles of hydrogen sulfide gas that form in the muscle. Gas gangrene is a serious and potentially fatal disease. Antibiotics are used to treat the infection and surgical methods are used to remove the infected tissue. Amputation may be required to prevent spreading

infection involving a limb. Hyperbaric oxygen therapy has been used, but clinical data supporting its efficacy has not been rigorously assessed.

Cellular Aging

Aging is a complex natural process in which there are physiologic and structural alterations in almost all organ systems.[1,2,34–38] Even in the absence of disease, beginning in the fourth decade of life, there is a progressive decline in muscle strength, cardiac reserve, vital capacity, nerve conduction time, and glomerular filtration rate. Although the biologic basis of aging is poorly understood, there is general consensus that its elucidation should be sought at the cellular level. Many cell functions decline with age. Oxidative phosphorylation by the mitochondria is reduced, as is synthesis of nucleic acids and transcription factors, cell receptors, and cell proteins.

A number of theories have been proposed to explain the cause of aging. The main theories are based on scientific observations at the molecular, cellular, organ, and system levels. In general, these theories can be divided into either programmed or error theories. The *programmed theories* propose that the changes that occur with aging are genetically programmed, whereas the *damage* or *error theories* maintain that the changes result from an accumulation of random events or environmental agents or influences that are associated with DNA damage.[35–39] Evidence suggests that the process of aging and longevity is multifaceted, with both genetic and environmental factors playing a role. In animal studies, genetics accounted for less than 35% of the effects of aging, whereas environmental influences accounted for over 65%.[36] In humans, long life appears to have a stronger genetic basis, which explains why centenarians and near centenarians tend to cluster in families.[40]

Replicative Senescence

Replicative senescence implies that cells have a limited capacity for replication. At the cellular level, Hayflick and Moorhead observed more than 40 years ago that cultured human fibroblasts have a limited ability to replicate (approximately 50 population doublings) and then die.[41] Before achieving this maximum, they slow their rate of division and manifest identifiable and predictable morphologic changes characteristic of senescent cells.

One explanation of replicative senescence is related to the length of the outermost regions of each chromosome, called *telomeres,* that contain short repeat sequences of DNA bases.[1,2,35] During mitosis, the molecular machinery that replicates DNA cannot copy the extreme ends of the chromosome. Thus, with each cell division, a small segment of telomeric DNA is lost. Over time, it is theorized that as the telomeres become progressively shorter, the DNA at the ends of the chromosomes cannot be protected, resulting in inhibition of cell replication. The lengths of the telomeres are normally maintained by an enzyme called *telomerase*, which is present in low levels in stem cells, but is usually absent in most adult cells. Therefore, as cells age, their telomeres become shorter and they lose their ability to replicate and replace damaged or senescent cells. Moreover, oxidative stress induces single-stranded damage to telomeric DNA, and this defect cannot be repaired in telomeres. In theory, such mechanisms could also provide a safeguard against uncontrolled cell proliferation of abnormal cells. It has been shown that telomerase is reactivated and telomeres are not shortened in immortal cancer cells, suggesting that telomere elongation may be important in tumor formation.

Genetic Influences

There is ongoing interest in genes that determine longevity. Longevity genes have been found in fruit flies and roundworms, organisms that have attracted considerable attention from scientists because of their short life span and their well-characterized genomes. One example is the mutation of the *Indy* (I'm Not Dead Yet) gene in the fruit fly, which can double the length of its life.[35] Scientists have also found genetic clues to the aging process in the tiny roundworm, *Caenorhabditis elegans*. By altering one of its *daf-2* genes, which codes for a protein that is similar to insulin and insulin growth factor (IGF)-1 receptors found in humans, researchers can substantially extend the longevity of these worms.[1,35] Pathways related to the *daf-2* gene, for example, may be responsible for relationships between caloric restriction and prolonged life span in rodents and other animals. Whether human counterparts of genes found in these laboratory organisms exist and whether they have similar effects remain an ongoing area of inquiry.

However, many genes that are associated with human life span are not intrinsically "longevity genes," per se. For example, because mutations in the tumor-suppressor genes BRAC1 and BRAC2 increase mortality associated with breast and ovarian cancer, they are rare among long-lived women.[40] Conversely, genes that reduce the risk of atherosclerosis may be more common in long-lived individuals. Genetic studies of biologic aging have also explored the involvement of variants of genes encoding apolipoproteins (proteins that bind lipids for transport in the circulatory system), in particular, the APOE gene encoding the synthesis of apolipoprotein E. The presence of the variant apoE4 is associated with an increased incidence of cardiovascular and neurodegenerative diseases, thereby shortening life span.[37,41]

Accumulation of Environmental and Genetic Damage

In addition to the importance of timing and a genetic clock, cellular life span may be determined by a balance between cellular damage resulting from metabolic events occurring within the cell and molecular responses that repair the damage. The damage eventually accumulates to a level sufficient to result in the physiologic decline

associated with aging. The most prominent example of the damage theory is the somatic mutation theory of aging, which states that the longevity and function of cells in various tissues of the body are determined by the double-stranded DNA molecule and its specific repair enzymes. Deoxyribonucleic acid undergoes continuous change in response to both exogenous agents and intrinsic processes. It has been suggested that aging results from conditions that produce mutations in DNA or deficits in DNA repair mechanisms.

The oxidative free radical explanation of aging is an error theory in which aging is thought to result partially from oxidative stress and the effects of free radical damage. The major by-products of oxidative metabolism include superoxides that react with DNA, ribonucleic acid, proteins, and lipids, leading to cellular damage and aging. Blood glucose is another suspect in cellular deterioration. In a process called *nonenzymatic glycation*, glucose molecules attach to proteins, setting in motion a chain of chemical reactions that ends with proteins binding together or cross-linking, thus altering their structure and function. Investigators hypothesize that glycation and oxidation are interdependent, since free radicals and cross-links seem to accelerate the formation of one another. Cross-links, also known as *advanced glycation end products (AGEs),* tend to stiffen tissues and cause some of the deterioration associated with aging.[2,35] For example, AGEs may help trap low-density cholesterol in arterial walls and thus contribute to atherosclerosis. They also have been linked to cataract formation, reduced kidney function, and neurologic disorders such as Alzheimer disease.

FIGURE 2-11. A 5-year-girl with progeria. (From National Human Genome Research Institute, National Institutes of Health.)

Syndromes of Premature Aging

The syndromes of premature aging, or *progeria*, represent a range of phenotypes seen in usual aging, but with much earlier ages of onset and more rapid rates of progression.[1] Hutchinson-Gilford progeria syndrome is a rare fatal genetic disorder characterized by accelerated aging in children.[42] The disorder is caused by a mutation in the *LMNA* gene, which codes for a precursor of lamin A—a scaffolding protein that lines the nucleus. The mutant gene leads to abnormal nuclear structure and altered gene regulation and DNA replication. Although they are born looking healthy, children with the disorder begin to display many characteristics of accelerated aging at around 18 to 24 months of age. Progeria signs include growth failure, loss of body fat and hair, aged-looking skin, cataracts, and coronary artery disease and stroke (Fig. 2-11). Death occurs at an early age of atherosclerotic heart disease (average age 13 years).

Other progeroid syndromes include Werner syndrome, also known as adult progeria, which does not have an onset until the late teens, with a life span into the 40s and 50s.[1] The gene responsible for the disorder has been localized to chromosome 8 and appears to code for an enzyme involved in unwinding DNA, a process that is necessary for DNA repair and replication.

SUMMARY CONCEPTS

- Cell injury can be caused by a number of agents, including physical agents, chemicals, biologic agents, and nutritional factors.
- Among the physical agents that generate cell injury are mechanical forces that produce tissue trauma, extremes of temperature, and electrical forces. Ionizing radiation can directly break chemical bonds, whereas nonionizing radiation exerts its harmful effects by causing vibration and rotation of atoms and molecules. Chemical agents can block enzymatic pathways, cause coagulation of tissues, or disrupt the osmotic or ionic balance of the cell. Biologic agents differ from other injurious agents in that they are able to replicate and continue to produce injury. Among the nutritional factors that contribute to cell injury are excesses and deficiencies of total energy, as well as individual nutrients.
- Injurious agents exert their effects largely through generation of reactive oxygen species (ROS)

and free radicals, promotion of cell hypoxia, or impaired regulation of intracellular calcium levels. Free radicals are an important cause of cell injury in hypoxia and after exposure to radiation and certain chemical agents. Lack of oxygen, which underlies the pathogenesis of cell injury in hypoxia and ischemic, can result from inadequate oxygen in the air, cardiopulmonary disease, cardiorespiratory disease, anemia, or the inability of the cells to use oxygen. Increased intracellular calcium activates a number of enzymes with potentially damaging effects.

- Injurious agents may produce sublethal and reversible cellular damage or may lead to irreversible cell injury and death. Cell death can involve two mechanisms: apoptosis or necrosis. Apoptosis involves controlled cell destruction and is the means by which the body removes and replaces cells that have been produced in excess, developed improperly, have genetic damage, or are worn out. Necrosis refers to cell death that is characterized by cell swelling, rupture of the cell membrane, and inflammation.
- A number of body functions decline with age, including muscle strength, cardiac reserve, vital capacity, nerve conduction time, and glomerular filtration rate. At the cellular level, oxidative phosphorylation by the mitochondria is reduced, as is the synthesis of nucleic acids and transcription factors, cell receptors, and structural and enzymatic proteins.

REVIEW EXERCISES

1. A 30-year-old man sustained a fracture of his leg 2 months ago. The leg has been encased in a cast and he has just had the cast removed. He is amazed at the degree to which the muscles in his leg have shrunk.

A. Explain.

2. A 45-year-old woman has been receiving radiation therapy for breast cancer.

A. Explain the effects of ionizing radiation in eradicating the tumor cells.
B. Why is the radiation treatment given in small divided, or fractionated, doses rather than as a single large dose?
C. Partway through the treatment schedule, the woman notices that her skin over the irradiated area has become reddened and irritated. What is the reason for this?

3. People who have had a heart attack may experience additional damage once blood flow has been restored, a phenomenon referred to as *reperfusion injury.*

A. What is the proposed mechanism underlying reperfusion injury?
B. What factors might influence this mechanism?

4. Every day blood cells in our body become senescent and die without producing signs of inflammation, yet massive injury or destruction of tissue, such as occurs with a heart attack, produces significant signs of inflammation.

A. Explain.

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Chapter 3

Inflammation, the Inflammatory Response, and Fever

Inflammation is a complex nonspecific response to tissue injury intended to minimize the effects of injury or infection, remove the damaged tissue, generate new tissue, and facilitate healing. As part of the innate immune system, inflammation dilutes, destroys, and gets rid of damaged or necrotic tissues and foreign agents, such as microbes. Although first described over 2000 years ago, the inflammatory response has been the subject of intense research during the past several decades. As a result, it is now recognized as playing a key role in both the contributing factors and consequences of numerous diseases and altered health states including, but not limited to, atherosclerosis, obesity and diabetes, many types of cancers, stroke, bronchial asthma, rheumatoid arthritis, and certain dementias, including Alzheimer disease.

The discussion in this chapter is divided into four sections: (1) the general features of inflammation, (2) acute inflammation, (3) chronic inflammation, and (4) systemic manifestations of inflammation, including fever. The innate and adaptive immune responses that are closely intertwined with the inflammatory response are discussed in Chapter 15.

General Features of Inflammation

Inflammation is the reaction of vascularized tissues to cell injury or death. It is characterized by the production and release of inflammatory mediators and the movement of fluid and leukocytes from the vasculature into the extravascular tissues.[1–4] Inflammatory conditions are commonly named by adding the suffix *-itis* to the affected organ or system. For example, *appendicitis* refers to inflammation of the appendix, *pericarditis* to inflammation of the pericardium, and *neuritis* to inflammation of the nerve.

Inflammation can be acute or chronic.[1,2] *Acute inflammation* is triggered by noxious stimuli, such as infection or tissue injury, is rapid in onset (typically minutes), and is of relatively short duration, lasting from a few minutes to several days. It is characterized by the exudation of fluid and plasma proteins and emigration of leukocytes. *Chronic inflammation* is of a longer duration, lasting for days to years, and is often associated with the proliferation of blood vessels (angiogenesis), tissue necrosis, and fibrosis (scarring). Acute and chronic inflammation may coexist, with episodes of acute inflammation being superimposed on chronic inflammation.

Cells of Inflammation

Many cells and tissue components are involved in the inflammatory process, including the endothelial cells that line blood vessels and form capillaries, circulating platelets and leukocytes, cells in the connective tissue (mast cells, fibroblasts, tissue macrophages), and components of the extracellular matrix (Fig. 3-1).[1–3] The principal leukocytes in acute inflammation are neutrophils, whereas macrophages, lymphocytes, eosinophils, and mast cells predominate in chronic infection.

Endothelial Cells

Endothelial cells, which make up the single-cell-thick linings of blood vessels, help to separate the intravascular and extravascular spaces.[1,2,5] They normally have a nonthrombogenic surface and produce agents that maintain vessel patency, as well as vasodilators and vasoconstrictors that regulate blood flow. Endothelial cells are also key players in the inflammatory response. As such, they provide a selective permeability barrier to exogenous (microbial) and endogenous inflammatory stimuli; regulate leukocyte extravasation by expression of adhesion molecules and receptor activation; contribute to the regulation and modulation of immune responses through synthesis and release of inflammatory mediators; and regulate immune cell proliferation through secretion of hematopoietic colony-stimulating factors (CSFs). Endothelial cells also participate in the repair process that accompanies inflammation through the production of growth factors that stimulate angiogenesis and extracellular matrix synthesis.

Platelets

Platelets or thrombocytes are small, membrane-bound disks circulating in the blood that play an active role in normal hemostasis (see Chapter 12). Activated platelets also release a number of potent inflammatory mediators, thereby increasing vascular permeability and altering the chemotactic, adhesive, and proteolytic properties of the endothelial cells.[6,7] When a platelet undergoes activation, over 300 proteins are released. While the functions of only a relatively small proportion of these proteins have been fully elucidated, it appears that many help mediate inflammation.[6] The association between the platelet and inflammatory diseases is highlighted by the number of inflammatory disease processes (e.g., atherosclerosis, migraine headaches, systemic lupus erythematosus) shown to be associated with platelet activation.[6]

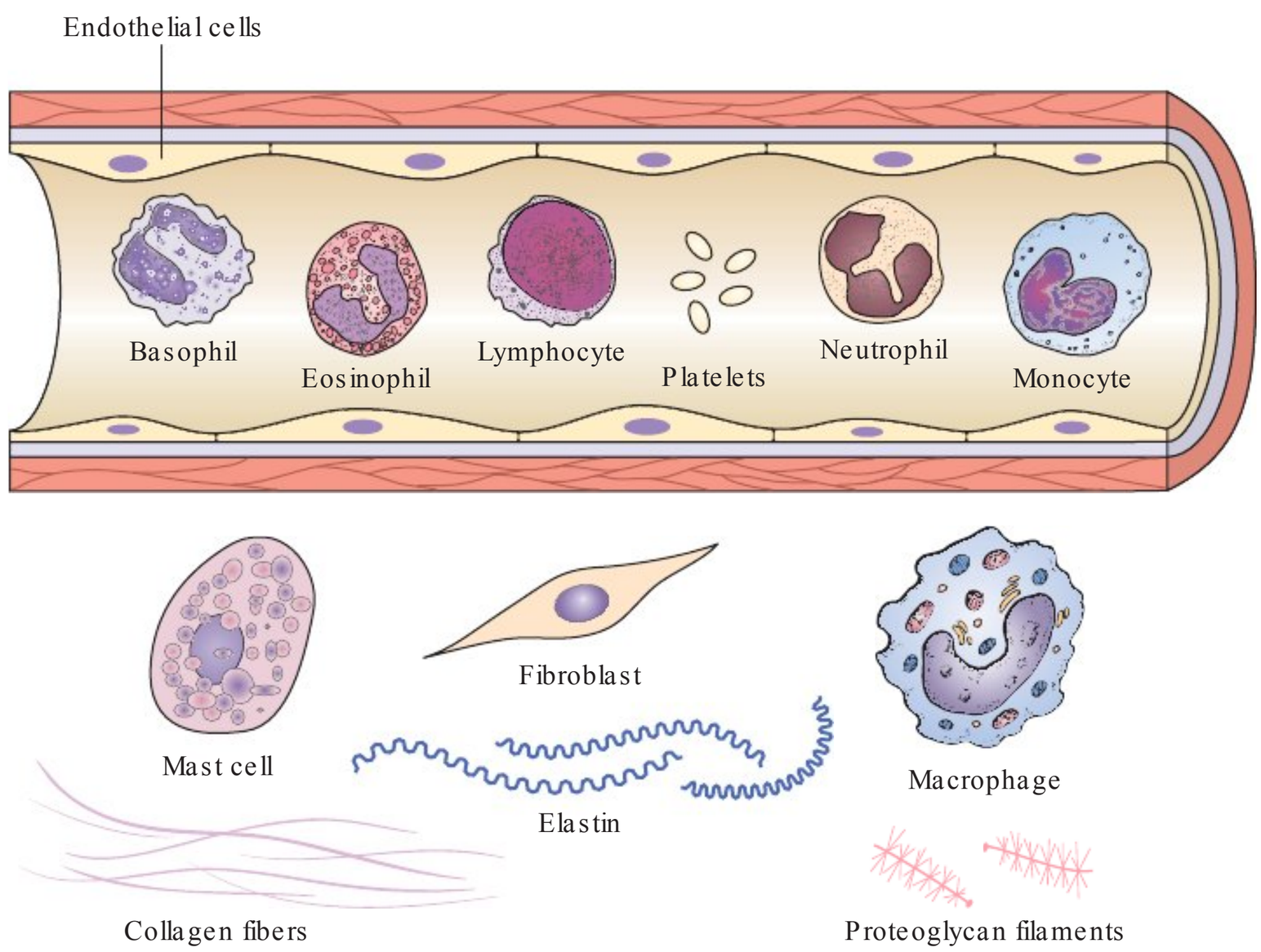


FIGURE 3-1. Cells involved in the inflammatory process.

Leukocytes

Leukocytes or white blood cells are the major cellular components of the inflammatory response. They include the granulocytes (neutrophils, eosinophils, and basophils), which contain specific cytoplasmic granules and a multilobed nucleus, and the agranulocytes (monocytes/macrophages and lymphocytes), which lack cytoplasmic granules and have a single nucleus.

Neutrophils. Neutrophils are the most numerous leukocytes in the circulating blood, accounting for 60% to 70% of all white blood cells. These leukocytes have nuclei that are divided into three to five lobes; therefore, they often are referred to as *polymorphonuclear neutrophils (PMNs).* Because of their ability to form pseudopods used in ameboid movement, neutrophils are highly mobile, and are the first cells to appear at the site of acute inflammation, usually arriving within 90 minutes of injury (Fig. 3-2A). Neutrophils are scavenger cells capable of engulfing bacteria and other cellular debris through phagocytosis. Their cytoplasmic granules, which resist staining and remain a neutral color, contain enzymes and other antibacterial substances that are used in destroying and degrading engulfed microbes and dead tissue.[3,8,9] Neutrophils also have oxygen-dependent metabolic pathways that generate toxic reactive oxygen (e.g., hydrogen peroxide) and nitrogen (e.g., nitric oxide) species that aid in the destruction of engulfed pathogens. Neutrophils have a short life span. They die by apoptosis and disappear within 24 to 48 hours after entering the site of inflammation.

Eosinophils. Eosinophils account for 2% to 3% of circulating leukocytes and are recruited to tissues in a similar way as the neutrophils. Their appearance at the site of inflammation occurs 2 to 3 hours after the neutrophils. This is, in part, because of their slower mobility and comparatively slower reaction to chemotactic stimuli.

The granules of eosinophils, which stain pink with the acid dye eosin, contain a protein that is highly toxic to large parasitic worms that cannot be phagocytized. Eosinophils also play an important role in allergic reactions by controlling the release of specific chemical mediators. They interact with basophils and are prominent in allergic reactions such as hay fever and bronchial asthma. Eosinophils have a longer life span than neutrophils and therefore are present in chronic inflammation.

Basophils and Mast Cells. Basophils are granulocytes with granules that stain blue with a basic dye. Although they account for less than 1% of the circulating leukocytes, they are important participants in inflammatory reactions and are most prominent in allergic reactions mediated by immunoglobulin E (IgE). Binding of IgE triggers release of histamine and vasoactive agents from the basophil granules.

Mast cells derive from the same hematopoietic stem cells as basophils but do not develop until they leave the circulation and lodge in tissue sites. They are particularly prevalent along mucosal surfaces of the lung, gastrointestinal tract, and dermis of the skin.[2,10] This distribution places them in a sentinel position between environmental antigens and the host for a variety of acute and chronic inflammatory conditions.[2] Activation of mast cells

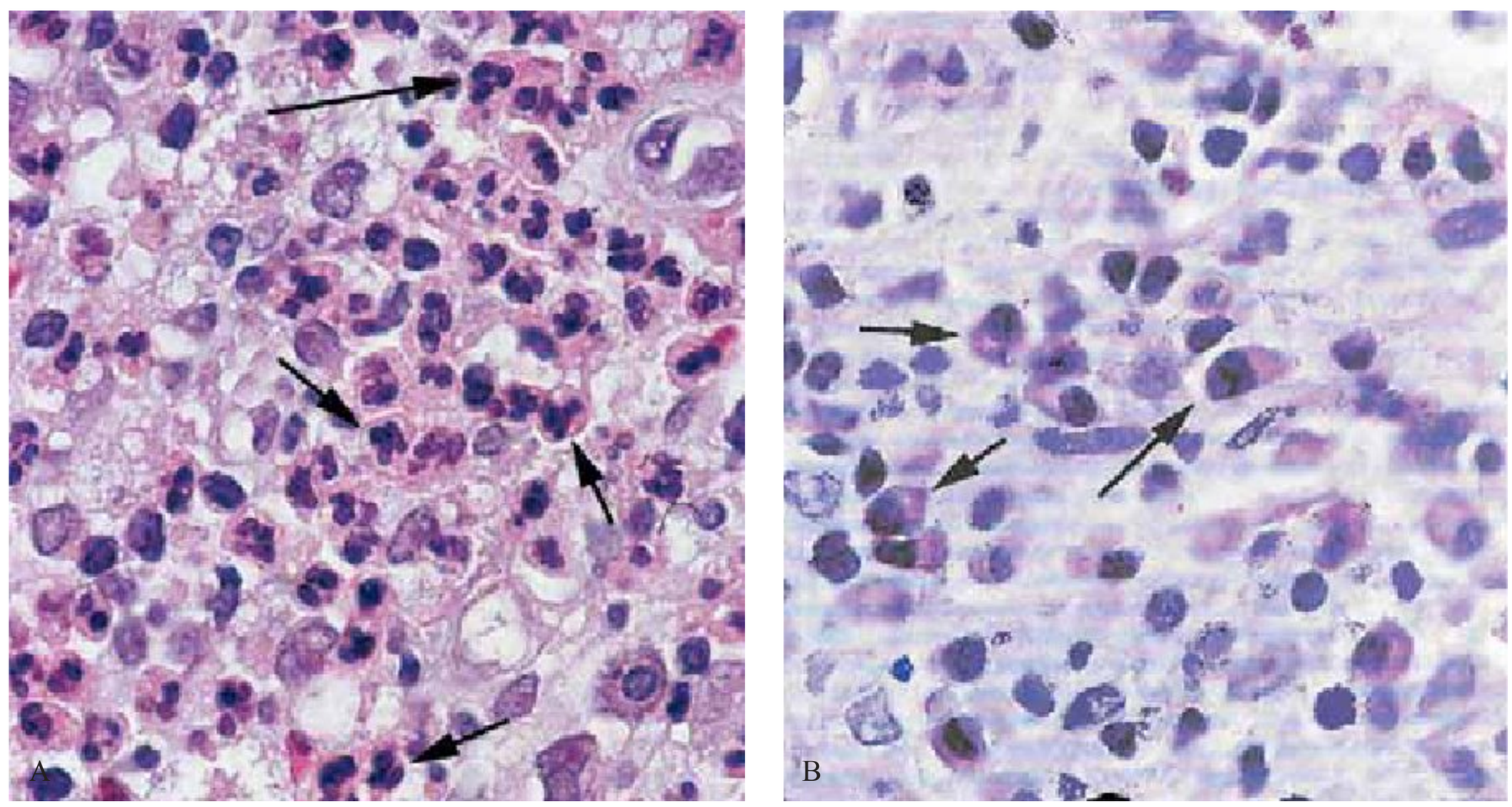


FIGURE 3-2. Inflammatory cells of acute and chronic inflammation. **(A)** Acute inflammation with densely packed polymorphonuclear neutrophils with multilobed nucleus (arrows). **(B)** Chronic inflammation with lymphocytes, plasma cells (arrows), and a few macrophages. (From Murphy HS. Inflammation. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008:39.)

results in release of the preformed contents of their granules (e.g., histamine, proteases, cytokines such as tumor necrosis factor-α [TNF-α] and interleukin-16 [IL-16], growth factors such as vascular endothelial growth factor [VEGF]) and synthesis of lipid mediators derived from cell membrane precursors (arachidonic acid metabolites, such as prostaglandins, and platelet-activating factor). Finally, the release of mast cell contents stimulates cytokine and chemokine synthesis by other inflammatory cells such as monocytes and macrophages.

Monocyte/Macrophages. *Monocytes* constitute 3% to 8% of the white blood cell count. They have a single kidney-shaped nucleus and are the largest of the circulating leukocytes. The half-life of circulating monocytes is about a day, after which they begin to migrate to the site of injury and mature into larger macrophages, which have a longer half-life and greater phagocytic ability than do blood monocytes. Circulating monocytes have been linked to a number of inflammatory disorders, particularly atherosclerosis, in which they are transformed into macrophages that accumulate in atherosclerotic plaques and turn into lipid-laden foam cells (see Chapter 18).

Monocyte/macrophages produce potent vasoactive mediators including prostaglandins and leukotrienes, platelet-activating factor (PAF), inflammatory cytokines, and growth factors that promote regeneration of tissues.[8,9] As their name implies, macrophages are capable of phagocytosis and are active in bacterial killing. They engulf larger and greater quantities of foreign material than the neutrophils, and their circulating life span is three to four times longer than that of any granulocyte. These longer-lived phagocytes help to destroy the causative agent, aid in the signaling processes of immunity, serve to resolve the inflammatory process, and contribute to initiation of the healing processes. Macrophages are especially important in maintaining chronic inflammation.

Lymphocytes and Plasma Cells. Lymphocytes are the smallest of the leukocytes and have a thin rim of cytoplasm surrounded by a deeply staining nucleus (Fig. 3-2B). They participate in immune-mediated inflammation caused by infectious agents as well as non–immune-mediated inflammation associated with cell injury and death. Both T and B lymphocytes (T and B cells) migrate into inflammatory sites using some of the same adhesion molecules and chemokines that recruit neutrophils and other leukocytes (discussed in Chapter 15). Lymphocytes and macrophages communicate in a bidirectional way, and these interactions play an important role in chronic inflammation. Macrophages display antigen to T cells, express membrane molecules called costimulators (meaning that their response requires the action of two signaling molecules), and produce cytokines that stimulate T-cell responses.[2] Activated T cells, in turn, produce cytokines that activate macrophages, increasing antigen presentation and further cytokine production. (Cytokines and other inflammatory mediators are discussed later in this chapter.) The result is a perpetuating cycle of cellular responses that fuel and sustain chronic inflammation.

Plasma cells develop from B lymphocytes that have become activated after encountering an antigen and receiving T cell help. In the inflammatory site, they produce antibodies directed against persistent antigens and altered tissue components. In some intense, chronic inflammatory reactions, plasma cells and other lymphocytes may accumulate to form geminal centers that resemble lymph nodes.[2] This pattern of lymphocyte accumulation, with formation of germinal centers, is often seen in the inflamed synovium of persons with long-standing rheumatoid arthritis.

Cell Adhesion Molecules

Several families of cell adhesion molecules, including selectins, integrins, and the immunoglobulin superfamily, are involved in leukocyte recruitment and trafficking (see Chapter 1).[8,11,12] The *selectins* are a family of three closely related proteins (E-selectin, L-selectin, P-selectin) that differ in their cellular distribution but all function in adhesion of leukocytes or platelets to endothelial cells. The *integrins* consist of different types of structurally similar transmembrane receptor proteins that function as heterodimers to promote cell-to-cell and cell–to–extracellular matrix interactions. The name *integrin* derives from the hypothesis that they *integrate* the signals of extracellular ligands with cytoskeleton-dependent motility, shape change, and phagocytic responses of immune cells. *Cell adhesion molecules* of the immunoglobulin superfamily include intercellular adhesion and vascular adhesion molecules, which interact with integrins on leukocytes to mediate their recruitment.

The importance of the leukocyte adhesion molecules is demonstrated in persons with an inherited disorder called *leukocyte adhesion deficiency (LAD) type I*, in which deficiency of a member of the integrin superfamily leads to severe leukocytosis and recurrent infections. A similar deficiency is seen in individuals with impaired expression of a member of the selectin superfamily and has been labeled *LAD type 2*.[8] There is also evidence that excessive expression of cell adhesion molecules or their receptors contributes to the pathogenesis of some chronic inflammatory diseases such as rheumatoid arthritis.

SUMMARY CONCEPTS

- Inflammation is the body's response to injury and is characterized by the elaboration of chemical mediators and movement of fluid and leukocytes from the vascular compartment into the extravascular tissue space.
- There are two types of inflammation: acute inflammation, which is of short duration and characterized by the exudation of fluid and

plasma proteins, and chronic inflammation, which is associated with angiogenesis, tissue necrosis, and fibrosis (scarring).

- Many cells and tissue components contribute to the inflammatory response, including the endothelial cells that form capillaries and line blood vessels, circulating platelets and white blood cells, cells in connective tissue, and components of the extracellular matrix.

Acute Inflammation

Acute inflammation is the early or almost immediate reaction of local tissues and their blood vessels to injury. It typically occurs before the adaptive immune response becomes established (see Chapter 15) and is aimed primarily at removing the injurious agent and limiting the extent of tissue damage. Acute inflammation can be triggered by a variety of stimuli, including infections, immune reactions, blunt and penetrating trauma, physical or chemical agents (e.g., burns, frostbite, irradiation, caustic chemicals), and tissue necrosis from any cause.

The classic description of inflammation has been handed down through the ages. In the first century AD, the Roman physician Aulus Celsus described the local reaction of injury in terms that are now known as the *cardinal signs* of inflammation.[1] These signs are *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, the Greek physician Galen added a fifth cardinal sign, *functio laesa* (loss of function). In addition to the cardinal signs that appear at the site of injury, systemic manifestations (e.g., fever) may occur as chemical mediators (e.g., cytokines) produced at the site of inflammation lead to increased levels in the plasma. The constellation of systemic manifestations and increases in serum proteins that may occur during acute inflammation is known as the *acute-phase response*.

Stages of Acute Inflammation

Acute inflammation has two stages: vascular and cellular. The vascular stage is characterized by increased blood flow (vasodilation) and structural changes (increased vascular permeability) that allow plasma proteins to leave the circulation. The cellular stage involves the emigration of leukocytes (mainly neutrophils) from the microcirculation and their accumulation at the site of injury or infection.

Vascular Stage

The vascular changes that occur with inflammation involve the arterioles, capillaries, and venules of the microcirculation. These changes begin almost immediately after injury and are characterized by vasodilation and changes in blood flow followed by increased vascular permeability and leakage of protein-rich fluid into the extravascular tissue space.[1,2]

Vasodilation, which is one of the earliest manifestations of inflammation, follows a transient constriction of the arterioles, lasting a few seconds. Dilation begins in the arterioles and opens capillary beds in the area. As a result, the area becomes congested, causing the redness (erythema) and warmth associated with acute inflammation. Vasodilation is induced by the action of several mediators, most notably histamine and nitric oxide.

Vasodilation is quickly followed by increased permeability of the microvasculature, with the outpouring of a protein-rich fluid (exudate) into the extravascular spaces. The loss of fluid results in an increased concentration of blood constituents (red blood cells, leukocytes, platelets, and clotting factors), stagnation of flow, and clotting of blood at the site of injury. This aids in limiting the spread of infectious microorganisms. The loss of plasma proteins reduces the intracapillary osmotic pressure and increases the osmotic pressure of the interstitial fluid, increasing fluid movement from the vascular compartment into the tissue space and producing the swelling, pain, and impaired function that are the cardinal signs of acute inflammation. The exudation of fluid into the tissue spaces also serves to dilute the offending agent.

The increased permeability characteristic of acute inflammation results from formation of endothelial gaps in the venules of the microcirculation. Binding of the chemical mediators to endothelial receptors causes contraction of endothelial cells and separation of intercellular junctions. This is the most common mechanism of vascular leakage and is elicited by histamine, bradykinin, leukotrienes, and many other classes of chemical mediators.

Depending on the severity of injury, the vascular changes that occur with inflammation follow one of three patterns of responses.[2] The first pattern is an *immediate transient response,* which occurs with minor injury. It develops rapidly after injury and is usually reversible and of short duration (15 to 30 minutes). The second pattern is an *immediate sustained response,* which occurs with more serious types of injury and continues for several days. It affects all levels of the microcirculation (arterioles, capillaries, and venules) and is usually due to direct damage of the endothelium by injurious stimuli, such as burns or the products of bacterial infections.[2] Neutrophils that adhere to the endothelium may also injure endothelial cells. The third pattern is a *delayed response,* in which the increased permeability begins after a delay of 2 to 12 hours, lasts for several hours or even days, and involves venules as well as capillaries.[2] A delayed response often accompanies injuries due to radiation, such as sunburn.

Cellular Stage

The cellular stage of acute inflammation is marked by changes in the endothelial cells lining the vasculature and movement of phagocytic leukocytes into the area of

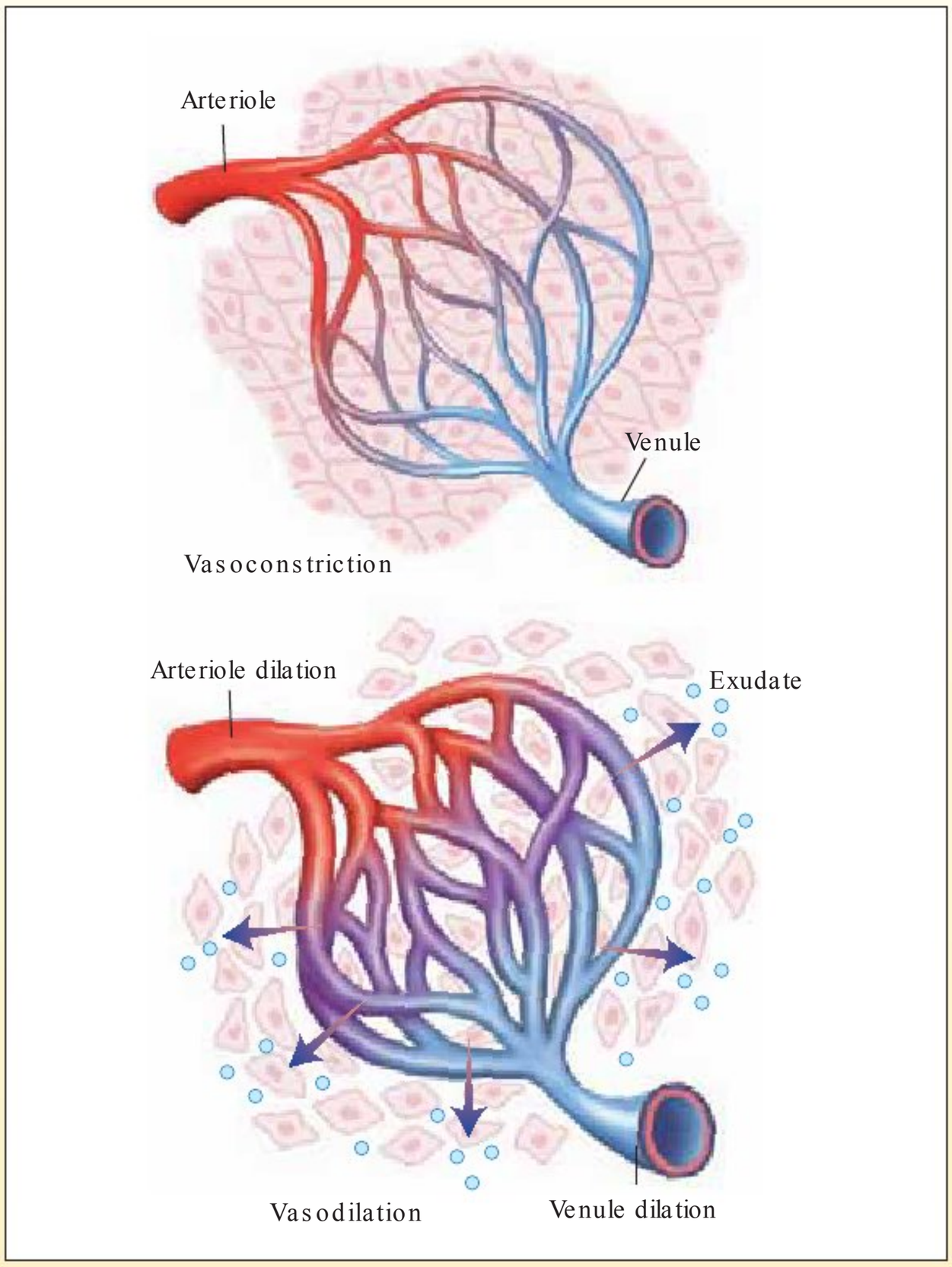
(*text continues on page 56*)

UNDERSTANDING → Acute Inflammation

Acute inflammation is the immediate and early response to an injurious agent. The response, which serves to control and eliminate altered cells, microorganisms, and antigens, occurs in two phases: (1) the vascular phase, which leads to an increase in blood flow and changes in the small blood vessels of the microcirculation; and (2) the cellular phase, which leads to the migration of leukocytes from the circulation and their activation to eliminate the injurious agent. The primary function of the inflammatory response is to limit the injurious effect of the pathologic agent and remove the injured tissue components, thereby allowing tissue repair to take place.

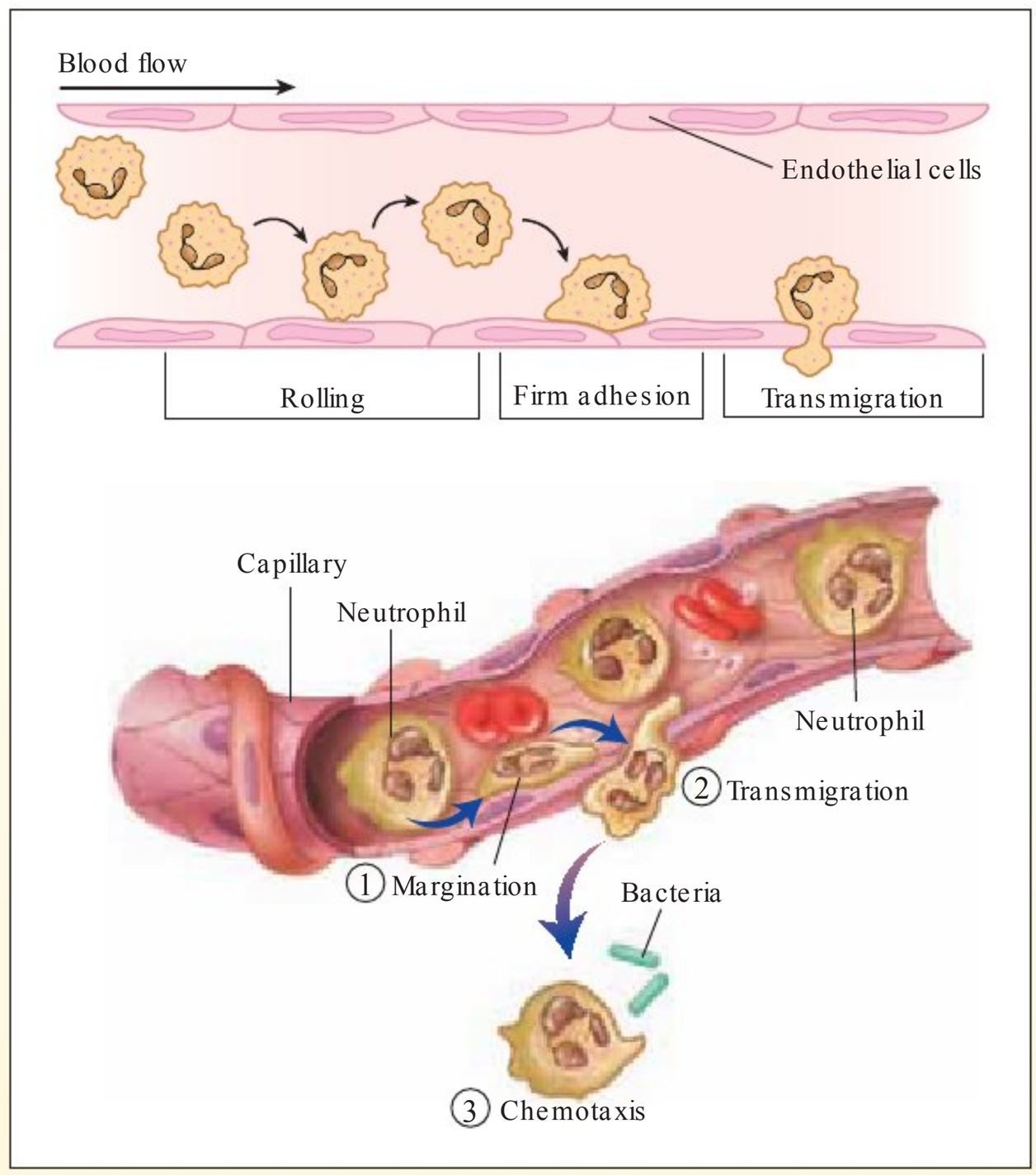
1

Vascular Phase. The vascular phase of acute inflammation is characterized by changes in the small blood vessels at the site of injury. It begins with momentary vasoconstriction followed rapidly by vasodilation. Vasodilation involves the arterioles and venules with a resultant increase in capillary blood flow causing heat and redness, which are two of the cardinal signs of inflammation. This is accompanied by an increase in vascular permeability with outpouring of protein-rich fluid (exudate) into the extravascular spaces. The loss of proteins reduces the capillary osmotic pressure and increases the interstitial osmotic pressure. This, coupled with an increase in capillary pressure, causes a marked outflow of fluid and its accumulation in the tissue spaces, producing the swelling, pain, and impaired function that represent the other cardinal signs of acute inflammation. As fluid moves out of the vessels, stagnation of flow and clotting of blood occur. This aids in localizing the spread of infectious microorganisms.



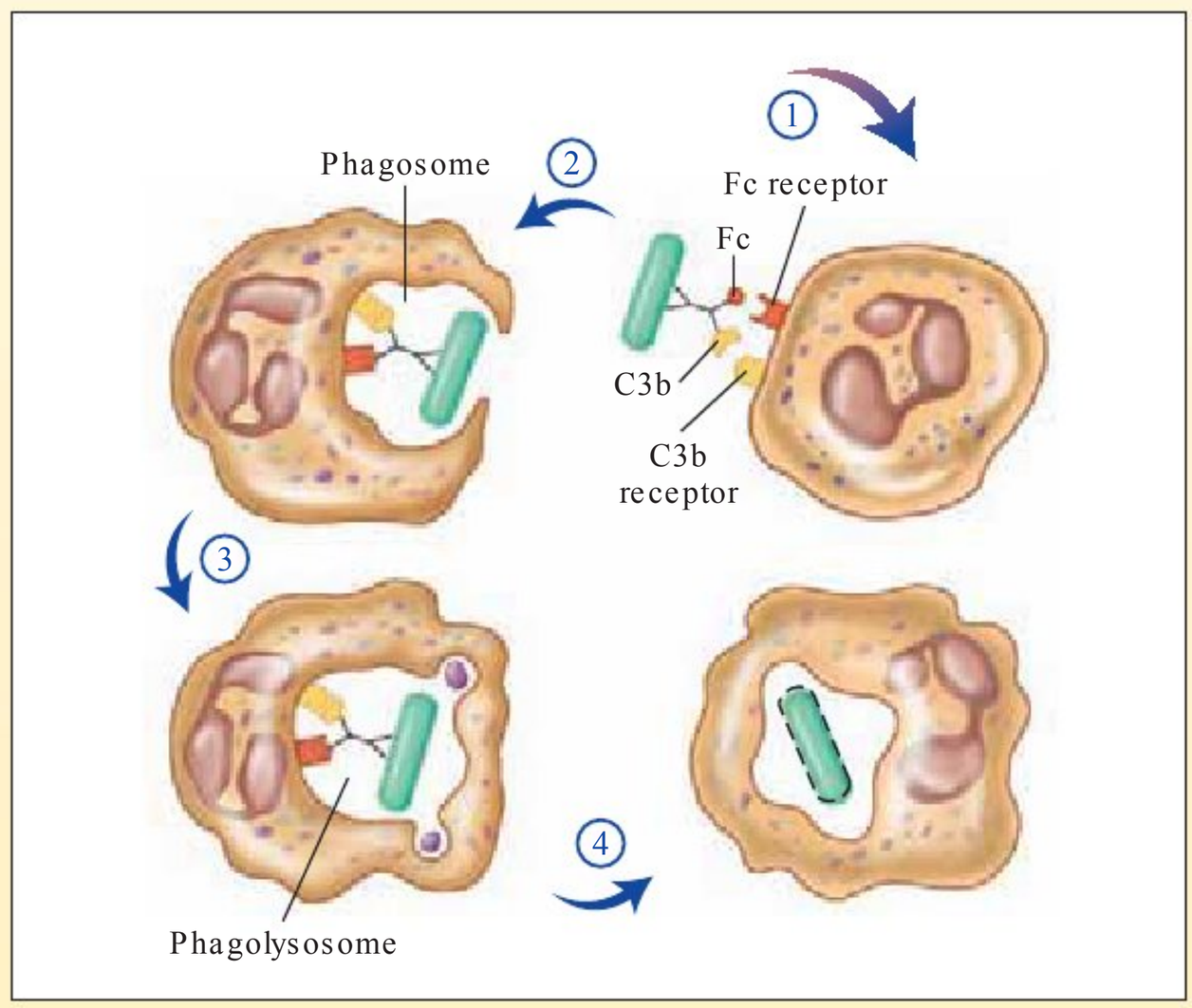
2

Cellular Phase: Leukocyte Margination, Adhesion, and Transmigration. The cellular phase of acute inflammation involves the delivery of leukocytes, mainly neutrophils, to the site of injury so they can perform their normal functions of host defense. The delivery and activation of leukocytes can be divided into the following steps: adhesion and margination, transmigration, and chemotaxis. The recruitment of leukocytes to the precapillary venules, where they exit the circulation, is facilitated by the slowing of blood flow and margination along the vessel surface. Leukocyte adhesion and transmigration from the vascular space into the extravascular tissue is facilitated by complementary adhesion molecules (e.g., selectins, integrins) on the leukocyte and endothelial surfaces. After extravasation, leukocytes migrate in the tissues toward the site of injury by chemotaxis, or locomotion oriented along a chemical gradient.



3

Leukocyte Activation and Phagocytosis. Once at the sight of injury, the products generated by tissue injury trigger a number of leukocyte responses, including phagocytosis and cell killing. Opsonization of microbes (1) by complement factor C3b and antibody facilitates recognition by neutrophil C3b and the antibody Fc receptor. Receptor activation (2) triggers intracellular signaling and actin assembly in the neutrophil, leading to formation of pseudopods that enclose the microbe within a phagosome. The phagosome (3) then fuses with an intracellular lysosome to form a phagolysosome into which lysosomal enzymes and oxygen radicals (4) are released to kill and degrade the microbe.



(*text continued from page 53*)

injury or infection. Although attention has been focused on the recruitment of leukocytes from the blood, a rapid response also requires the release of chemical mediators from certain resident cells in the tissues (mast cells and macrophages). The sequence of events in the cellular response to inflammation includes leukocyte (1) margination and adhesion, (2) transmigration, (3) chemotaxis, and (4) activation and phagocytosis.[1–3]

During the early stages of the inflammatory response, signaling between blood leukocytes and the endothelial cells defines the inflammatory event and ensures arrest of the leukocytes along the endothelium.[9] As a consequence, blood flow—and leukocyte circulation—slows. This process of leukocyte accumulation is called *margination*. The subsequent release of cell communication molecules called *cytokines* causes the endothelial cells lining the vessels to express cell adhesion molecules that bind to carbohydrates on the leukocytes. This interaction, which is called *tethering,* slows their flow and causes the leukocytes to roll along the endothelial cell surface, finally coming to rest and adhering strongly to intercellular adhesion molecules on the endothelium.[1,2] The adhesion is followed by endothelial cell separation, allowing the leukocytes to extend pseudopodia and *transmigrate* through the vessel wall and then, under the influence of chemotactic factors, migrate into the tissue spaces.

Chemotaxis is a dynamic and energy-directed process of cell migration.[1] Once leukocytes exit the capillary, they move through the tissue guided by a gradient of secreted chemoattractants, such as chemokines, bacterial and cellular debris, and fragments generated from activation of the complement system (see Chapter 15). Chemokines, an important subgroup of chemotactic cytokines, are small proteins that direct the trafficking of leukocytes during the early stages of inflammation or injury.[13] Several immune (e.g., macrophages) and nonimmune cells secrete these chemoattractants to ensure the directed movement of leukocytes to the site of infection.

During the next and final stage of the cellular response, neutrophils, monocytes, and tissue macrophages are activated to engulf and degrade the bacteria and cellular debris in a process called *phagocytosis*.[1,2,14] Phagocytosis involves three distinct steps: recognition and adherence, engulfment, and intracellular killing. It is initiated by recognition and binding of particles by specific receptors on the surface of phagocytic cells. This binding is essential for trapping the agent, triggering engulfment, and intracellular killing of microbes. Microbes can be bound directly to the membrane of phagocytic cells by several types of pattern recognition receptors (e.g., toll-like and mannose receptors) or indirectly by receptors that recognize microbes coated with carbohydrate-binding lectins, antibody, and/or complement (see innate immunity, Chapter 15). The enhanced binding of an antigen to a coated microbe or particle is called *opsonization*. Engulfment follows the recognition of an agent as foreign. During the process of engulfment, extensions of cytoplasm move around and eventually enclose the particle in a membrane-surrounded phagocytic vesicle or *phagosome*. Once in the cell cytoplasm, the phagosome fuses with a cytoplasmic lysosome containing antibacterial molecules and enzymes that can kill and digest the microbe (see Chapter 1).

Intracellular killing of pathogens is accomplished through several mechanisms, including toxic reactive oxygen- and nitrogen-containing species, lysozymes, proteases, and defensins. The metabolic burst pathways that generate toxic reactive oxygen- and nitrogen-containing species (e.g., hydrogen peroxide, nitric oxide) require oxygen and metabolic enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthetase. Individuals who are born with genetic defects in some of these enzymes have immunodeficiency conditions that make them susceptible to repeated bacterial infection.

Inflammatory Mediators

Having described the events of acute inflammation, we can now turn to a discussion of the chemical mediators responsible for the events. Inflammatory mediators may be derived from the plasma or produced locally by cells at the site of inflammation (Fig. 3-3). The *plasma-derived mediators*, which are synthesized in the liver, include the acute-phase proteins, coagulation (clotting) factors (discussed in Chapter 12), and complement proteins (discussed in Chapter 15). These mediators are present in the plasma in a precursor form that must be activated by a series of proteolytic processes to acquire their biologic properties. *Cell-derived mediators* are normally sequestered in intracellular granules that need to be secreted (e.g., histamine from mast cells) or newly synthesized (e.g., cytokines) in response to a stimulus. The major sources of these mediators are platelets, neutrophils, monocyte/macrophages, and mast cells, but most endothelial cells, smooth muscle cells, and fibroblasts can be induced to produce some of the mediators.

Mediators can act on one or a few target cells, have diverse targets, or have differing effects on different types of cells. Once activated and released from the cell, most mediators are short-lived. They may be transformed into inactive metabolites, inactivated by enzymes, or otherwise scavenged or degraded.

Plasma-Derived Mediators

The plasma is the source of inflammatory mediators that are products of three major protein cascades or systems: the kallikrein–kininogen system, which generates kinins; the coagulation system, which includes the important fibrin end product; and the complement system that includes the various complement proteins. Kinins are products of the liver and factors in the coagulation system (see Chapter 12). One kinin, bradykinin, causes increased capillary permeability and pain. The coagulation system also contributes to the vascular phase of inflammation mainly through formation of the fibrin mesh formed during the final steps of the clotting process. The complement system consists of a cascade of plasma proteins that play important roles in both immunity and inflammation. These proteins contribute to the inflammatory response by (1) causing vasodilation and

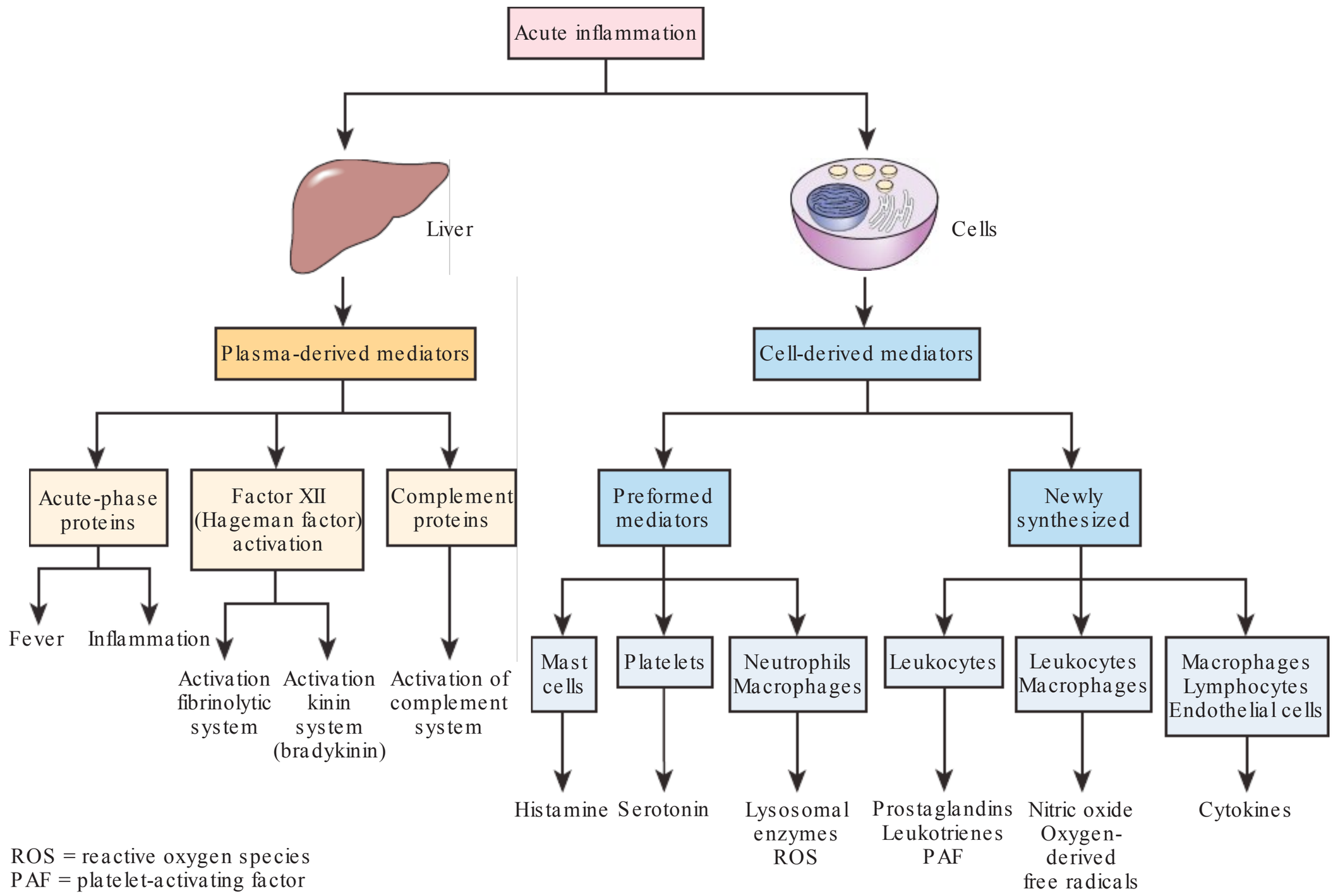


FIGURE 3-3. Plasma- and cell-derived mediators of acute inflammation.

increasing vascular permeability; (2) promoting leukocyte activation, adhesion, and chemotaxis; and (3) augmenting phagocytosis (see Chapter 15).

Cell-Derived Mediators

The cell-derived mediators are released from cells that are present at sites of inflammation. Tissue macrophages, mast cells, endothelial cells, as well as leukocytes that are recruited to the site from the blood are all capable of releasing the different mediators of inflammation, as are platelets, which are cellular fragments (see Fig. 3-3).

Histamine and Serotonin. Histamine and serotonin are classified as *vasoactive amines*, meaning they are derived from amino acids (histamine from histidine and serotonin from tryptamine) and act by producing changes in blood vessel tone. Both histamine and serotonin are stored as preformed molecules in mast cells and other cells and are among the first mediators to be released in acute inflammatory reactions.

Preformed histamine is widely distributed in tissues, the highest concentrations being found in mast cells adjacent to blood vessels.[1,2] It is also found in circulating platelets and basophils and is released in response to a variety of stimuli, including trauma and immune reactions involving binding of IgE to basophils and mast cells. Histamine produces dilation of arterioles and increases the permeability of venules. It acts at the level of the microcirculation by binding to histamine$_1$ (H_1) receptors on endothelial cells and is considered the principal mediator of the immediate transient phase of increased vascular permeability in the acute inflammatory response. Antihistamine drugs (H_1 receptor antagonists), which bind to the H_1 receptors, act to competitively antagonize many of the effects of the immediate inflammatory response. Serotonin (5-hydroxytryptamine) is also a preformed vasoactive mediator, with effects similar to histamine. It is found primarily within platelet granules and is released during platelet aggregation.

Arachidonic Acid Metabolites. Arachidonic acid is a 20-carbon unsaturated fatty acid found in the phospholipids of cell membranes. Release of arachidonic acid by phospholipases initiates a series of complex reactions that lead to the production of the *eicosanoid* family of inflammatory mediators (prostaglandins, leukotrienes, and related metabolites).[15] Eicosanoid synthesis follows one of two pathways: the cyclooxygenase pathway, which culminates in the synthesis of prostaglandins; and the lipoxygenase pathway, which culminates in the synthesis of the leukotrienes (Fig. 3-4). The corticosteroid drugs block the inflammatory effects of both pathways by inhibiting phosphodiesterase activity and thus preventing the release of arachidonic acid.[16]

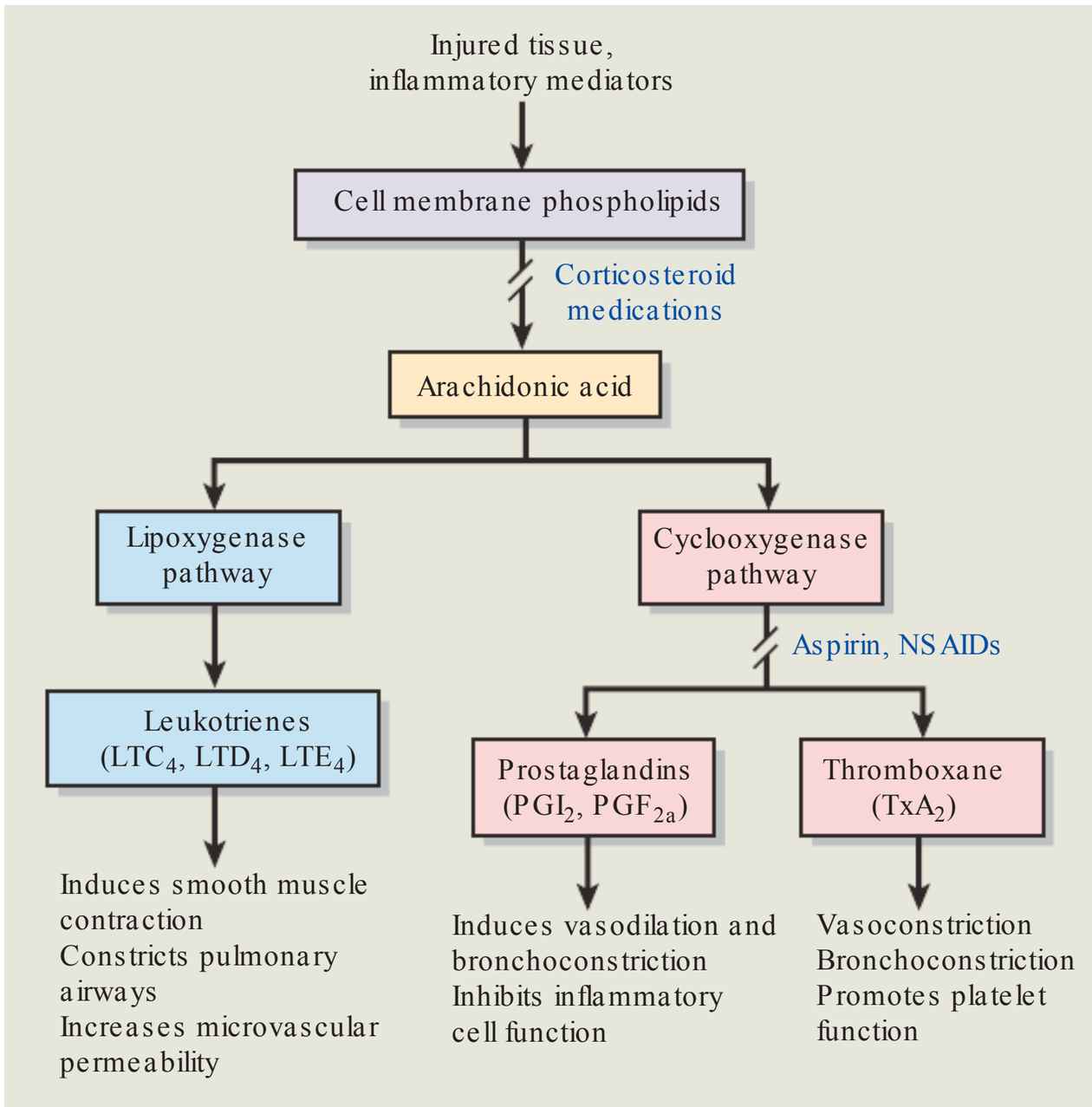


FIGURE 3-4. The cyclooxygenase and lipoxygenase pathways and sites where the corticosteroid and nonsteroidal anti-inflammatory drugs (NSAIDs) exert their action.

Several prostaglandins are synthesized from arachidonic acid through the cyclooxygenase metabolic pathway.[15] The prostaglandins (e.g., PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2) induce inflammation and potentiate the effects of histamine and other inflammatory mediators. The prostaglandin thromboxane A_2 promotes platelet aggregation and vasoconstriction. Aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation by inactivating the first enzyme in the cyclooxygenase pathway for prostaglandin synthesis.

Like the prostaglandins, the leukotrienes are formed from arachidonic acid, but through the lipoxygenase pathway. Histamine and leukotrienes have similar functions; however, histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized. The leukotrienes also have been reported to affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and the extravasation and chemotaxis of neutrophils, eosinophils, and monocytes. Leukotriene (LT) C_4, LTD_4, and LTE_4, collectively known as the *slow-reacting substance of anaphylaxis* (SRS-A), cause slow and sustained constriction of the bronchioles and are important inflammatory mediators in bronchial asthma and anaphylaxis.

Omega-3 Polyunsaturated Fatty Acids. There has been recent interest in dietary modification of the inflammatory response through the use of *omega-3 polyunsaturated fatty acids.* These include *eicosapentaenoic acid* and *docosahexaenoic acid*, which are present in oily fish and fish oil,[17,18] but can be derived in limited quantities from α-*linolenic acid*. The α-*linolenic acid*, which is present in flax seed, canola oil, green leafy vegetables, walnuts, and soybeans, is an essential omega-3 fatty acid that cannot be produced in the body and must be obtained through the diet. The omega-3 polyunsaturated fatty acids, which are considered antithrombotic and anti-inflammatory, are structurally different from the prothrombotic and proinflammatory omega-6 polyunsaturated fatty acids, which are present in most seeds, vegetable oils, and meats. Typically, the cell membranes of inflammatory cells contain high proportions of omega-6 arachidonic acid, which is the source of prostaglandin and leukotriene inflammatory mediators. Eating oily fish and other foods that are high in omega-3 fatty acids results in partial replacement of omega-6 arachidonic acid in inflammatory cell membranes by eicosapentaenoic acid, a change that leads to decreased production of arachidonic acid–derived inflammatory mediators. This response alone is a potentially beneficial effect of omega-3 fatty acids. However, omega-3 fatty acids may have a number of other anti-inflammatory effects that occur downstream of altered eicosanoid production or might be independent of this function.

Platelet-Activating Factor. Originally named for its ability to cause platelet aggregation and granulation, PAF is another phospholipid-derived mediator with a broad spectrum of inflammatory effects. Platelet-activating factor is generated from the membrane phospholipids of virtually all activated inflammatory cells and affects a variety of cell types. In addition to activating platelets, PAF stimulates neutrophils, monocytes/macrophages, endothelial cells, and vascular smooth muscle. Platelet activating

factor-induced platelet aggregation and degranulation at the site of injury enhances serotonin release, thereby causing changes in vascular permeability. It also enhances leukocyte adhesion, chemotaxis, and leukocyte degranulation and stimulates the synthesis of other inflammatory mediators, especially the prostaglandins.

Cytokines and Chemokines. Cytokines are low-molecular-weight proteins that are important cellular messengers. They modulate the function of cells by paracrine and autocrine mechanisms to cause responses in neighboring cells and the cells that produced the cytokine, respectively. They are produced by many cell types, including activated macrophages and lymphocytes, endothelial cells, epithelial cells, and fibroblasts.[1,2,18] Although well known for their role in adaptive immune responses, these proteins also play important roles in both acute and chronic inflammation.

Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are two of the major cytokines that mediate inflammation. The major cellular source of TNF-α and IL-1 is activated macrophages (Fig. 3-5). Interleukin-1 is also produced by many other cell types, including neutrophils, endothelial cells, and epithelial cells (e.g., keratinocytes). The secretion of TNF-α and IL-1 can be stimulated by bacterial toxins, immune cells, injury, and a variety of inflammatory stimuli. TNF-α and IL-1 induce endothelial cells to express adhesion molecules and release other cytokines, chemokines, and reactive oxygen species. Tumor necrosis factor-α induces priming and aggregation of neutrophils, leading to augmented responses of these cells to other mediators. Interleukin-1 and TNF-α are also mediators of the acute-phase responses associated with infection or injury. Features of these systemic responses include fever, hypotension and increased heart rate, anorexia, release of neutrophils into the circulation, and increased levels of corticosteroid hormones.

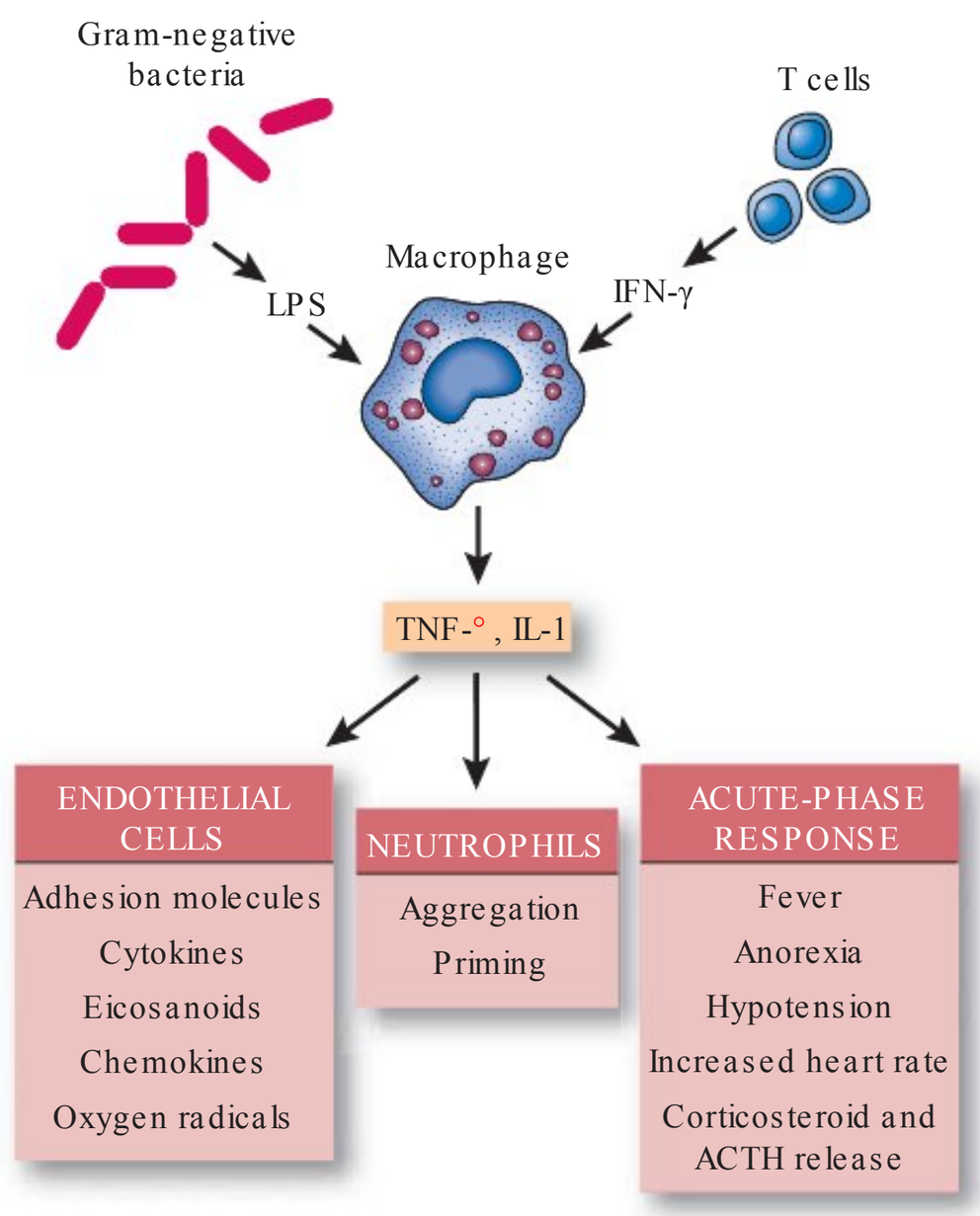


FIGURE 3-5. Central role of interleukin (IL)-1 and tumor necrosis factor (TNF)-α in inflammation. Lipopolysaccharide (LPS) and interferon (IFN)-γ activate macrophages to release inflammatory cytokines, principally IL-1 and TNF-α, responsible for directing both local and systemic inflammatory responses. ACTH, adrenocorticotrophic hormone. (From Murphy HS. Inflammation. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:60.)

Chemotactic cytokines, or *chemokines*, are a family of small proteins that act primarily as chemoattractants that both recruit and direct the migration of inflammatory and immune cells[20] (see Chapter 15). Chemokines generate a chemotactic gradient by binding to proteoglycans on the surface of endothelial cells or in the extracellular matrix.[20] As a result, high concentrations of chemokines persist at sites of tissue injury or infection. Two classes of chemokines have been identified: inflammatory chemokines and homing chemokines. Inflammatory chemokines are produced in response to bacterial toxins and inflammatory cytokines (i.e., IL-1, TNF-α). These chemokines recruit leukocytes during an inflammatory response. Homing chemokines are constantly produced, with the genes that control their production being up-regulated during inflammatory reactions.

Nitric Oxide. Nitric oxide (NO), which is produced by a variety of cells, plays multiple roles in inflammation, including relaxation of vascular smooth muscle; antagonism of platelet adhesion, aggregation, and degranulation; and as regulator of leukocyte recruitment.[2] Blocking of NO production under normal conditions promotes leukocyte rolling and adhesion to postcapillary venules and delivery of exogenous NO reduces leukocyte recruitment. Thus, production of NO appears to be an endogenous compensatory mechanism that reduces the cellular phase of inflammation. Impaired production of NO by vascular endothelial cells is implicated in the inflammatory changes that occur with atherosclerosis (see Chapter 18). Nitric oxide and its derivatives also have antimicrobial actions, and thus NO is also a host mediator against infection.

Reactive Oxygen Species. Reactive oxygen species may be released extracellularly from leukocytes after exposure to microbes, cytokines, and immune complexes, or in the phagocytic process that occurs during the cellular phase of the inflammatory process. The superoxide radical, hydrogen peroxide, and hydroxyl radical (discussed in Chapter 2) are the major species produced within the cell. These species can combine with NO to form other reactive nitrogen intermediates. Extracellular release of low levels of these potent mediators can increase the expression of cytokines and endothelial adhesion molecules, amplifying the cascade that elicits the inflammatory process,[2] and increase cell

proliferation. However, at higher levels these mediators can produce endothelial cell damage, with a resultant increase in vascular permeability; inactivate antiproteases, such as α_1-antitrypsin, which protect against lung damage in smokers; and produce injury to other cell types, including red blood cells.[2] Thus, the influence of ROS in any inflammatory process depends on a balance between the generation and inactivation of these metabolites.

Local Manifestations

The local manifestations of acute inflammation, which are determined by severity of the reaction, its specific cause, and the site of involvement, can range from mild swelling and redness to abscess formation or ulceration. As part of the normal defense reaction, inflammation can also injure adjacent tissues.[2] In some infections, such as tuberculosis and certain viral infections, the host response can cause more damage than the microbe itself. As a normal attempt to clear damaged and dead tissues (e.g., after a myocardial infarction), the inflammatory response may prolong and exacerbate the injurious consequences of the infarction.

Characteristically, the acute inflammatory response involves the production of exudates. These exudates vary in terms of fluid type, plasma protein content, and presence or absence of cells. They can be serous, hemorrhagic, fibrinous, membranous, or purulent. Often the exudate is composed of a combination of these types. *Serous exudates* are watery fluids low in protein content that result from plasma entering the inflammatory site. *Hemorrhagic exudates* occur when there is severe tissue injury that causes damage to blood vessels or when there is significant leakage of red cells from the capillaries. *Fibrinous exudates* contain large amounts of fibrinogen and form a thick and sticky meshwork, much like the fibers of a blood clot. *Membranous* or *pseudomembranous exudates* develop on mucous membrane surfaces and are composed of necrotic cells enmeshed in a fibropurulent exudate.

A *purulent* or *suppurative exudate* contains pus, which is composed of degraded white blood cells, proteins, and tissue debris. The term *pyogenic* refers to "pus forming." Certain pyogenic microorganisms, such as *Staphylococcus*, are more likely to induce localized suppurative inflammation than others. An *abscess* is a localized area of inflammation containing a purulent exudate. Abscesses typically have a central necrotic core containing purulent exudates surrounded by a layer of neutrophils.[2] Fibroblasts may eventually enter the area and wall off the abscess. Because antimicrobial agents cannot penetrate the abscess wall, surgical incision and drainage may be required as a cure.

An *ulceration* refers to a site of inflammation where an epithelial surface (e.g., skin or gastrointestinal epithelium) has become necrotic and eroded, often with associated subepithelial inflammation. Ulceration may occur as the result of traumatic injury to the epithelial surface (e.g., peptic ulcer) or because of vascular compromise (e.g., foot ulcers associated with diabetes). In chronic lesions where there is repeated insult, the area surrounding the ulcer develops fibroblastic proliferation, scarring, and accumulation of chronic inflammatory cells.[2]

Resolution

Although the manifestations of acute inflammation are largely determined by the nature and intensity of injury, the tissue affected, and the person's ability to mount a response, the outcome generally results in one of three processes: resolution, progression to chronic inflammation, or substantial scarring and fibrosis.[2] Resolution involves the replacement of any irreversibly injured cells and return of tissues to their normal structure and function.[21,22] It is seen with short-lived and minimal injuries and involves neutralization or degradation of inflammatory mediators, normalization of vascular permeability, and cessation of leukocyte infiltration. Progression to chronic inflammation may follow acute inflammation if the offending agent is not removed. Depending on the extent of injury, as well as the ability of the affected tissues to regenerate, chronic inflammation may be followed by restoration of normal structure and function. Scarring and fibrosis occurs when there is substantial tissue injury or when inflammation occurs in tissues that do not regenerate.

Although the mechanisms involved in the resolution of acute inflammation have remained somewhat elusive, emerging evidence suggests that an active, coordinated program of resolution begins in the first hours after an inflammatory response begins.[2,21] Studies suggest that after entering the site of acute inflammation, neutrophils trigger a switch from the previously described proinflammatory eicosanoids (e.g., prostaglandins and leukotrienes) to other anti-inflammatory classes of eicosanoids, also generated from arachidonic acid. These eicosanoids initiate the termination sequence during which neutrophil recruitment ceases and programmed cell death by apoptosis commences. The apoptotic neutrophils then undergo phagocytosis by macrophages, leading to their clearance and release of anti-inflammatory and reparative cytokines. Although much new information regarding the resolution of inflammation has been obtained over the past few years, many issues require further clarification. New therapeutic targets are currently being investigated and potential proresolution properties of existing drugs studied. These discoveries may bring profound advances in therapies aimed at reducing the adverse effects of persistent inflammation.

SUMMARY CONCEPTS

- The classic signs of an acute inflammatory response are redness, swelling, local heat, pain, and loss of function. These manifestations can be attributed to the immediate vascular changes that occur (vasodilation and increased capillary

permeability), the influx of inflammatory cells such as neutrophils, and, in some cases, the widespread effects of inflammatory mediators, which produce fever and other systemic signs and symptoms.

- Chemical mediators are integral to initiation, amplification, and termination of inflammatory processes. The plasma is the source of mediators derived from three major protein cascades that are activated during inflammation. These protein cascades include the kallikrein-kininogen system, the coagulation system, and the complement system. Cell-derived mediators, including histamine, bradykinin, the arachididonic metabolites, platelet activating factor (PAF), and many others are released from cells at the site of inflammation.
- Acute inflammation may involve the production of exudates containing serous fluid (serous exudate), red blood cells (hemorrhagic exudate), fibrinogen (fibrinous exudate), or tissue debris and white blood cell breakdown products (purulent exudate).
- The outcome of acute inflammation generally results in one of three processes: resolution, progression to chronic inflammation, or substantial scarring and fibrosis.

Chronic Inflammation

In contrast to acute inflammation, which is usually self-limited and of short duration, chronic inflammation is self-perpetuating and may last for weeks, months, or even years.[1,2,23] It may develop as a result of a recurrent or progressive acute inflammatory process or from low-grade, smoldering responses that fail to evoke an acute response. Instead of the vascular permeability changes, edema, and predominantly neutrophilic infiltration seen in acute inflammation, chronic inflammation is characterized by infiltration with mononuclear cells (macrophages, lymphocytes, and plasma cells) and attempted connective tissue repair involving angiogenesis and fibrosis. Although it may follow acute inflammation, chronic inflammation often begins insidiously as a low-grade, smoldering, and asymptomatic process. This type of process is the cause of tissue damage in some of the most common disabling diseases such as atherosclerosis, chronic lung disease, rheumatoid arthritis, and inflammatory bowel disease.

There is also evidence that recurrent and persistent inflammation induces, promotes, and/or influences susceptibility to cancer by causing deoxyribonucleic acid (DNA) damage, inciting tissue reparative proliferation, and/or creating an environment that is enriched with cytokines and growth factors that favor tumor development and growth (see Chapter 7).[23] Among the cancers associated with chronic infection and inflammation are cervical cancer (human papillomavirus [HPV]), cancer of the liver (hepatitis B and C), cancer of the stomach (*Helicobacter pylori*), and cancer of the gallbladder (chronic cholecystitis and cholelithiasis).

Causes of Chronic Inflammation

Agents that evoke chronic inflammation typically are low-grade, persistent infections or irritants that are unable to penetrate deeply or spread rapidly.[1,2] Among the causes of chronic inflammation are foreign agents such as talc, silica, asbestos, and surgical suture materials. Many viruses provoke chronic inflammatory responses, as do certain bacteria, such as the tubercle bacillus and the actinomyces, as well as fungi, and larger parasites of moderate to low virulence. The presence of injured tissue such as that surrounding a healing fracture also may incite chronic inflammation. Diseases that cause excessive and inappropriate activation of the immune system are increasingly being recognized as causes of chronic inflammation. Under certain conditions, immune reactions may develop against the person's own tissues, leading to autoimmune disease.

Obesity is a newly suspected cause of chronic inflammation.[24–26] During the last decade, white adipose tissue was recognized to be an active endocrine organ and a source of a number of proinflammatory mediators. Many of the mediators appear to play an important role in the pathogenesis of obesity-related diseases including accelerated atherosclerosis and diabetes mellitus. The link between obesity and inflammation dates back to the discovery that adipose tissue was a source of the proinflammatory cytokine TNF-α, and that adipose tissue TNF-α concentrations are correlated with insulin resistance both in persons with and without type 2 diabetes mellitus. It was later found that obesity is related not only to increased number and size of adipocytes, but also to infiltration of adipose tissue by macrophages that possess the ability to produce TNF-α, nitric oxide, and other inflammatory mediators. The mechanisms mediating the proinflammatory state associated with obesity are still unclear, but recent studies suggest that circulating free fatty acids may play a role.

Granulomatous Inflammation

A granulomatous lesion is a distinctive form of chronic inflammation.[1,2] A granuloma typically is a small, 1- to 2-mm lesion in which there is a massing of macrophages surrounded by lymphocytes. The macrophages are modified and, because they resemble epithelial cells, sometimes are called epithelioid cells. Like other macrophages, these epithelioid cells are derived originally from blood monocytes. Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal

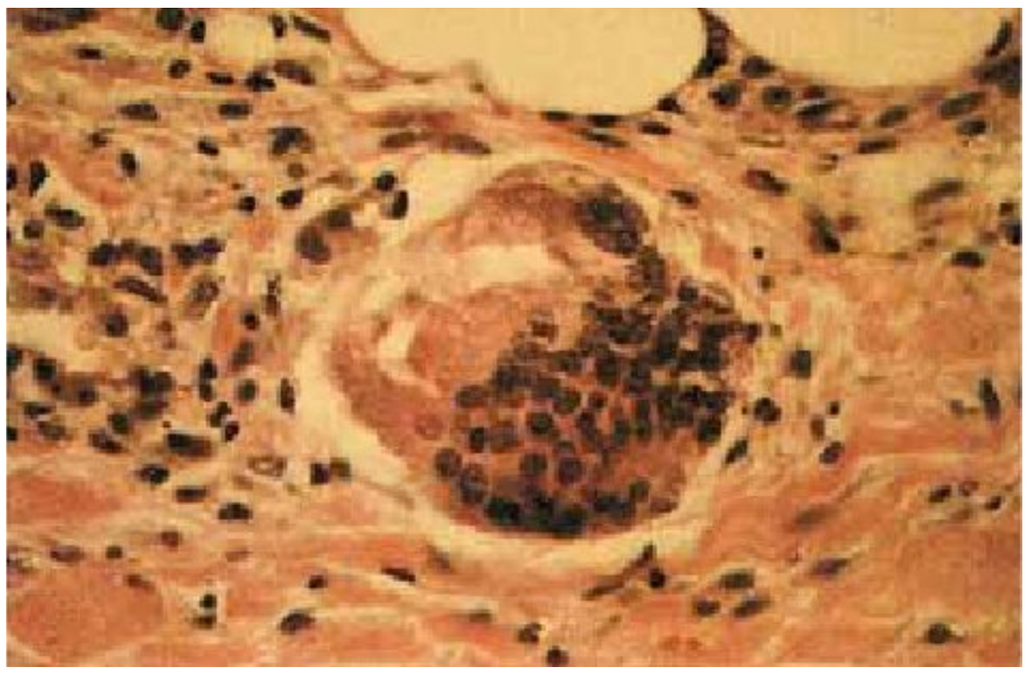


FIGURE 3-6. Foreign body giant cell. The numerous nuclei are randomly arranged in the cytoplasm. (From Rubin E, Farber LL. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:40.)

infections, and brucellosis. These types of agents have one thing in common: they are poorly degraded and usually are not easily controlled by other inflammatory mechanisms. The epithelioid cells in granulomatous inflammation may clump in a mass or coalesce, forming a multinucleated giant cell (often referred to as a foreign body giant cell) that attempts to surround the foreign agent (Fig. 3-6). A dense membrane of connective tissue eventually encapsulates the lesion and isolates it.

SUMMARY CONCEPTS

- Chronic inflammation involves infiltration with macrophages, lymphocytes, and fibroblasts, leading to persistent inflammation, fibroblast proliferation, and scar formation.
- Among the conditions associated with chronic inflammation and inappropriate activation of the immune system are low-grade inflammation associated with atherosclerosis and type 2 diabetes mellitus; autoimmune disorders; and susceptibility to cancer due to deoxyribonucleic acid damage, increased tissue proliferation, and creation of an environment rich in cytokines and growth factors that favor tumor cell development and growth.
- A granulomatous lesion is a distinctive form of chronic inflammation characterized by aggregates of epithelioid macrophages that "wall off" the causal agent. Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal infections, and brucellosis.

Systemic Manifestations of Inflammation

Under optimal conditions, the inflammatory response remains confined to a localized area. In some cases, however, local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation. The most prominent systemic manifestations of inflammation include the acute-phase response, alterations in white blood cell count (leukocytosis or leukopenia), and fever. Localized acute and chronic inflammation may extend to the lymphatic system and lead to a reaction in the lymph nodes that drain the affected area. Painful palpable lymph nodes are more commonly associated with inflammatory processes, whereas nonpainful nodes are more characteristic of neoplasms.

Acute-Phase Response

Along with the cellular responses that occur during the inflammatory response, a constellation of systemic effects called the *acute-phase response* occurs.[1,2] The acute-phase response, which usually begins within hours or days of the onset of inflammation or infection, includes changes in the concentrations of plasma proteins, skeletal muscle catabolism, negative nitrogen balance, elevated erythrocyte sedimentation rate, and increased numbers of leukocytes. Other manifestations of the acute-phase response include fever, increased heart rate, anorexia, somnolence, and malaise.

Acute-Phase Proteins

During the acute-phase response, the liver dramatically increases the synthesis of acute-phase proteins such as fibrinogen, C-reactive protein (CRP), and serum amyloid A protein (SAA) that serve several different defense functions.[1,2] The synthesis of these proteins is stimulated by cytokines, especially TNF-α, IL-1 (for SAA), and IL-6 (for fibrinogen and CRP).

C-reactive protein was named because it precipitated with the C fraction (C polypeptide) of pneumococci. The function of CRP is thought to be protective, in that it binds to the surface of invading microorganisms and targets them for destruction by complement and phagocytosis. Although everyone maintains a low level of CRP, this level rises when there is an acute inflammatory response.[27] Recent interest has focused on the use of high-sensitivity CRP (hsCRP) serum measurements as a marker for increased risk of myocardial infarction in persons with coronary heart disease.[28,29] It is believed that inflammation involving atherosclerotic plaques in coronary arteries may predispose to thrombosis and myocardial infarction (see Chapter 18).

During the acute-phase response, SAA protein replaces apolipoprotein A, a component of high-density lipoprotein (HDL) particles (see Chapter 18). This presumably increases the transfer of HDLs from liver cells to macrophages, which can then utilize these particles

for energy. The rise in fibrinogen causes red blood cells to form stacks (rouleaux) that settle or sediment more rapidly than individual erythrocytes. This is the basis for the accelerated erythrocyte sedimentation rate (ESR) that occurs in disease conditions characterized by the systemic inflammatory response.

White Blood Cell Response

Leukocytosis, or the increase in white blood cells, is a frequent sign of an inflammatory response, especially those caused by bacterial infection. In acute inflammatory conditions, the white blood cell count commonly increases from a normal value of 4000 to 10,000 cells/μL to 15,000 to 20,000 cells/μL. After being released from the bone marrow, circulating neutrophils have a life span of only about 10 hours and therefore must be constantly replaced if their numbers are to be adequate. With excessive demand for phagocytes, immature forms of neutrophils (bands) are released from the bone marrow. The phrase "a shift to the left" in a white blood cell differential count refers to the increase in immature neutrophils seen in severe infections.

Bacterial infections produce a relatively selective increase in neutrophils (neutrophilia), while parasitic and allergic responses induce eosinophilia. Viral infections tend to produce a decrease in neutrophils (neutropenia) and an increase in lymphocytes (lymphocytosis).[3] A decrease in white blood cells (leukopenia) may also occur in persons with overwhelming infections or impaired ability to produce white blood cells.

Systemic Inflammatory Response

In severe bacterial infections (sepsis), the large quantities of microorganisms in the blood result in an uncontrolled inflammatory response with the production and release of enormous quantities of inflammatory cytokines (most notably IL-1 and TNF-α) and development of what is referred to as the *systemic inflammatory response syndrome* (see Chapter 20).[30] A decrease in total white blood cells (leukopenia) may occur in persons with overwhelming infections or impaired ability to produce white blood cells.

Fever

Fever (pyrexia) is an elevation in body temperature caused by an upward displacement of the set point of the thermoregulatory center in the hypothalamus.[31–33] It is one of the most prominent manifestations of the acute-phase response.[1,2]

Body Temperature Regulation

The temperature in the deep tissues of the body (core temperature) is normally maintained within a range of 36.0°C to 37.5°C (97.0°F to 99.5°F).[31,32] Within this range, there are individual differences and diurnal variations; internal core temperatures reach their highest point in late afternoon and evening and their lowest point in the early morning hours (Fig. 3-7). Virtually all biochemical processes in the body are affected by

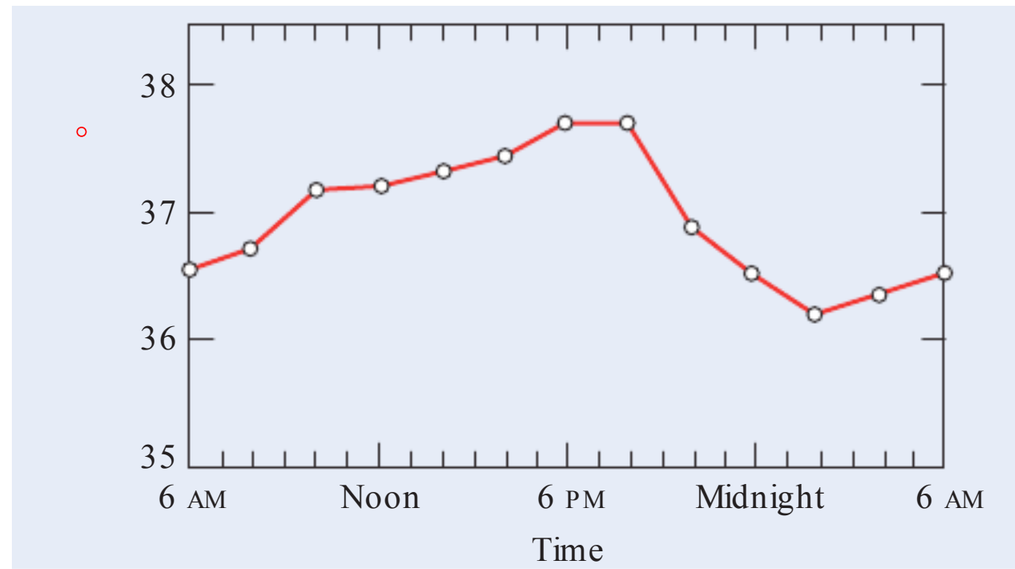


FIGURE 3-7. Normal diurnal variations in body temperature.

changes in temperature. Metabolic processes speed up or slow down depending on whether body temperature is rising or falling.

Body temperature, which reflects the difference between heat production and heat loss, is regulated by the *thermoregulatory center* in the hypothalamus. Body heat is generated in the tissues of the body, transferred to the skin surface by the blood, and then released into the environment surrounding the body. The thermoregulatory center regulates the temperature of the deep body tissues, or "core" of the body, rather than the surface temperature. It does so by integrating input from cold and warmth receptors located throughout the body and participating in negative feedback mechanisms.

The *thermostatic set point* of the thermoregulatory center is the level at which body temperature is regulated so that core temperature is maintained within the normal range. When body temperature begins to rise above this set point, heat-dissipating behaviors are initiated, and when the temperature falls below the set point, heat production is increased. A core temperature greater than 41°C (105.8°F) or less than 34°C (93.2°F) usually indicates that the body's thermoregulatory ability is impaired (Fig. 3-8). Body responses that produce, conserve, and dissipate heat are described in Table 3-1. Spinal cord injuries that transect the cord at T6 or above can seriously impair temperature regulation because the hypothalamus no longer can control skin blood flow or sweating.

In addition to physiologic thermoregulatory mechanisms, humans engage in voluntary behaviors to help regulate body temperature. These behaviors include the selection of proper clothing and regulation of environmental temperature through heating systems and air conditioning. Body positions that hold the extremities close to the body (e.g., huddling) prevent heat loss and are commonly assumed in cold weather.

Mechanisms of Heat Production. Metabolism is the body's main source of heat production. The sympathetic neurotransmitters epinephrine and norepinephrine, which are released when an increase in body temperature is needed, act at the cellular level to shift body metabolism to heat production rather than energy generation. This may be one of the reasons fever tends to produce feelings of weakness and fatigue. Thyroid hormone

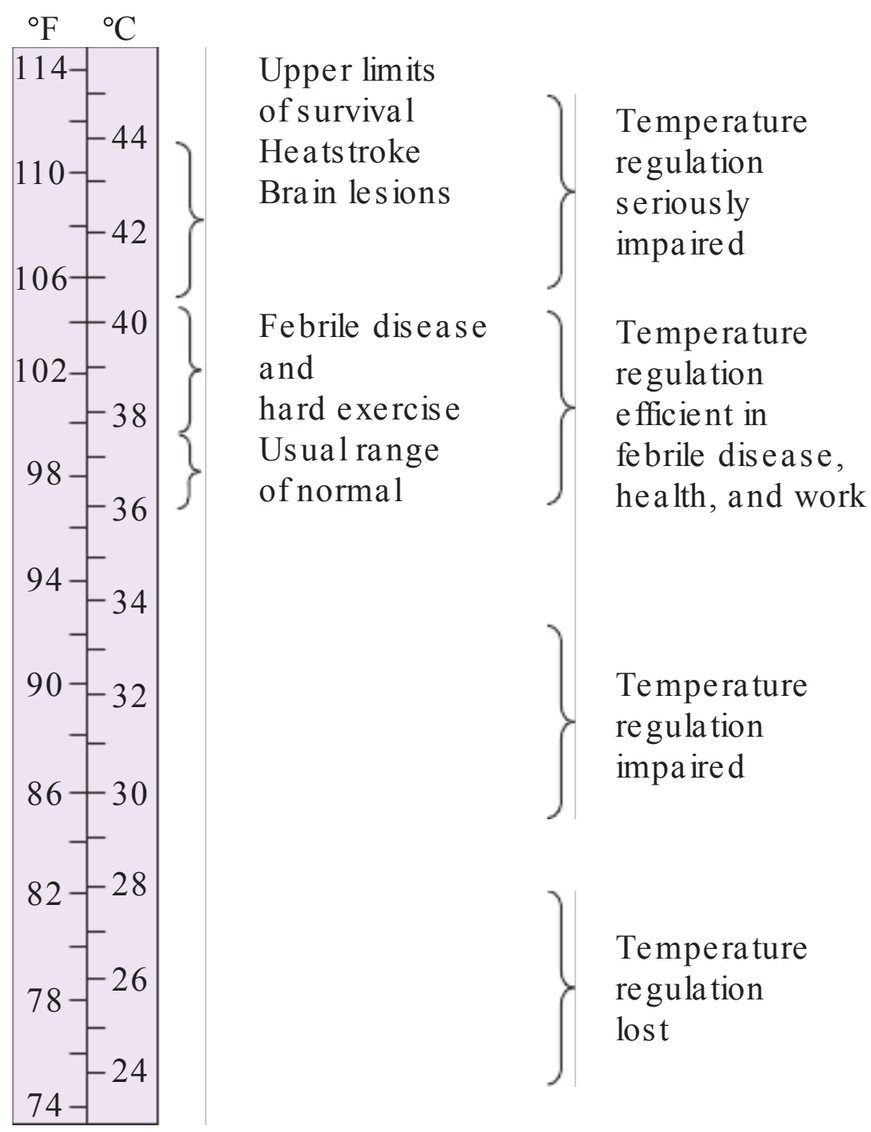


FIGURE 3-8. Body temperatures under different conditions. (From Dubois EF. Fever and the Regulation of Body Temperature. Springfield, IL: Charles C. Thomas; 1948.)

increases cellular metabolism, but this response usually requires several weeks to reach maximal effectiveness.

Fine involuntary actions such as shivering and chattering of the teeth can produce a threefold to fivefold increase in body temperature. *Shivering* is initiated by impulses from the hypothalamus. The first muscle change that occurs with shivering is a general increase in muscle tone, followed by an oscillating rhythmic tremor involving the spinal-level reflex that controls muscle tone. Because no external work is performed, all of the energy liberated by the metabolic processes from shivering is in the form of heat. Contraction of the *pilomotor muscles* of the skin, which raises the skin hair and produces goose bumps, reduces the surface area available for heat loss.

Physical exertion also increases body temperature. With strenuous exercise, more than three fourths of the increased metabolism resulting from muscle activity appears as heat within the body, and the remainder appears as external work.

Mechanisms of Heat Loss. Most of the body's heat is produced by the deeper core tissues (i.e., muscles and viscera) and then transferred in the blood to the body surface, where it is released into the environment.

There are numerous *arteriovenous (AV) shunts* under the skin surface that allow blood to move directly from the arterial to the venous system.[31] These AV shunts are much like the radiators in a heating system. When the shunts are open, body heat is freely dissipated to the skin and surrounding environment; when the shunts are closed, heat is retained in the body. The blood flow in the AV shunts is controlled almost exclusively by the sympathetic nervous system in response to changes in core temperature and environmental temperature. The transfer of heat to the body's surface is influenced by blood volume. In hot weather, the body compensates by increasing blood volume as a means of dissipating heat. Exposure to cold produces a cold diuresis and a reduction in blood volume as a means of controlling the transfer of heat to the body's surface.

Heat is lost from the body through radiation and conduction from the skin surface; through evaporation

TABLE 3-1 **Heat Gain and Heat Loss Responses Used in Regulation of Body Temperature**

Heat Gain		Heat Loss	
Body Response	Mechanism of Action	Body Response	Mechanism of Action
Vasoconstriction of the superficial blood vessels	Confines blood flow to the inner core of the body, with the skin and subcutaneous tissues acting as insulation to prevent loss of core heat	Dilatation of the superficial blood vessels	Delivers blood containing core heat to the periphery where it is dissipated through radiation, conduction, and convection
Contraction of the pilomotor muscles that surround the hairs on the skin	Reduces heat loss from the skin	Sweating	Increases heat loss through evaporation
Assumption of the huddle position with the extremities held close to the body	Reduces the surface area for heat loss		
Shivering	Increases heat production by the muscles		
Increased production of epinephrine	Increases the heat production associated with metabolism		
Increased production of thyroid hormone	Is a long-term mechanism that increases metabolism and heat production		

of sweat and insensible perspiration; through exhalation of air that has been warmed and humidified; and through heat lost in urine and feces. Of these mechanisms, only heat losses that occur at the skin surface are directly under hypothalamic control.

Radiation involves the transfer of heat through the air or a vacuum. Heat loss through radiation varies with the temperature of the environment. Environmental temperature must be less than that of the body for heat loss to occur. About 60% of body heat loss typically occurs through radiation.[31] *Conduction* involves the direct transfer of heat from one molecule to another. Blood carries, or conducts, heat from the inner core of the body to the skin surface. Normally, only a small amount of body heat is lost through conduction to a cooler surface. Cooling blankets and mattresses that are used for reducing fever rely on conduction of heat from skin to the cooler surface of the mattress or blanket. Heat can also be conducted in the opposite direction—from the external environment to the body surface. For instance, body temperature may rise slightly after a hot bath.

Convection refers to heat transfer through the circulation of air currents. Normally, a layer of warm air tends to remain near the body's surface; convection causes continual removal of the warm layer and replacement with air from the surrounding environment. The wind-chill factor that often is included in the weather report combines the effect of convection caused by wind with the still-air temperature.

Evaporation involves the use of body heat to convert water on the skin to water vapor. Water that diffuses through the skin independent of sweating is called *insensible perspiration*. Insensible perspiration losses are greatest in a dry environment. Sweating occurs through the sweat glands and is controlled by the sympathetic nervous system, using acetylcholine as a neurotransmitter. This means that anticholinergic drugs, such as atropine, can interfere with heat loss by interrupting sweating.

Evaporative heat losses involve both insensible perspiration and sweating, with 0.58 calorie being lost for each gram of water that is evaporated.[31] As long as body temperature is greater than the atmospheric temperature, heat is lost through radiation. However, when the temperature of the surrounding environment becomes greater than skin temperature, evaporation is the only way the body can rid itself of heat. Any condition that prevents evaporative heat losses causes the body temperature to rise.

The Febrile Response

Fever, or pyrexia, describes an elevation in body temperature that is caused by a cytokine-induced upward displacement of the set point of the hypothalamic thermoregulatory center. It is resolved when the factor that caused the increase in the set point is removed. Fevers that are regulated by the hypothalamus usually do not rise above 41°C (105°F), suggesting a built-in thermostatic regulatory mechanism. Temperatures above that level are usually the result of superimposed activity, such as convulsions, hypermetabolic states, or direct impairment of the temperature control center.

Causes of Fever. Fever can be caused by a number of microorganisms and substances that are collectively called pyrogens.[33–35] Many proteins, including lipopolysaccharide toxins released from bacterial cell membranes, can raise the set point of the hypothalamic thermostat. Noninfectious disorders, such as myocardial infarction and pulmonary emboli, also produce fever. In these conditions, the injured or abnormal cells incite the production of fever-producing pyrogens. Some malignant cells, such as those of leukemia and Hodgkin disease, also secrete pyrogens.

Some pyrogens act directly and immediately on the hypothalamic thermoregulatory center to increase its set point. Other pyrogens, often referred to as *exogenous pyrogens,* act indirectly and may require several hours to produce their effect.[31] Exogenous pyrogens induce host cells, such as blood leukocytes and tissue macrophages, to produce fever-producing mediators called *endogenous pyrogens* (e.g., IL-1). For example, the breakdown products of phagocytosed bacteria that are present in the blood lead to the release of endogenous pyrogens. The endogenous pyrogens are thought to increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E_2 (PGE_2) (Fig. 3-9).[31] In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established.

A fever that has its origin in the central nervous system is sometimes referred to as a *neurogenic fever.*[36] It usually is the result of damage to the hypothalamus caused by central nervous system trauma, intracerebral bleeding, or an increase in intracranial pressure. Neurogenic fevers are characterized by a high temperature that is resistant to antipyretic therapy and is not associated with sweating.

Purpose of Fever. The purpose of fever is not completely understood. However, from a purely practical standpoint, fever signals the presence of an infection and may legitimize the need for medical treatment. In ancient times, fever was thought to "cook" the poisons that caused the illness. With the availability of antipyretic drugs in the late 19th century, the belief that fever was useful began to wane, probably because most antipyretic drugs also had analgesic effects.

Fever Patterns. The patterns of temperature change in persons with fever vary and may provide information about the nature of the causative agent.[37] These patterns can be described as intermittent, remittent, sustained, or relapsing (Fig. 3-10). An intermittent fever is one in which temperature returns to normal at least once every 24 hours. Intermittent fevers are commonly associated with conditions such as gram-negative/-positive sepsis, abscesses, and acute bacterial endocarditis. In a remittent fever, the temperature does not return to normal and varies a few degrees in either direction.

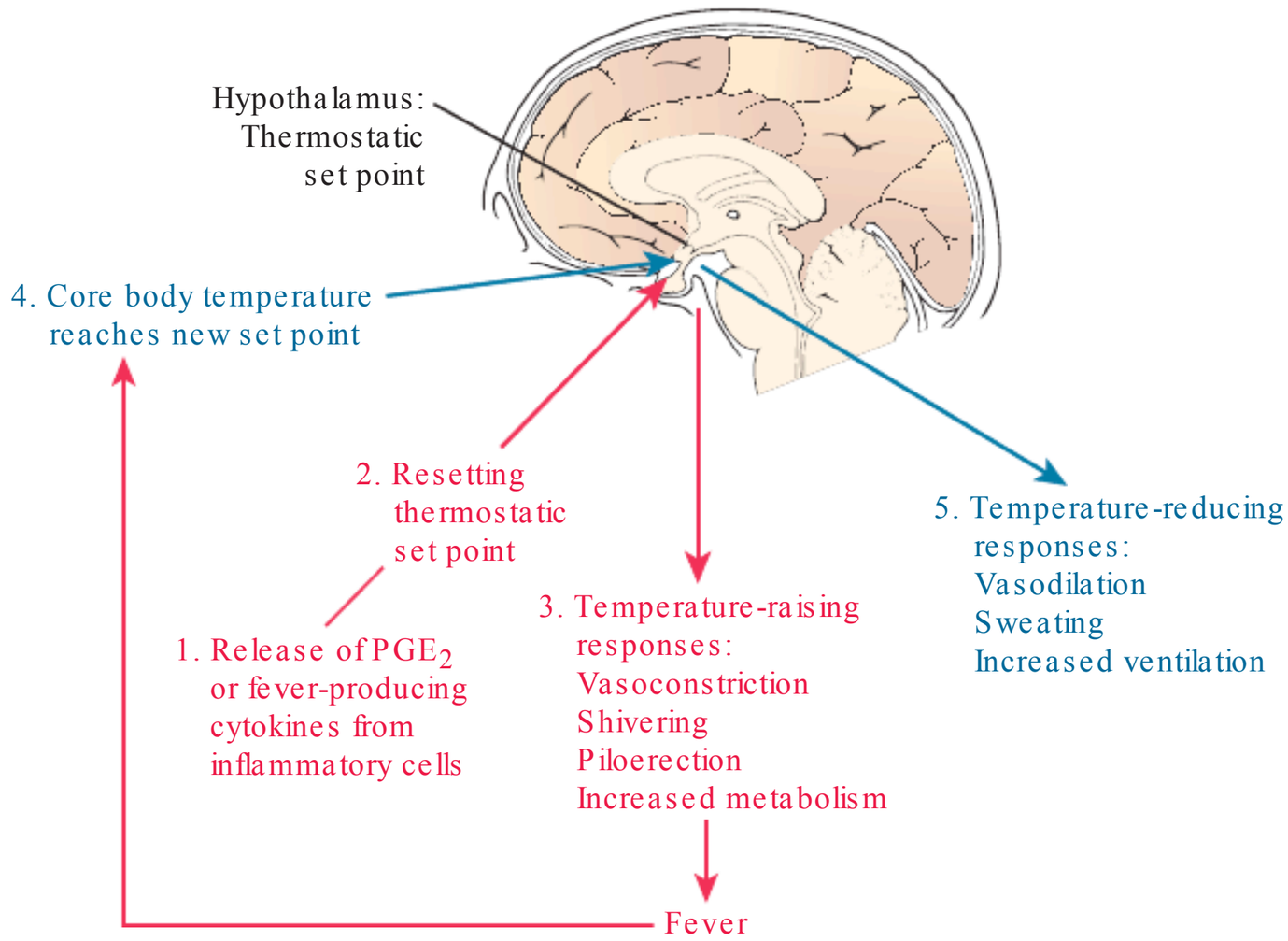


FIGURE 3-9. Mechanisms of fever. (1) Release of prostaglandin E_2 (PGE_2) or fever-producing cytokines from inflammatory cells, (2) resetting of the thermoregulatory set point in the hypothalamus to a higher level (prodrome), (3) generation of hypothalamic-mediated responses that raise body temperature (chill), (4) development of fever with elevation of body to new thermostatic set point, and (5) production of temperature-lowering responses (flush and defervescence) and return of body temperature to a lower level.

In a sustained or continuous fever, the temperature remains above normal with minimal variations (usually less than 0.55°C or 1°F). Sustained fevers are seen in persons with drug-induced fever in which a drug inadvertently leads to a hypermetabolic fever-inducing state.[38] A recurrent or relapsing fever is one in which there is one or more episodes of fever, each as long as several days, with one or more days of normal temperature between episodes. Relapsing fevers may be caused by a variety of infectious diseases, including tuberculosis, fungal infections, Lyme disease, and malaria.

Critical to the analysis of a fever pattern is the relation of heart rate to the level of temperature elevation. Most persons respond to an increase in temperature with an appropriate increase in heart rate. The observation that a rise in temperature is not accompanied by the anticipated change in heart rate can provide useful information about the cause of the fever. For example, a heart rate that is slower than would be anticipated can occur with Legionnaires' disease and drug fever, and a heart rate that is more rapid than anticipated can be symptomatic of hyperthyroidism.

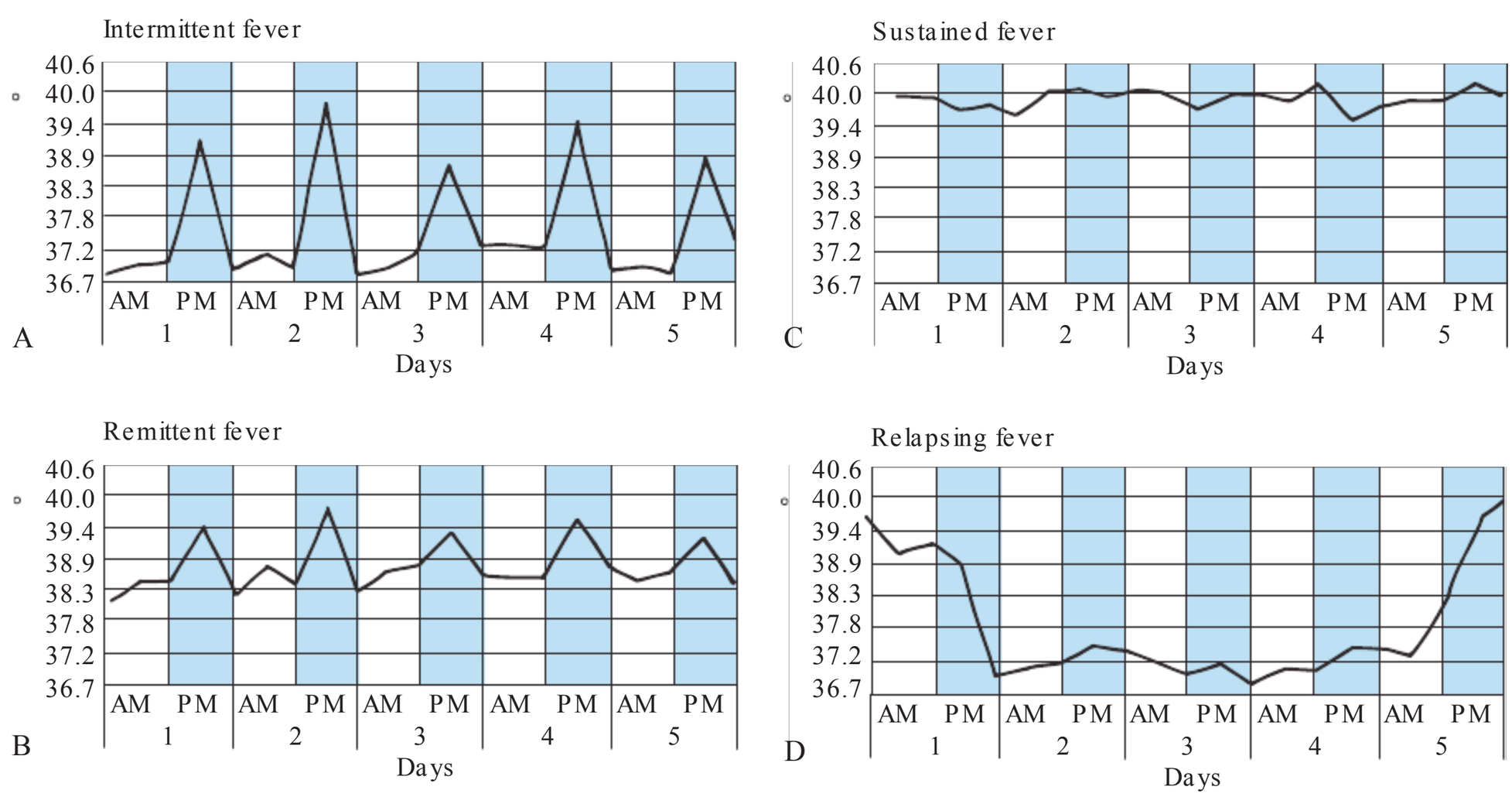


FIGURE 3-10. Schematic representation of fever patterns: **(A)** intermittent, **(B)** remittent, **(C)** sustained, and **(D)** recurrent or relapsing.

Manifestations of Fever

The physiologic behaviors that occur during the development of fever can be divided into four successive stages: a prodrome; a chill, during which the temperature rises; a flush; and defervescence (see Fig. 3-9). During the *first* or *prodromal* period, there are nonspecific complaints, such as mild headache and fatigue, general malaise, and fleeting aches and pains. During the *second stage* or *chill,* there is the uncomfortable sensation of being cold and the onset of generalized shaking, although the temperature is rising. Vasoconstriction and piloerection usually precede the onset of shivering. At this point the skin is pale and covered with goose flesh. There is an urge to put on more clothing or covering and to curl up in a position that conserves body heat. When the shivering has caused the body temperature to reach the new set point of the temperature control center, the shivering ceases, and a sensation of warmth develops. At this point, the *third stage* or *flush* begins, during which cutaneous vasodilatation occurs and the skin becomes warm and reddened. The *fourth,* or *defervescence,* stage of the febrile response is marked by the initiation of sweating. Not all persons proceed through all four stages of fever development. Sweating may be absent, and fever may develop gradually, with no indication of a chill or shivering.

Common manifestations of fever are anorexia, myalgia, arthralgia, and fatigue. These discomforts are worse when the temperature rises rapidly or exceeds 39.5°C (103.1°F). Respiration is increased, and the heart rate usually is elevated. Dehydration occurs because of sweating and the increased vapor losses caused by the rapid respiratory rate. The occurrence of chills commonly coincides with the introduction of pyrogen into the circulation. This is one of the reasons that blood cultures to identify the organism causing the fever are usually drawn during the first signs of a chill.

Many of the manifestations of fever are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source. During fever, the body switches from using glucose (an excellent medium for bacterial growth) to metabolism based on protein and fat breakdown. With prolonged fever, there is increased breakdown of endogenous fat stores. If fat breakdown is rapid, metabolic acidosis may result (see Chapter 8).

Headache is a common accompaniment of fever and is thought to result from the vasodilatation of cerebral vessels occurring with fever. Delirium is possible when the temperature exceeds 40°C (104°F). In the elderly, confusion and delirium may follow moderate elevations in temperature. Because of the increasingly poor oxygen uptake by the aging lung, pulmonary function may prove to be a limiting factor in the hypermetabolism that accompanies fever in older persons. Confusion, incoordination, and agitation commonly reflect cerebral hypoxemia. Febrile seizures can occur in some children.[39] They usually occur with rapidly rising temperatures and/or at a threshold temperature that differs with each child.

Herpetic lesions, or fever blisters, develop in some persons during fever. They are caused by a separate infection by the type 1 herpes simplex virus that established latency in the regional ganglia and is reactivated by a rise in body temperature.

Management of Fever

Fever usually is a manifestation of a disease state, and as such, determining the cause of a fever is an important aspect of its treatment. Sometimes it is difficult to establish the cause. A prolonged fever for which the cause is difficult to ascertain is often referred to as *fever of unknown origin* (FUO). Fever of unknown origin is defined as a temperature of 38.3°C (101°F) or higher that is present for 3 weeks or longer.[40,41] Among the causes of FUO are malignancies (i.e., lymphomas, metastases to the liver or central nervous system); infections such as human immunodeficiency virus or tuberculosis, or abscessed infections; and drug fever. Malignancies, particularly non-Hodgkin lymphoma, are important causes of FUO in the elderly. Cirrhosis of the liver is another cause of FUO.

The methods of fever treatment focus on modifications of the external environment intended to increase heat transfer from the internal to the external environment, support of the hypermetabolic state that accompanies fever, protection of vulnerable body organs and systems, and treatment of the infection or condition causing the fever. Because fever is a disease symptom, its manifestation suggests the need for treatment of the primary cause.

Modification of the environment ensures that the environmental temperature facilitates heat transfer away from the body. Sponge baths with cool water or an alcohol solution can be used to increase evaporative heat losses. More profound cooling can be accomplished through the use of a cooling blanket or mattress, which facilitates the conduction of heat from the body into the coolant solution that circulates through the mattress. Care must be taken so that cooling methods do not produce vasoconstriction and shivering that decrease heat loss and increase heat production.

Adequate fluids and sufficient amounts of simple carbohydrates are needed to support the hypermetabolic state and prevent the tissue breakdown that is characteristic of fever. Additional fluids are needed for sweating and to balance the insensible water losses from the lungs that accompany an increase in respiratory rate. Fluids also are needed to maintain an adequate vascular volume for heat transport to the skin surface.

Antipyretic drugs, such as aspirin, ibuprofen, and acetaminophen, often are used to alleviate the discomforts of fever and protect vulnerable organs, such as the brain, from extreme elevations in body temperature. These drugs act by resetting the hypothalamic temperature control center to a lower level, presumably by blocking the activity of cyclooxygenase, an enzyme that is required for the conversion of arachidonic acid to prostaglandin E_2.

Fever in Children

Fever occurs frequently in infants and young children (i.e., ages 1 day to 3 years) and is a common reason for visits to the clinic or emergency department.[42,43] The differential diagnosis of fever is broad and includes both infectious and noninfectious causes, with the majority of febrile children having an underlying infection. The most common causes are minor or more serious infections of the respiratory system, gastrointestinal tract, urinary tract, or central nervous system. The epidemiology of serious bacterial disease has changed dramatically with the introduction of the *Haemophilus influenzae* and *Streptococcus pneumoniae* vaccines in developed countries. *H. influenzae* type b has been nearly eliminated and the incidence of pneumococcal disease has declined substantially. Febrile children who are younger than 1 year of age and females between 1 and 2 years of age should be considered at risk for a urinary tract infection (see Chapter 24).

While most children have identifiable causes for their fevers, many have fevers without localizing signs or symptoms. These fevers, which are usually of rapid onset and present for less than a week, are commonly referred to as *fever without source*. The American College of Emergency Physicians has developed clinical guidelines for use in the treatment of previously healthy infants and children ages 1 day to 3 years with fever without a source. The guidelines define fever in this age group as a rectal temperature of at least 38°C (100.4°F). The reliability of other methods of temperature measurements (e.g., axillary, ear) is lower and must be considered when making decisions about the seriousness of the fever.[43]

The approach to the young child who has fever without a source varies depending on the age of the child (neonate [0 to 28 days], young infant [1 to 3 months], and older infants and toddlers [3 to 36 months]).[44] All have decreased immunologic function and are more commonly infected with virulent organisms. Neonates are at particularly high risk for serious bacterial infections that can cause bacteremia or meningitis. Also, neonates and young infants demonstrate limited signs of infection, often making it difficult to distinguish between serious bacterial infections that require immediate medical attention and other causes of an elevated temperature.

Fever without source in children younger than age 3 months requires careful history and physical examination.[42] The temperature-lowering response to antipyretic medications does not change the likelihood of a child having a serious bacterial infection and should not be used as an indicator of infection severity.[45] Neonates with signs of toxicity (and high risk) including lethargy, poor feeding, hypoventilation, poor tissue oxygenation, and cyanosis usually require hospitalization and treatment with antibiotics. Diagnostic tests such as white blood cell count, blood and urine cultures, chest radiographs, and lumbar puncture usually are done to determine the cause of fever. Infants with fever who are considered to be at low risk for bacterial infections often are managed on an outpatient basis provided the parents or caregivers are deemed reliable. Older children with fever without source also may be treated on an outpatient basis.

Fever in the Elderly

In the elderly, even slight elevations in temperature may indicate serious infection, most often caused by bacteria, or disease. This is because the elderly often have a lower baseline temperature (36.4°C [97.6°F] in one study) than younger persons, and although their temperature increases during an infection, it may fail to reach a level that is equated with significant fever.[45,46] Therefore, it has been recommended that the definition of fever in the elderly be expanded to include an elevation of temperature of at least 1.1°C (2°F) above baseline values.

The absence of fever may delay diagnosis and initiation of antimicrobial treatment. Unexplained changes in functional capacity, worsening of mental status, weakness and fatigue, and weight loss are signs of infection in the elderly and should be viewed as possible signs of infection and sepsis when fever is absent. A thorough history and physical examination are critically important.[47] The probable mechanisms for the blunted fever response include a disturbance in sensing of temperature by the thermoregulatory center in the hypothalamus, alterations in release of endogenous pyrogens, and the failure to elicit responses such as vasoconstriction of skin vessels, increased heat production, and shivering that increase body temperature during a febrile response.

Another factor that may delay recognition of fever in the elderly is the method of temperature measurement. Oral temperature remains the most commonly used method, but research suggests that rectal and tympanic membrane methods are more effective in detecting fever in the elderly.[47] This is because conditions such as mouth breathing, tongue tremors, and agitation often make it difficult to obtain accurate oral temperatures in the elderly.

SUMMARY CONCEPTS

- The systemic manifestations of inflammation include the effects of the acute-phase response, such as fever and lethargy; increased erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP), other acute-phase proteins, and white blood cells; and enlargement of the lymph nodes that drain the affected area. In severe bacterial infections (sepsis), large quantities of microorganisms in the blood result in the production and release of enormous quantities of inflammatory cytokines and development of what is referred to as the systemic inflammatory response syndrome.

- Fever, an elevation in body temperature, is one of the most prominent manifestations of the acute-phase response, especially if inflammation is caused by infection. It is produced in response to pyrogens that act by prompting the release of prostaglandin E_2 or fever-producing cytokines, which in turn resets the hypothalamic thermoregulatory center.
- The reactions that occur during fever consist of four stages: a prodromal period with nonspecific complaints, such as mild headache and fatigue; a chill, during which the temperature rises; a flush, during which the skin becomes warm and flushed; and a defervescence stage, which is marked by the initiation of sweating.
- The approach to fever in children varies depending on the age of the child. Infants and young children have decreased immunologic function and are more commonly infected with virulent organisms.
- The elderly tend to have a lower baseline temperature, so that serious infections may go unrecognized because of the perceived lack of a significant fever.

REVIEW EXERCISES

1. A 15-year-old boy presents with abdominal pain, a temperature of 38°C (100.5°F), and an elevated white blood cell count of 13,000/μL, with an increase in neutrophils. A tentative diagnosis of appendicitis is made.

A. Explain the significance of pain as it relates to the inflammatory response.
B. What is the cause of the fever and elevated white blood cell count?
C. What would be the preferred treatment for this boy?

2. Aspirin and other nonsteroidal anti-inflammatory drugs are often used to control the manifestations of chronic inflammatory disorders such as arthritis.

A. Explain their mechanism of action in terms of controlling the inflammatory response.

3. Persons with long-standing ulcerative colitis, an inflammatory bowel disease, have a higher risk of colorectal cancer than the general population.

A. Hypothesize on cancer-producing mechanisms of this chronic inflammatory disease.

4. A 3-year-old child is seen in a pediatric clinic with a temperature of 39°C (103°F). Her skin is warm and flushed, her pulse is 120 beats per minute, and her respirations are shallow and rapid at 32 breaths per minute. Her mother states that she has complained of a sore throat and has refused to drink or take medications to bring her fever down.

A. Explain the physiologic mechanisms of fever generation.
B. Are the warm and flushed skin, rapid heart rate, and respirations consistent with this level of fever?
C. After receiving an appropriate dose of acetaminophen, the child begins to sweat, and the temperature drops to 37.2°C. Explain the physiologic mechanisms responsible for the drop in temperature.

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Cell Proliferation and Tissue Regeneration
Cell Proliferation Versus Differentiation
The Cell Cycle
Proliferative Capacity of Tissues
Stem Cells
Influence of Growth Factors
Extracellular Matrix and Cell–Matrix Interactions
Healing by Connective Tissue Repair
Phases of Repair
Angiogenesis and Ingrowth of Granulation Tissue
Emigration of Fibroblasts and Deposition of Extracellular Matrix
Maturation and Remodeling of the Fibrous Tissue
Cutaneous Wound Healing
Healing by Primary and Secondary Intention
Phases of Healing
Factors That Affect Wound Healing
Nutritional Status
Blood Flow and Oxygen Delivery
Impaired Inflammatory and Immune Responses
Infection, Wound Separation, and Foreign Bodies
Wound Healing in the Elderly

Chapter 4

Cell Proliferation and Tissue Regeneration and Repair

Tissue repair, which overlaps the inflammatory process that was discussed in Chapter 3, refers to the restoration of tissue structure and function after an injury. Tissue repair can take the form of regeneration, in which injured cells are replaced with cells of the same type, sometimes leaving no residual trace of previous injury; or it can take the form of replacement by connective (fibrous) tissue, which leads to scar formation or fibrosis in organs such as the liver or lung. For many types of common injuries, both regeneration and connective tissue replacement contribute to tissue repair. This chapter is divided into two parts. The first part discusses cell proliferation and regeneration, the cell cycle, the role of stem cells, growth factors, and the extracellular matrix in tissue renewal. The second focuses on connective tissue repair, cutaneous wound healing, factors that affect wound healing, and the effect of aging on wound healing.

Cell Proliferation and Tissue Regeneration

Tissue repair involves the proliferation of various cells, and close interactions between cells and the extracellular matrix (ECM). Body organs and tissues are composed of two types of tissues: parenchymal and stromal. The parenchymal tissues consist of the functioning cells of an organ or body part: whereas, the stromal tissues contain the supporting connective tissues, blood vessels, fibroblasts, nerve fibers, and extracellular matrix.

Cell Proliferation Versus Differentiation

Cell proliferation refers to the process of increasing cell numbers by mitotic division. *Cell differentiation* is the process whereby a cell becomes more specialized in

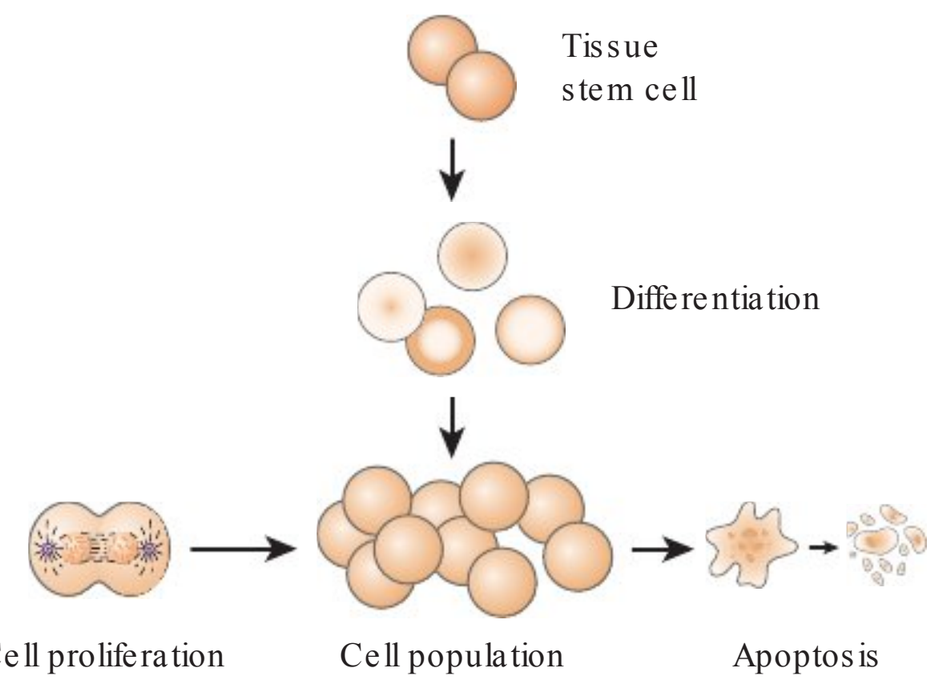

FIGURE 4-1. In normal tissues, the size of the cell population is determined by a balance of cell proliferation, death by apoptosis, and emergence of newly differentiated cells from stem cells.

terms of structure and function.[1,2] Stem cells are undifferentiated cells that have the capacity to generate multiple cell types (to be discussed). In normal tissue the size of the cell population is determined by a balance of cell proliferation, death by apoptosis (see Chapter 2), and emergence of newly differentiated cells from stem cells[2] (Fig. 4-1). Several cell types proliferate during tissue repair including remnants of injured parenchymal tissue cells, vascular endothelial cells, and fibroblasts. The proliferation of these cell types is driven by proteins called *growth factors*. The production of growth factors and the ability of these cells to respond and expand in sufficient numbers are important determinants of the repair process.

All of the different cell types in the body originate from a single cell—the fertilized ovum. As the embryonic cells increase in number, they differentiate, facilitating the development of all the different cells and organs of the body. The process of differentiation is regulated by a combination of internal processes involving the expression of specific genes and external stimuli provided by neighboring cells, the ECM, and a variety of growth factors. The process occurs in orderly steps, with each progressive step being exchanged for a loss of ability to develop different cell characteristics. As a cell becomes more highly specialized, the stimuli that are able to induce mitosis become more limited. Neurons, which are highly specialized cells, lose their ability to proliferate once development of the nervous system is complete. In other, less-specialized tissues, such as the skin and mucosal lining of the gastrointestinal tract, a high degree of cell renewal continues throughout life. Even in these continuously renewing cell populations, the more specialized cells are unable to divide. Many of these cell populations rely on *progenitor* or *parent cells* of the same lineage. Progenitor cells are sufficiently differentiated so that their daughter cells are limited to the same cell line, but they have not reached the point of differentiation that precludes the potential for active proliferation. Some cell populations have self-renewing multipotent stem cells, such as the epithelial stem cells, that can differentiate into the different cell types throughout life.

The Cell Cycle

In order to understand cell proliferation, whether physiologic (as in tissue regeneration and repair) or pathologic (as in cancer), it is important to learn about the cell cycle, an orderly sequence of events in which a cell duplicates its genetic contents and divides. During the cell cycle, the duplicated chromosomes are appropriately aligned for distribution between two genetically identical daughter cells.

The cell cycle is divided into four distinct phases referred to as G_1, S, G_2, and M. Gap 1 (G_1) is the postmitotic phase during which deoxyribonucleic acid (DNA) synthesis ceases while ribonucleic acid (RNA) and protein synthesis and cell growth take place (see Understanding the Cell Cycle).[1–4] During the *S phase,* DNA synthesis occurs, giving rise to two separate sets of chromosomes, one for each daughter cell. G_2 is the premitotic phase and is similar to G_1 in that DNA synthesis ceases while RNA and protein synthesis continue. Collectively, G_1, S, and G_2 are referred to as *interphase*. The *M phase* is the phase of nuclear division and cytokinesis. Continually dividing cells, such as the stratified squamous epithelium of the skin, continue to cycle from one mitotic division to the next. When environmental conditions are adverse, such as nutrient or growth factor unavailability, or cells become terminally differentiated (i.e., highly specialized), cells may exit the cell cycle, becoming mitotically quiescent and reside in a special resting state known as G_0. Cells in G_0 may reenter the cell cycle in response to extracellular nutrients, growth factors, hormones, and other signals such as blood loss or tissue injury that trigger cell renewal. Highly specialized and terminally differentiated cells, such as neurons, may permanently stay in G_0.

Within the cell cycle are checkpoints where pauses or arrests can be made if the specific events in the phases of the cell cycle have not been completed. There are also opportunities for ensuring the accuracy of DNA replication. These DNA damage checkpoints allow for any defects to be edited and repaired, thereby ensuring that each daughter cell receives a full complement of genetic information, identical to that of the parent cell.[1–3]

The *cyclins* are a family of proteins that control the entry and progression of cells through the cell cycle.[1–4] Cyclins bind to (thereby activating) proteins called *cyclin-dependent kinases* (CDKs). Kinases are enzymes that phosphorylate proteins. The CDKs phosphorylate specific target proteins and are expressed continuously during the cell cycle but in an inactive form, whereas the cyclins are synthesized during specific phases of the cell cycle and then degraded once their task is completed. Different arrangements of cyclins and CDKs are associated with each stage of the cell cycle. For example, cyclin B and CDK1 control the transition from G_2 to M. As the cell moves into G_2, cyclin B is synthesized and binds to CDK1. The cyclin B–CDK1 complex then directs the

events leading to mitosis, including DNA replication and assembly of the mitotic spindle. Although each phase of the cell cycle is monitored carefully, the transition from G_2 to M is believed to be one of the most important checkpoints in the cell cycle. In addition to the synthesis and degradation of the cyclins, the cyclin–CDK complexes are regulated by the binding of CDK inhibitors. The CDK inhibitors are particularly important in regulating cell cycle checkpoints during which mistakes in DNA replication are repaired. The finding that the cell cycle can be reactivated by removing CDK inhibitors in quiescent and nonproliferating cells has potential implications for tissue repair and cell replacement therapy.[4]

Proliferative Capacity of Tissues

The capacity for regeneration varies with the tissue and cell type. Body tissues are divided into three types depending on the ability of their cells to undergo regeneration: (1) continuously dividing, (2) stable, and (3) permanent tissues.[1,2]

Continuously dividing or *labile* tissues are those in which the cells continue to divide and replicate throughout life, replacing cells that are continually being destroyed. They include the surface epithelial cells of the skin, oral cavity, vagina, and cervix; the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; the transitional epithelium of the urinary tract; and bone marrow cells. These tissues can readily regenerate after injury as long as a pool of stem cells is preserved. Bleeding, for example, stimulates the rapid proliferation of replacement cells by the blood-forming progenitor cells of the bone marrow.

Stable tissues contain cells that normally stop dividing when growth ceases. Cells in these tissues remain quiescent in the G_0 stage of the cell cycle. However, these cells are capable of undergoing regeneration when confronted with an appropriate stimulus; thus, they are capable of reconstituting the tissue of origin. Stable cells constitute the parenchyma of solid organs such as the liver and kidney. They also include smooth muscle cells, vascular endothelial cells, and fibroblasts, the proliferation of which is particularly important to wound healing.

The cells in *permanent* tissues do not proliferate. The cells in these tissues are considered to be terminally differentiated and do not undergo mitotic division in postnatal life. The permanent cells include nerve cells, skeletal muscle cells, and cardiac muscle cells. These cells do not normally regenerate; once destroyed, they are replaced with fibrous scar tissue that lacks the functional characteristics of the destroyed tissue.

Stem Cells

Another type of tissue cell, called a *stem cell,* remains incompletely differentiated throughout life.[1,2,5] In most continuously dividing tissues, the mature cells are terminally differentiated and short lived. As mature cells die the tissue is replenished by the differentiation of cells

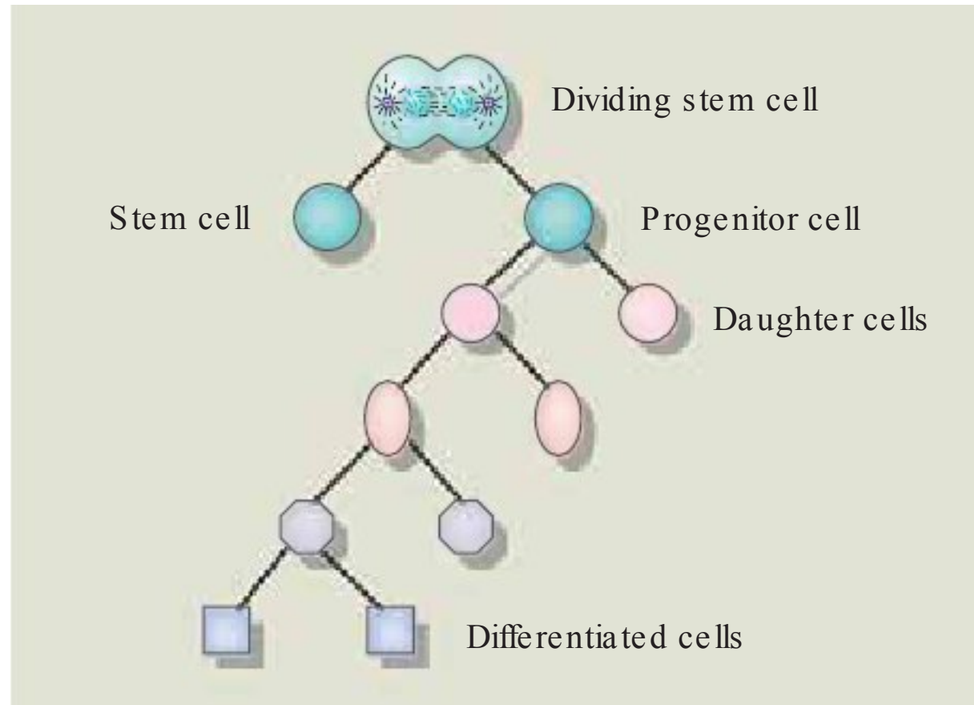

FIGURE 4-2. Mechanisms of stem cell–mediated cell replacement. Division of a stem cell with an unlimited potential for proliferation results in one daughter cell, which retains the characteristics of a stem cell, and a second daughter cell that differentiates into a progenitor or parent cell, with limited potential for differentiation and proliferation. As the daughter cells of the progenitor cell proliferate they become more differentiated, until they reach the stage where they are fully differentiated.

generated from stem cells. Stem cells are reserve cells that remain quiescent until there is a need for cell replenishment, in which case they divide, producing other stem cells and cells that can carry out the functions of the differentiated cell. When a stem cell divides, one daughter cell retains the stem cell characteristics, and the other daughter cell becomes a progenitor cell that undergoes a process that leads to terminal differentiation (Fig. 4-2).

Stem cells are characterized by three important properties: self-renewal, asymmetric replication, and differential potential.[1,2] *Self-renewal* means that the stem cells can undergo numerous mitotic divisions while maintaining an undifferentiated state. *Asymmetric replication* means that after each cell division, some progeny of the stem cell enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity. The progeny of each progenitor cell follows a more restricted genetic program, with the differentiating cells undergoing multiple mitotic divisions in the process of becoming a more mature cell type, and with each generation of cells becoming more specialized. In this way, a single stem cell can give rise to the many cells needed for normal tissue repair or blood cell production.

The term *potency* is used to define the differentiation potential of stem cells. *Totipotent stem cells* are those produced by a fertilized ovum. The first few cells produced after fertilization are totipotent and can differentiate into embryonic and extraembryonic cells. Totipotent stem cells give rise to *pluripotent stem cells* that can differentiate into the three germ layers of the embryo. *Multipotent stem cells* are cells such as hematopoietic stem cells that give rise to a family of cells, including the red blood cells and all the various types of leukocytes. Finally, *unipotent stem cells* produce only one cell type but retain the property of self-renewal.

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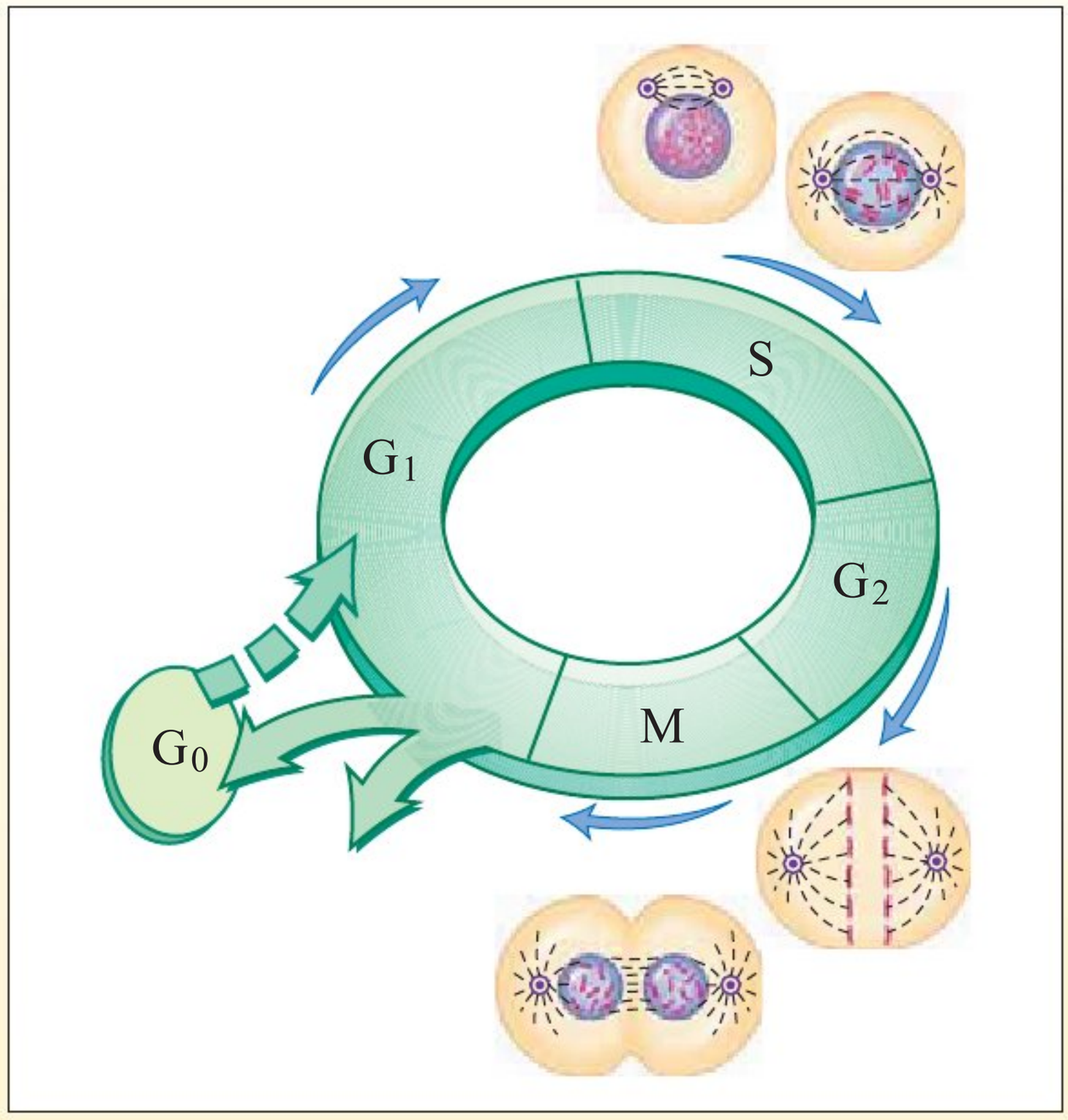
UNDERSTANDING → The Cell Cycle

A cell reproduces by performing an orderly sequence of events called the cell cycle. The cell cycle is divided into four phases of unequal duration that include the (1) synthesis (S) and mitosis (M) phases that are separated by (2) two gaps (G_1 and G_2). There is also (3) a dormant phase (G_0) during which the cell may leave the cell cycle. Movement through each of these phases is mediated at (4) specific checkpoints that are controlled by specific enzymes and proteins called cyclins.

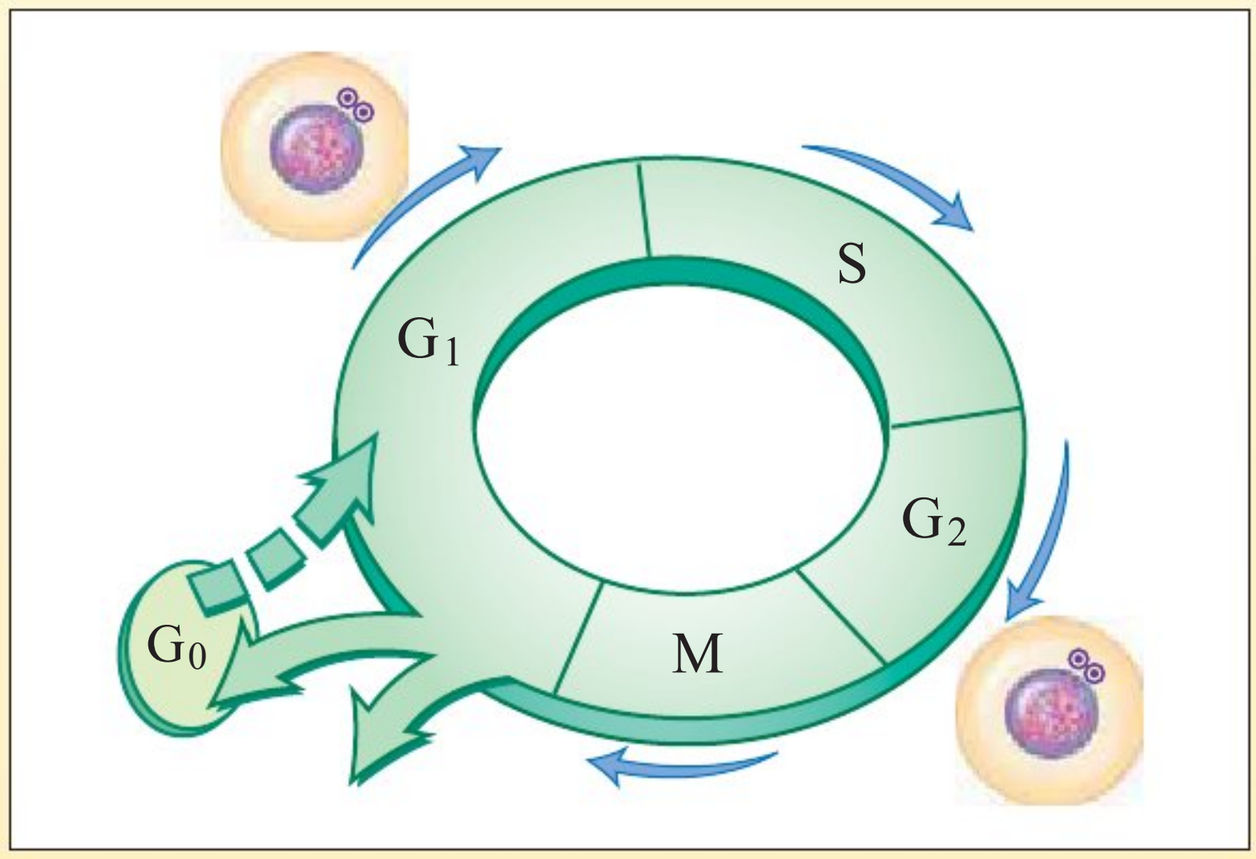
1

Synthesis and Mitosis. Synthesis (S) and mitosis (M) represent the two major phases of the cell cycle. The S phase, which takes about 10 to 12 hours, is the period of DNA synthesis and replication of the chromosomes. The M phase, which usually takes less than an hour, involves formation of the mitotic spindle and cell division with formation of two daughter cells.



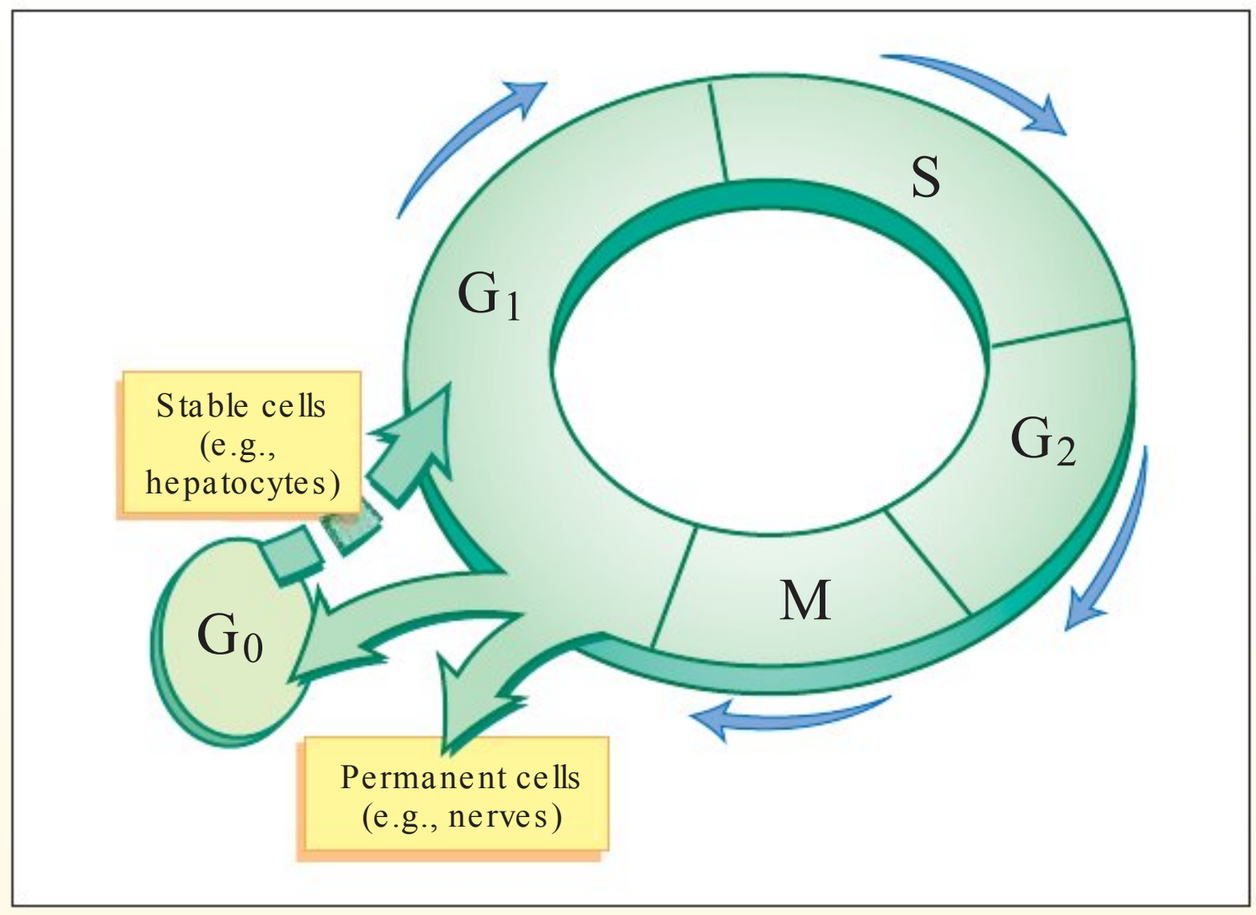
2

Gaps 1 and 2. Because most cells require time to grow and double their mass of proteins and organelles, extra gaps (G) are inserted into the cell cycle. G_1 is the stage during which the cell is starting to prepare for DNA replication and mitosis through protein synthesis and an increase in organelle and cytoskeletal elements. G_2 is the premitotic phase. During this phase, enzymes and other proteins needed for cell division are synthesized and moved to their proper sites.



3

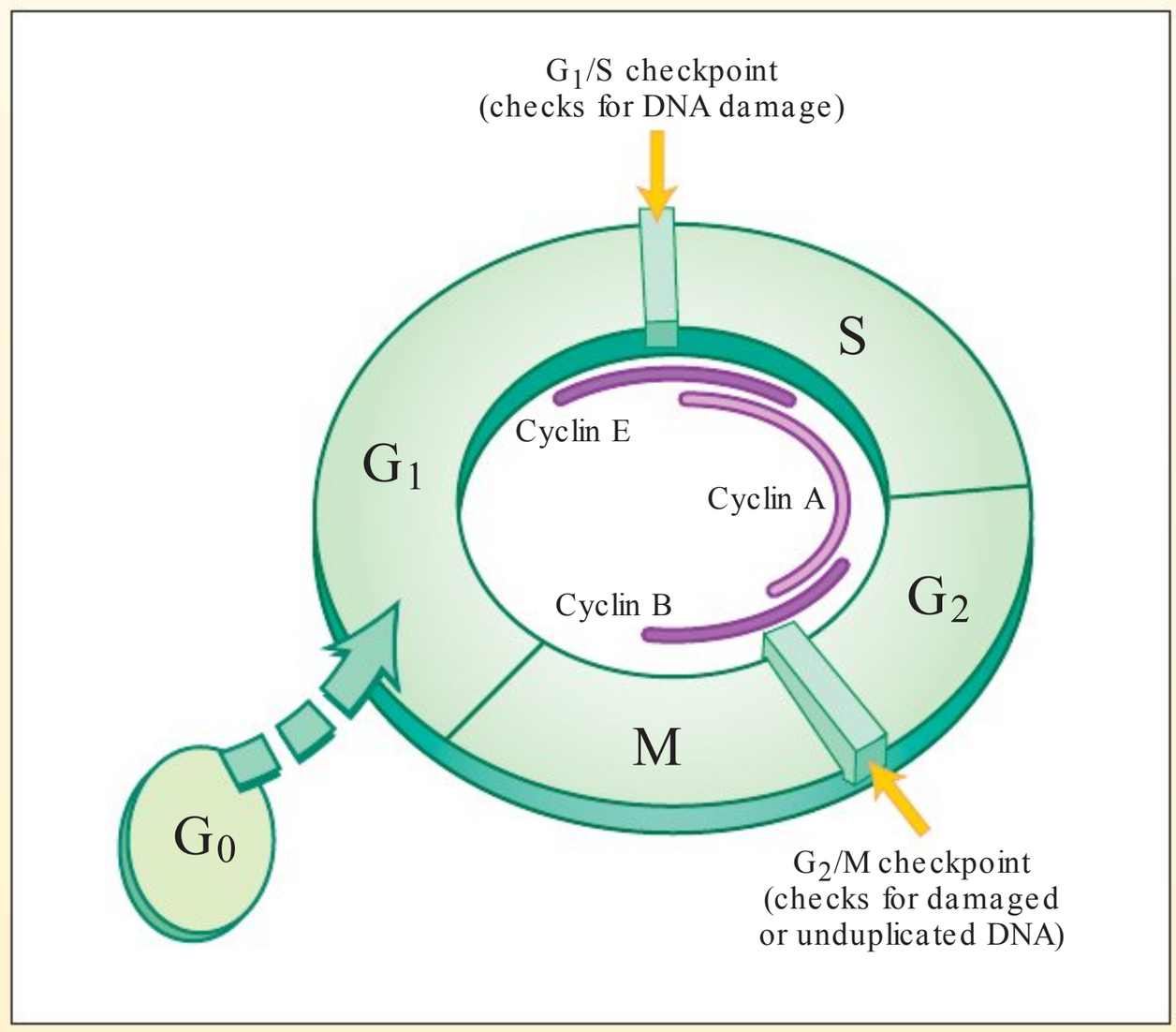
Gap 0. G_0 is the stage after mitosis during which a cell may leave the cell cycle and either remain in a state of inactivity or reenter the cell cycle at another time. Labile cells, such as blood cells and those that line the gastrointestinal tract, do not enter G_0 but continue cycling. Stable cells, such as hepatocytes, enter G_0 after mitosis but can reenter the cell cycle when stimulated by the loss of other cells. Permanent cells, such as neurons that become terminally differentiated after mitosis, leave the cell cycle and are no longer capable of cell renewal.



4

Checkpoints and Cyclins. In most cells there are several checkpoints in the cell cycle, at which time the cycle can be arrested if previous events have not been completed. For example, the G_1/S checkpoint monitors whether the DNA in the chromosomes is damaged by radiation or chemicals, and the G_2/M checkpoint prevents entry into mitosis if DNA replication is not complete.

The cyclins are a family of proteins that control entry and progression of cells through the cell cycle. They function by activating proteins called cyclin-dependent kinases (CDKs). Different combinations of cyclins and CDKs are associated with each stage of the cell cycle. In addition to the synthesis and degradation of the cyclins, the cyclin–CDK complexes are regulated by the binding of CDK inhibitors. The CDK inhibitors are particularly important in regulating cell cycle checkpoints during which mistakes in DNA replication are repaired.



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In recent years, it has become useful to categorize stem cells into two basic categories: embryonic and adult stem cells.[1,2,5,6] Embryonic stem cells are pluripotent cells derived from the inner cell mass of the blastocyst stage of the embryo. These pluripotent stem cells have the capacity to generate multiple cell lines. As mentioned earlier, unipotential stem cells are normally present in proliferative tissues and generate cell lineages specific to that tissue. It is now recognized, however, that stem cells with the capacity to generate multiple lineages are present in the bone marrow and several other tissues of adult individuals. These cells are called adult stem cells or tissue stem cells. Whether adult stem cells have a differentiation capacity similar to that of embryonic stem cells remains the subject of current debate and research.[2] Thus far, bone marrow stem cells have been shown to have very broad differentiation capabilities, being able to generate not only blood cells, but also fat, cartilage, bone, endothelial, and muscle cells.

A new field of medicine—*regenerative medicine*—is mainly concerned with the regeneration and restoration of damaged organs using embryonic and adult stem cells.[2,6,7] One of the most exciting prospects in this area is a type of stem cell therapy known as therapeutic cloning. Other potential therapeutic strategies that use stem cells involve the transplantation of stem cells into areas of injury, mobilization of stem cells from the bone marrow into injured tissues, and use of stem cell culture systems to produce large amounts of differentiated stem cells for transplantation into injured tissue.

Influence of Growth Factors

Cell proliferation can be triggered by chemical mediators including growth factors, hormones, and cytokines.[1,2,8–11] The term *growth factor* is generally applied to small proteins that increase cell size and cell division.[2] In addition to cell proliferation, most growth factors have other effects. They assist in regulating the inflammatory process; serve as chemoattractants for neutrophils, monocytes (macrophages), fibroblasts, keratinocytes, and epithelial cells; stimulate angiogenesis; and contribute to the generation of the ECM. Some growth factors stimulate the proliferation of some cells and inhibit the cycling of other cells. In fact, a growth factor can have opposite effects on the same cell depending on its changing concentration during the healing process.

Many of the growth factors are produced by leukocytes recruited to the site of injury or activated at the site by the inflammatory process. Other growth factors are produced by parenchymal cells or stromal cells in response to injury or loss. Growth factors are named for their tissue of origin (e.g., platelet-derived growth factor [PDGF], fibroblast growth factor [FGF]), their biologic activity (e.g., transforming growth factor [TGF]), or the cells on which they act (e.g., vascular endothelial growth factor [VEGF]). The sources and functions of selected growth factors are described in Table 4-1.

The signaling pathways for the growth factors are similar to those of other cellular receptors that recognize extracellular ligands. The binding of a growth factor to its receptor triggers a series of events by which extracellular signals are transmitted into the cell, leading to the stimulation or inhibition of gene expression. These genes typically have several functions—they relieve blocks on cell cycle progression (thus promoting cell proliferation), prevent apoptosis, and enhance synthesis of cellular proteins in preparation for mitosis. Signaling may occur in the cell producing the growth factor (autocrine signaling), in cells in the immediate vicinity of the cell releasing the growth factor (paracrine signaling), or in distant target cells through growth factors that are released into the bloodstream (endocrine signaling).

TABLE 4-1 Growth Factors Involved in Tissue Regeneration and Wound Healing

Growth Factor	Source	Function
Epidermal growth factor (EGF)	Activated macrophages, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; simulates keratinocyte migration and granulation tissue formation
Transforming growth factor-α (TGF-α)	Activated macrophages, T lymphocytes, keratinocytes, and many other cells	Similar to EGF; stimulates replication of hepatocytes and many epithelial cells
Transforming growth factor-β (TGF-β)	Platelets, macrophages, T lymphocytes, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; stimulates angiogenesis and production of fibrous tissue; inhibits proteinase production and keratinocyte proliferation
Vascular endothelial cell growth factor (VEGF)	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells of blood vessels
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; stimulates production of proteinases, fibronectin, and hyaluronic acid; stimulates angiogenesis and wound remodeling
Fibroblast growth factor (FGF)	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts, and many other tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates angiogenesis, wound contraction, and matrix deposition
Keratinocyte growth factor (KGF)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

tahir99-VRG & vip.persianss.ir