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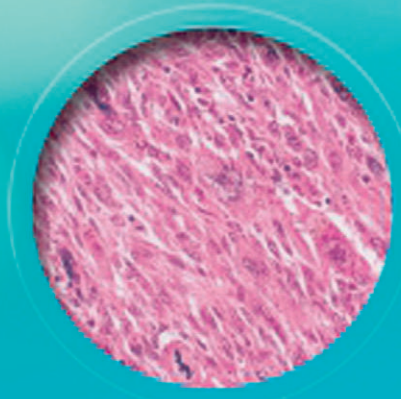

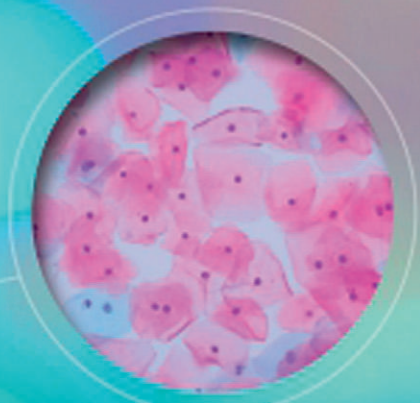

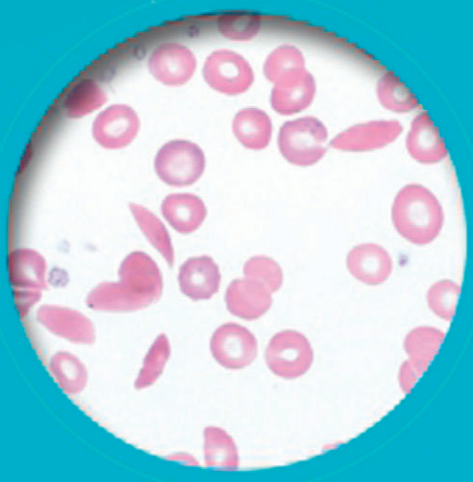

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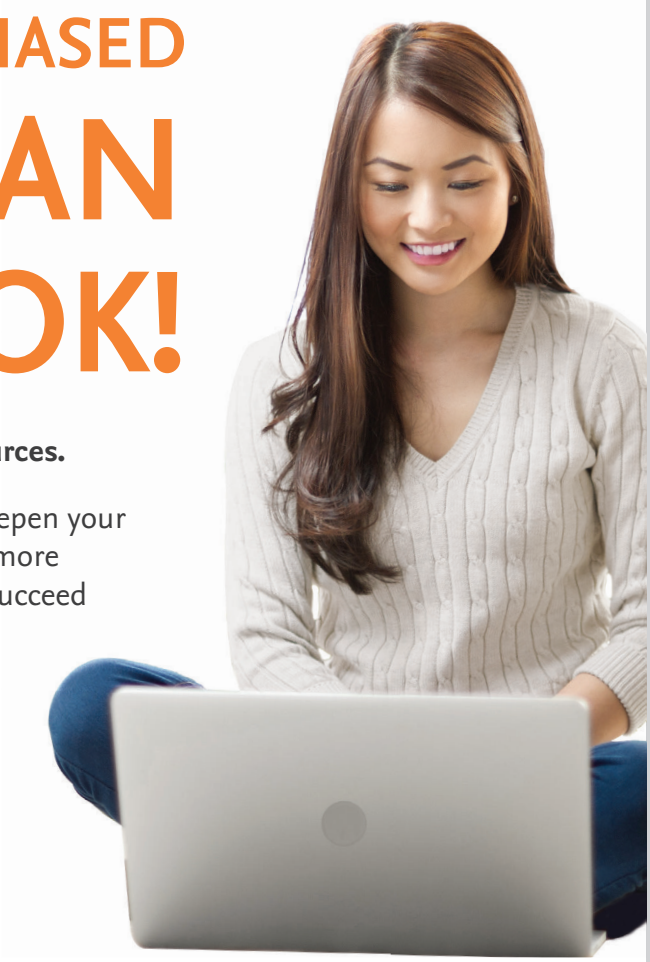

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SIXTH EDITION

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To the senior author's agathodemons, Ivana and Milena Damjanov,
and the newcomers Anabelle and Katarina Perry
with a quote from Gandhi:
"Almost anything you do will be insignificant,
but it is very important that you do it."
Optimistically, for a better and more just World.

I.D., A.M.P. and K.D.P.

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It is our pleasure to acknowledge the contributions of our St. Louis–based Elsevier technical support team who made this edition possible. Above all, our thanks go to Senior Content Development Specialist, Danielle Frazier, Project Manager, Srividhya Vidhyashankar, Senior Content Development Manager, Lisa Newton, and Senior Content Strategist, Yvonne Alexopoulos. They acted as our guardian angels, kept us on track, and supported us from the beginning to the bitter end. They also coordinated and organized anonymous external reviews from experts who helped with the previous edition.

Ivan would also like to thank his Croatian editor Ms. Andja Raič for allowing us to reproduce several figures from the book: Damjanov I, Seiwerth S, Jukić S, Nola M (editors): *Patologija,* fourth edition, Medicinska naklada, Zagreb, Croatia, 2014. These figures, listed by their numbers in the Croatian book, are as follows: Fig. 1-18, Fig. 2-11, Fig. 2-17, Fig. 2-24, Fig. 5-14, Fig. 10-2, and Fig. 14-16.

Finally, let us finish these paragraphs with a nod of appreciation to the past and future readers of this textbook and especially our colleagues, the professors who keep recommending the book to their students.

Ivan Damjanov, Anamarija M. Perry, and
Kyle D. Perry
June 1, 2020
Kansas City, Kansas, and Ann Arbor, Michigan

PREFACE

More than 25 years have passed since the first edition of this book appeared in print. The book sales and the comments made by our colleagues and by students across the country indicated that it was well received. I was most gratified by this response, and I readily accepted the invitation from the publisher to prepare subsequent editions.

The first edition that appeared in 1996 was prepared for students in allied health professions. As the popularity of the book grew, I discovered that the book was used not only by students of laboratory medicine, future nurses, and radiology technicians, but also by students preparing themselves to become pathology assistants, physician assistants, pharmacists, veterinarians, and other health care professionals. Their comments and suggestions helped me prepare the new edition, and I hope that it will meet with their approval and expectations.

Like the previous four editions, this book covers both general and systemic pathology. The material is presented in a standard manner to enable students to study efficiently and gain knowledge systematically. The book is divided into 23 chapters, grouped into two major sections: general pathology and organ system pathology. More pages and emphasis are given to systemic pathology to meet the requirements of most curricula.

Each chapter is a self-contained teaching unit. Each begins with an outline and a list of key terms and concepts. Learning objectives are provided to guide students and help them focus on the core material. Students should return to these opening pages for review after reading each chapter. Students who can discuss comprehensively, in their own words, all of the learning objectives should be assured that they know the material.

At the beginning of each chapter, students are reminded that pathologic processes occur in organs and tissues that were normal before the disease began. A brief review of the normal structure and function of each organ is included to emphasize the most important aspects of normal anatomy, histology, and physiology that are essential to an understanding of pathology. Diagrams of the normal organs are also included, and these will help students refresh their knowledge of material that was covered in anatomy and physiology courses.

This book contains so many new facts and concepts that students might easily be lost in the details. To enable students to keep their perspective, the beginning of each chapter on systemic pathology is devoted to an overview of major diseases and how they relate to the normal organ. The core information in each chapter is presented in these sections. Students are advised to keep these brief statements in mind as they study the material in greater detail later in the chapter. Students should spend as much time as possible thinking about these concepts because they are essential to an understanding of the details. These statements are the actual take-home messages that should remain with the student a long time after most of the minutiae are forgotten. Students should avoid, at any cost, memorizing details taken out of context. An understanding of general principles and concepts is encouraged.

Pathology is too vast a subject to be covered in one semester. To produce a book that could be read in a time frame mandated by most current curricula, many diseases had to be eliminated, and concentration was focused on a few salient pathologic processes and entities that could serve as prototypes or instructional paradigms. These diseases, which are discussed in detail, were chosen either because they are common and thus frequently encountered in practice or because they illustrate important principles and thus provide significant insight into the reaction pattern of an injured organ. Understanding the principles of these paradigmatic diseases will facilitate the understanding of other similar or related disorders.

Each major disease is presented in a standardized format that includes, whenever feasible, a comprehensive **D**efinition or description of basic features of a disease; discussions of **E**tiology, **P**athogenesis, **P**athology, and **C**linical features; and a brief comment about **T**herapy or prognosis. I advise students to use this approach (which I call **DEPPICT**) in their studies of pathology, as well as in their studies of clinical medicine in general. It is a didactic approach that has repeatedly proved its validity and usefulness in practice.

Because the students reading this text will practice clinical medicine rather than pathology, all of the data presented here have a clinical slant and were included with the ultimate goal of preparing students for their work with living patients and enabling them to understand various clinical aspects of specific diseases. To this end, we have included a plethora of illustrations. Colorful diagrams and photographs of pathologic lesions contain important information, and students should spend time studying them. Illustrations can reinforce the written message, and often a concept can be made more vivid with figures than with words. To reinforce the message, at the end of each chapter, students will find review questions pertaining to the main topics covered in that chapter.

Students of pathology are asked to master a new vocabulary and memorize hundreds of new words. Most of these new pathologic terms are explained when they are first mentioned in the text. Additional definitions and explanations can be found in the glossary at the end of the book.

The contemporary layout and multicolor print were designed to facilitate reading and comprehension and to keep students' attention focused on important concepts during long hours of study. To enliven the text, material of human interest was inserted in boxes titled "Did You Know?" The brief stories and curious facts presented here should serve as a reminder that, although pathology is a clinical discipline, the knowledge acquired from this book can be used not only in a medical setting but in everyday life as well.

The task of revising the original work was facilitated by the input of "users"—that is, teachers and students who sent in suggestions and pointed out typos, misspellings, and inaccuracies. Under ideal circumstances, they would all be listed, but that is almost impossible; thus, I hope that they will accept this brief acknowledgment as my heartfelt thank-you note.

In addition to making the necessary corrections, the text has been updated to include new concepts and discoveries. At the suggestion of several teachers, a set of review questions has been inserted. To stimulate students to actively use these questions, the answers have not been included in the textbook. However, the professors may find them in the *Instructor's Manual* (IM) on the Evolve website that accompanies this text. The IM also contains clinicopathologic reviews. Some professors use these clinicopathologic case studies to enrich small group discussions or as material for students' homework assignments. The IM includes matching and multiple-choice questions, as well.

For the student, we have included an anatomy review coloring book and PowerPoint® lecture notes for valuable review.

To help my fellow teachers prepare their lecture presentations, the image collection for this text can be found in the instructor resources on the text's Evolve website. These lectures contain the material in the form in which it is presented in the textbook. We have also embedded images into the PowerPoint® slides, along with wonderful video animations. The PowerPoint slides reflect my own approach to pathology, and they can be readily altered or custom adapted to reflect each professor's personal style of lecturing. This edition features Audience Response System questions embedded within the PowerPoints as appropriate. I hope that the professors and students will appreciate this novelty. This student assessment tool is in the form of questions to be used for quick feedback or the review of the material.

All of these materials can be found on the text's accompanying Evolve website: http://evolve.elsevier.com/Damjanov/pathologyHP/. I was reminded by a friend that good textbooks share some common features with the best Hollywood movies but differ from them in one important aspect: textbook sequels are almost always better than the original. I hope that I have maintained this tradition.

Ivan Damjanov

p.s. This Preface is the modified version of the previous one printed in the Fifth edition of this Textbook four years ago. It has been included here to summarize the salient features of the original Textbook, which was updated and revised to reflect the new developments and advances in the field of basic and clinical pathology, and relevant sciences such as genetics, biochemistry, immunohistochemistry and molecular biology, and above all clinical medicine.

In 2018 I have retired and became a Professor Emeritus at my University. To help me out with the revision of the Fifth edition I have therefore two collaborators, hoping that Anamarija and Kyle Perry would continue publishing the book over the coming years. I can be reached still by e-mail at idamjano@kumc.edu although I would prefer if you could send all the correspondence pertaining to the textbook to Anamarija M. Perry using her email address as follows: anaperry@med.umich.edu.

CONTENTS

INTRODUCTION

WELCOME TO THE WONDERFUL WORLD OF PATHOLOGY!

In this book, you will read about pathology—the basic medical science concerned with diseases. The term *pathology* is derived from two Greek words: *pathos*, meaning disease, and *logos*, meaning science. Thus *pathology* is the science that studies diseases. It is also a medical specialty traditionally divided into anatomic and clinical pathology. Anatomic pathology—or, as the British like to call it, *morbid anatomy*—deals with the dissection and microscopic examination of human tissues removed from cadavers at postmortem autopsies or from biopsies taken from living patients to diagnose tumors and other diseases. Clinical pathology, on the other hand, is a vast field that includes medical chemistry, microbiology, immunopathology, hematopathology, and blood banking. It is therefore also called *laboratory medicine*. All of you will interact with and come to know pathologists, and some of you will work in pathology laboratories. To assist you in becoming knowledgeable of and conversant in pathology, this book is presented to you in the hope that it will provide you with the medical knowledge essential for the understanding of diseases.

The primary goal of this book is to teach you the basic concepts underlying various pathologic processes. You will study the *pathogenesis* of diseases, learn their mechanisms, and understand how they develop. You will learn the *etiology* of pathologic changes and understand the causes of many diseases. However, it is important for you to know that, although many diseases are well delineated, such as cancer and AIDS, others are still shrouded in mystery and only poorly understood.

You will be shown gross and microscopic specimens of human organs and tissues affected by various diseases in order to visualize the *morphology* of various lesions. These pathoanatomic facts that you learn will be correlated with biochemical and immunologic findings, as well as with the clinical symptoms with which a specific disease presents in the living patient. Through *clinicopathologic* correlations, you will see how important the understanding of pathology is for your future medical practice.

Some of you will be caring for living patients and will encounter pathology every day in different guises. Others will be working in laboratories examining pathologic specimens on a daily basis. Nonetheless, all of you will be involved with people, and to understand and fully appreciate their problems, you will have to understand pathology. Why? Because pathology is the basis of all medical practice. Dr. William Osler, the famous clinician who worked in the great hospitals of Baltimore, Philadelphia, and Boston at the turn of the twentieth century, noted that our clinical practice is only as good as our understanding of pathology. This adage is the motto of our textbook. Remember that you are laying the scientific foundations of your future medical career. Be sure that they are solid.

In the end, you will recall that the greatest pleasure from having done a job well stems from having done it at all. Nothing worthwhile ever comes easily. Persevere and your efforts will be rewarded.

Good Luck and Enjoy Your Studies

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1

Cell Pathology

OUTLINE

LEARNING OBJECTIVES

After reading this chapter, the student should be able to:

1. Describe the essential components of a typical cell and its functions.
2. Explain homeostasis and the integrated response of the cell to external stimuli.
3. Define reversible cell injury.
4. Explain the cytoplasmic changes in reversible cell injury and the concept of hydropic change.
5. Compare and contrast reversible and irreversible cell injuries.
6. List the most important causes of cell injury.
7. Describe three types of cell adaptations.
8. Give three examples of atrophy.
9. Define and explain hypertrophy and hyperplasia and give appropriate examples of each.
10. Compare and contrast metaplasia and dysplasia and give appropriate examples of each.
11. Define various forms of intracellular accumulation.
12. Explain the pathogenesis of fatty liver.
13. Explain the significance of cellular aging.
14. Explain the concept of brain death.
15. Compare the two forms of cell death: necrosis and apoptosis.
16. List examples of coagulative, liquefactive, caseous, and enzymatic necrosis.
17. Explain the difference between dystrophic and metastatic calcification.

KEY TERMS AND CONCEPTS

Adaptations
Aging
Anoxia
Anthracosis
Apoptosis
Atrophy
Calcification
Cytoplasmic organelles
Cytoskeleton
Death
Gangrene
Golgi apparatus
Hemosiderin
Homeostasis
Hyaloplasm
Hydropic change
Hyperplasia
Hypertrophy
Hypoxia
Intracellular accumulations

Lipid accumulation
Lysosomes
Metaplasia
Mitochondria
Necrosis
Nucleus
Oxygen radicals
Plasma membrane
Ribosomes
Rough endoplasmic reticulum (RER)
Smooth endoplasmic reticulum (SER)

The foundation of modern pathology can be traced back to the nineteenth century, when German scientists realized that the cell represents the basic functional unit of the body and that all diseases can be related to disturbances in cell function. Rudolf Virchow (1821–1902), a German scientist, first introduced the concept of cellular pathology and is thus considered the father of modern pathology.

The concepts of cellular pathology have been expanded on and modified since Virchow's time, but most remain unchallenged. Today, we know that cells consist of smaller functional units and cellular organelles, which can be seen under an electron microscope. Organelles consist of molecules that can be further dissected and studied by using the techniques of molecular biology. These research endeavors have laid the groundwork for the field of *molecular pathology,* a science that will encompass all living phenomena and provide explanations for pathologic processes at the level of the most basic units, which comprise all living things: subatomic particles, atoms, and molecules. However, until this longtime goal of pathologists becomes a reality, we limit our discussions to cells *(cell pathology),* tissues *(histopathology),* and organs *(organ pathology).*

STRUCTURE AND FUNCTION OF NORMAL CELLS

Almost all normal cells of the human body have some common features and consist of the same basic components. These include the nucleus, the cytoplasm, and the cell (plasma) membrane (Fig. 1.1).

Nucleus

All human cells, except the erythrocytes and platelets, need a **nucleus** for survival. The nucleus is the essential component of most living cells. It consists of nucleic acids, such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and nuclear proteins. In resting cells, these components are arranged into aggregates known as *chromatin* and a specialized organelle composed primarily of RNA known as the *nucleolus.* In the dividing of cells—that is, during *mitosis*—the chromatin is restructured, and the strands of DNA condense into *chromosomes.* The resting cells have a nuclear membrane, which delimits the nucleus from the cytoplasm. This membrane disintegrates in mitosis and reappears after mitosis is completed.

The DNA of the nucleus contains essential genetic material that is identical for all somatic cells that form the various tissues and organs of the body. This genetic material consists of genes that are differentially expressed in tissues and organs. Differential expression of genes allows the cells to assume unique features in tissues and organs and to perform specialized functions. Such cells are called *differentiated,* in contrast to embryonic cells, which have not undergone specialization and are therefore termed *undifferentiated.*

The genetic information encoded in DNA is transcribed into nuclear RNA. From nuclear RNA, the message is transmitted by transfer RNA (tRNA) and messenger RNA (mRNA) into the cytoplasm (Fig. 1.2). The ribosomal RNA (rRNA) serves as a template for translating the genetic messages into *amino acids,* which are assembled into *polypeptides* and *proteins.* Protein synthesis is essential for maintenance of life. Proteins are needed for cellular growth, replication, metabolism, respiration, and other essential functions. Proteins also act as structural elements, maintaining the cell's shape and the internal organization of the cytoplasm. None of these elementary functions (and many others that are mentioned later) would be possible without the nucleus, which acts as the main overseer of all critical cytoplasmic events.

Cytoplasm

All cells have a cytoplasm, but the amount of cytoplasm and its structure vary from one cell to another. In embryonic cells, the cytoplasm is scant and contains few distinct components called *organelles.* In specialized, highly differentiated cells, such as liver or kidney cells, the cytoplasm is more abundant and is replete with organelles.

The principal **cytoplasmic organelles** are the *mitochondria, ribosomes, endoplasmic reticulum, Golgi apparatus,* and *lysosomes.* In addition to these, some cells have organelles for

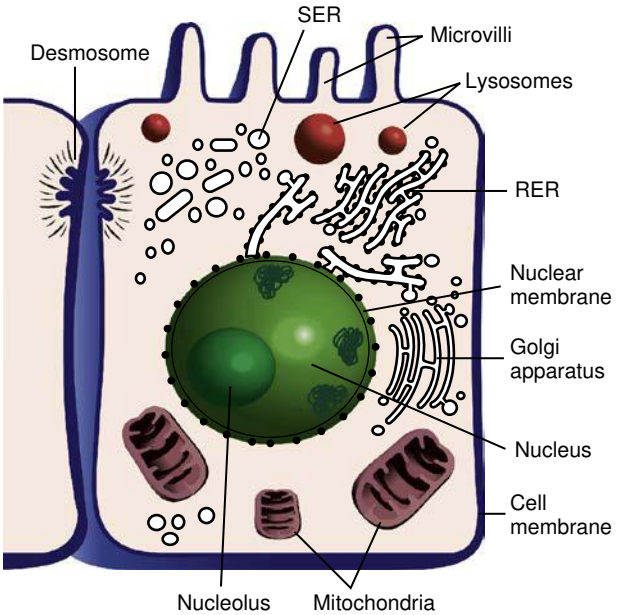


FIG. 1.1 Normal cells have a nucleus and a cytoplasm. On the outside, the cell is delimited by a plasma membrane. In the cytoplasm, there are organelles, such as mitochondria, smooth and rough endoplasmic reticulum (SER and RER, respectively), the Golgi apparatus, and lysosomes.

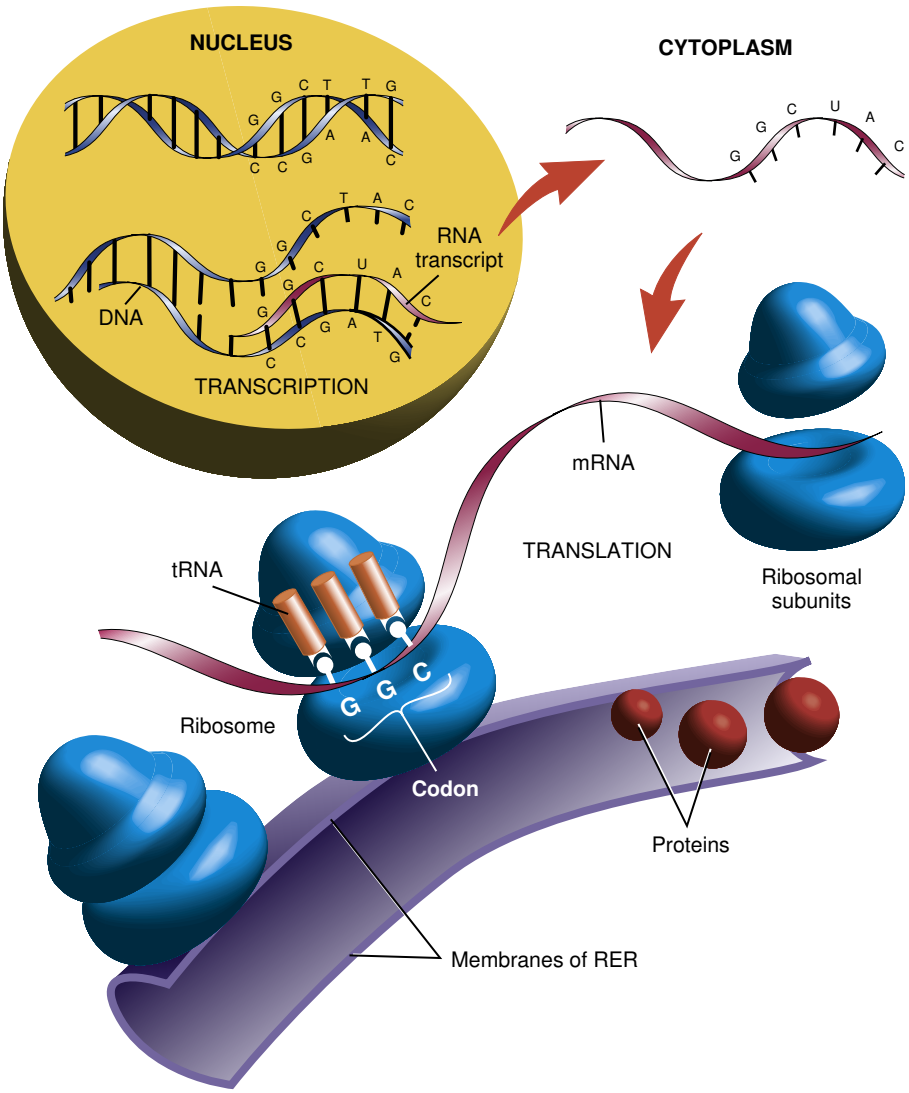


FIG. 1.2 Transcription and translation by ribonucleic acid (RNA) of the genetic code stored in the deoxyribonucleic acid (DNA) leads to protein synthesis on ribosomes. *mRNA,* Messenger RNA; *RER,* rough endoplasmic reticulum; *tRNA,* transfer RNA.

specialized functions. For example, muscle cells have myofilaments composed of actin and myosin, which are essential for contraction; glandular cells have secretory granules, which contain enzymes or mucus destined for excretion. Furthermore, it is important to note that the cytoplasmic ground substance of all cells consists of an amorphous matrix, called *hyaloplasm,* and a fibrillar meshwork, called *cytoskeleton.* Each cell is also enclosed by an outer *plasma membrane,* which forms the border between the cytoplasm and the extracellular space.

Mitochondria

Mitochondria are cytoplasmic organelles involved primarily in the generation of energy (see Fig. 1.1). Hence, mitochondria contain *oxidative enzymes* (e.g., cytochrome oxidase) that participate in cellular respiration and in the formation of energy-rich compounds, such as adenosine triphosphate (ATP). Because this process uses oxygen, it is called *oxidative phosphorylation.* ATP generated by mitochondria is essential for all other cellular functions. Cells with complex functions, such as liver cells and nerve cells, require a considerable amount of energy and therefore contain numerous mitochondria. By comparison, undifferentiated cells, including many malignant tumor cells, have few mitochondria.

Ribosomes

Ribosomes are small granules composed of RNA. They may be arranged into aggregates that float freely in the cytoplasm, called *polysomes* or *free ribosomes,* or they may be attached to the membranes of the **rough endoplasmic reticulum (RER)**. The ribosomes are involved in protein synthesis. Structural proteins and enzymes needed for the maintenance of basic cell functions ("proteins for internal purposes") are synthesized on the free ribosomes. Those intended for excretion ("export or luxury proteins") are synthesized on the RER and discharged from cells through the cisternae lined by the membranes of the RER.

Endoplasmic Reticulum

The endoplasmic reticulum is a meshwork of membranes that is continuous with the outer plasma membranes on one side and the nuclear membrane on the other. With the use of electron microscopy, one can distinguish two forms of

endoplasmic reticulum: the RER and the **smooth endoplasmic reticulum (SER)** (see Fig. 1.1).

As stated earlier, the RER is the site of *protein synthesis* for export and secretion. Cells producing large amounts of proteins for export have a well-developed RER. For example, liver cells, which synthesize blood proteins (e.g., albumin and the blood clotting factors), and plasma cells, which synthesize immunoglobulins, contain prominent stacks of RER.

The SER has complex metabolic functions, the most important of which are the *catabolism* (i.e., metabolic degradation) of drugs, hormones, and various nutrients and the *synthesis of steroid hormones.* To perform these functions, liver cells have a well-developed SER, which takes part in the metabolic degradation, inactivation, or activation of many chemicals, including drugs and hormones. Likewise, hormone-secreting gonadal cells of the testes and the ovaries, and the adrenocortical cells that synthesize steroid hormones (e.g., estrogens, androgens, and corticosteroids) also have a prominent SER.

Golgi Apparatus

The **Golgi apparatus** is a synthetic organelle composed of tubules and flattened cisternae adjacent to the nucleus (see Fig. 1.1). Many proteins synthesized in the endoplasmic reticulum pass through the Golgi apparatus, where they are biochemically modified before being packaged into secretory granules or lysosomes budding from the cisternae of this organelle. Proteins to be incorporated into the internal cell membranes (e.g., endoplasmic reticulum) or the outer plasma membrane are also glycosylated in the Golgi apparatus.

Lysosomes

Lysosomes are membrane-bound digestive cytoplasmic organelles that are rich in lytic enzymes. They originate as small vesicles budding from enzymes on the lateral sides of the Golgi apparatus (Fig. 1.3). These *primary lysosomes* contain acid hydrolases, which are digestive enzymes that are maximally active in an acidic milieu (i.e., at low pH levels). Under normal circumstances, the lytic enzymes are tightly enclosed by a lysosomal outer membrane and do not harm the cell. Even if some lysosomal content is spilled into the cytoplasm, the acid hydrolases would cause little damage in normal cytoplasm, which has a neutral pH. However, if the cell is injured and the pH of the cytoplasm becomes acidic, enzymes released from lysosomes could cause damage, as we will see in the section on cell injury.

The primary lysosomes fuse with other cytoplasmic vesicles to form *secondary lysosomes.* Typically, they fuse with the absorptive vesicles originating from the invaginated plasma membrane to form secondary lysosomes, which are also called *heterophagosomes.* Secondary lysosomes that are involved in the digestion of a cell's own organelles are called *autophagosomes.* The digestive enzymes in secondary lysosomes degrade the material enclosed within its membrane. The metabolites obtained through this intracellular digestion are reused within the cell's cytoplasm. The undigested residues are extruded from the cytoplasm into the extracellular spaces by a process called *exocytosis.* Some of the undigested material, mostly complex lipids derived from cell membranes, may remain within the cytoplasm as "residual bodies." These residual bodies typically contain a lipid-rich brown pigment known as *lipofuscin. Lipofuscin* is also known as the "brown pigment of aging" because it is commonly found in aging cells. With aging, all cellular processes become less efficient. Energy-dependent processes, such as lysosomal digestion and exocytosis, are especially affected. Therefore, cells in an old organism contain more lipofuscin than those in a metabolically active, more vigorous, young body.

The function of lysosomes and the formation of phagocytic vacuoles are well controlled in healthy cells. Most important, the cells must control the inadvertent leakage of lysosomal enzymes into the hyaloplasm because these enzymes could damage other organelles. Formation of autophagosomes and the orderly removal of worn out organelles are also well regulated in healthy cells. In damaged or abnormal cells, autophagy may escape control and lead to cell destruction ("cell death by autophagy").

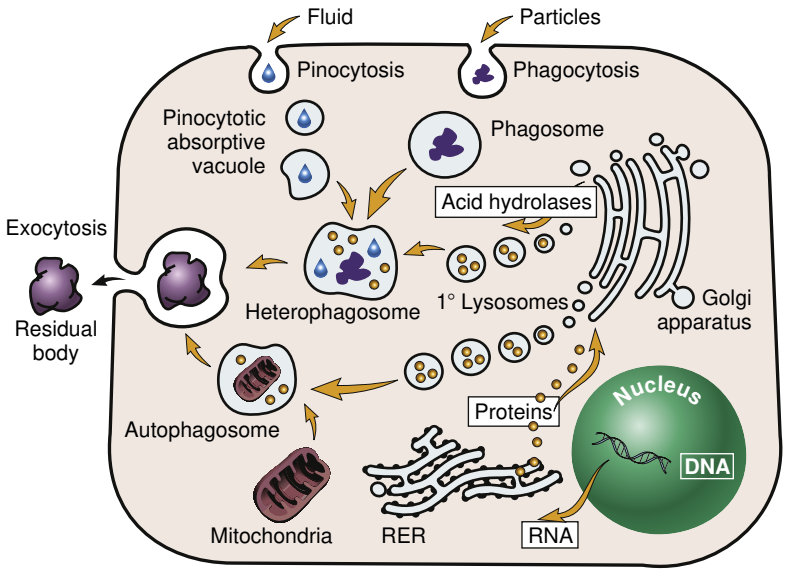


FIG. 1.3 Lysosomes. Primary (first-degree) lysosomes, which originate from the Golgi apparatus, give rise to heterophagosomes and autophagosomes. Undigested material in phagosomes is extruded from the cell or remains in the cytoplasm as lipofuscin-rich residual bodies. *RER,* Rough endoplasmic reticulum.

Hyaloplasm and cytoskeleton

The **hyaloplasm**, which is the ground substance of the cytoplasm, has no distinct structure and appears as an "empty" space on electron microscopic studies. Biochemically, the hyaloplasm consists predominantly of water but also contains minerals, proteins, carbohydrates, and lipids, which keep its osmolarity constant. The hyaloplasm is the fluid portion of the cell that contains the organelles. In between the organelles, the hyaloplasm is traversed by a network of filaments that form the **cytoskeleton**. Three types of filaments are recognized: *microfilaments* composed of actin and myosin and measuring 5 nm in diameter; *microtubules,* which are 22-nm thick and composed of tubulin; and *intermediate filaments,* named so because their diameter (10 nm) is intermediate between those of microfilaments and microtubules.

The function of the cytoskeleton is to maintain cell shape and to enable the cell to adapt to external mechanical pressure. Cytoskeletal filaments are important for cell movement and the traffic of organelles in the cytoplasm. Microtubules also form the mitotic spindle during cell division.

Plasma Membrane

The **plasma membrane** forms the outer surface of the cell (Fig. 1.4) and is composed of proteins, lipids, and carbohydrates arranged in a polarized complex bilayer that has an internal surface and an external surface. On the internal side, the plasma membrane is in continuity with the membrane of the endoplasmic reticulum. Invaginations of the plasma membrane give rise to endocytic vesicles, mediating the intake of fluids *(pinocytosis)* or particulate matter *(phagocytosis)* (see Fig. 1.3).

The external surface of the plasma membrane serves as the site of contact between one cell and another and also between the cell and the environment. This interaction is maintained through the action of specialized portions of the cell membrane that serve as receptors, adhesion molecules, transducers of signals, or metabolic channels. The complexity of the plasma membrane varies from one cell type to another.

The plasma membrane is a living structure that is maintained by active expenditure of energy and a constant supply of ATP. The structural integrity of the plasma membrane is a prerequisite for the maintenance of all essential cellular functions. Rupture or major damage of the cell membrane that cannot be repaired invariably leads to *cell death.*

Integration and Coordination of Cell Functions and Response to Injury

Integration of Function of Normal Cells

Cells of the human body are arranged into tissues, and these tissues form organs. Organs are part of organ systems, all of which function in concert to meet the basic vital requirements of the body and enable the body to perform many complex functions. The integration of cells, tissues, and organs into functional units

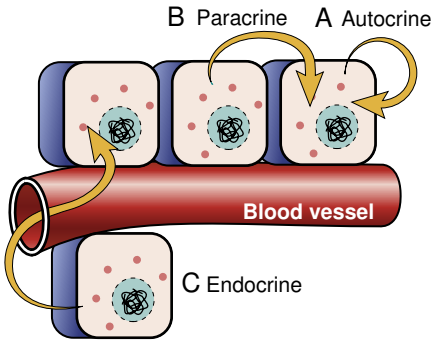


FIG. 1.5 Integration of cell functions occurs through interaction with other cells in the body. *A,* Autocrine stimulation: secretions from the cell may attach to the cell's own surface receptors, providing autocrine stimulation. *B,* Paracrine stimulation: closely adjacent cells act on each other. *C,* Endocrine stimulation: hormones secreted by endocrine cells reach target cells via blood.

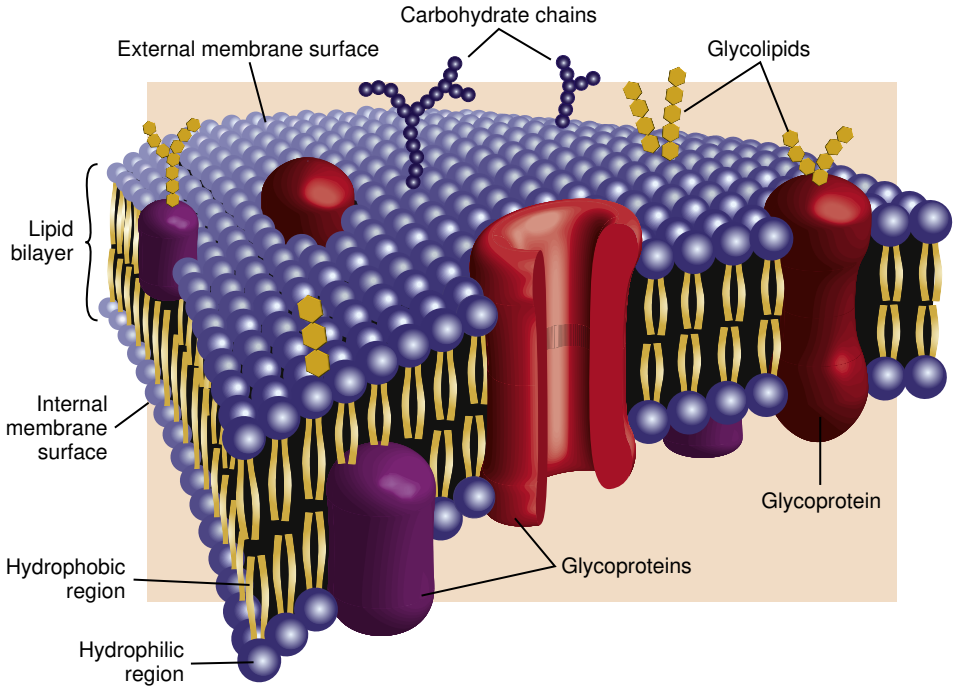


FIG. 1.4 Plasma membrane. The bilipid layer also contains proteins and carbohydrates, which perform complex functions and serve as receptors, adhesion molecules, and transducers of signals.

is achieved through several mechanisms, best illustrated by the response of cells to growth-stimulating factors (Fig. 1.5).

The simplest form of integration occurs at the level of the single cell. For example, T lymphocytes secrete *cytokines,* which stimulate the growth of other cells, such as fibroblasts, but at the same time act on the very cells that produced them—that is, act as their own growth factors. This self-stimulation, known as *autocrine stimulation,* is feasible because T lymphocytes have surface receptors for their own secretory products.

More complex integration of cells requires transmission of hormonal signals from one cell to another. This is done through the release of mediators from one cell and their uptake by another, a process called *paracrine stimulation.* Paracrine stimulation is typically mediated by biogenic amines (e.g., epinephrine) and neuropeptide hormones (e.g., glucagon and gastrin). The best example is the release of hydrochloric acid from gastric chief cells under the influence of gastrin. Gastrin is a hormone released by neuroendocrine G cells, which are in the gastric mucosa and are adjacent to the hydrochloric acid–secreting chief cells. Gastrin extruded from neuroendocrine cells attaches to receptors on the chief cells, triggering hydrochloric acid release.

Endocrine stimulation is achieved by hormones released into the blood circulation. This is clearly a higher form of integration of cell functions because it may involve cells in several anatomically distinct organs. For example, insulin, secreted by the islet cells of the pancreas, affects the liver, muscle, fat cells, and many others. A similarly high level of integration of cell functions can be achieved through *neural stimulation.* The central and autonomic nervous systems are the ultimate coordinators of body functions.

From the point of view of cell pathology, each cell is best considered a distinct functional unit, in a defined *internal milieu,* formed by intercellular fluids. To maintain its life and normal functions, the cell must be in homeostasis with its environment. **Homeostasis** is defined as the state of balance between opposing pressures operating in and around a cell or a tissue. From the environment, the cell receives nutrients, oxygen, water, and essential minerals; it generates energy by burning some of the calories derived from the nutrients. By maintaining its own integrity, the cell contributes to the stability of the internal milieu. A normal internal milieu is essential for the normal functioning of the cell; likewise, the milieu remains normal only if all the cells are functioning properly.

The supply of essential minerals and of the water in which these minerals are dissolved is also of paramount importance for the maintenance of homeostasis. The essential minerals include sodium, chloride, potassium, calcium, and iron. Magnesium, zinc, copper, and selenium—known as *oligominerals* because they are needed in minute amounts—are essential for the functioning of several important enzymes.

The life of a cell is critically dependent on a constant supply of oxygen and nutrients, provided to cells by the circulation of the fluids that surround cells. At the same time, the circulating fluids carry away the degradation products of cellular metabolism.

When equilibrium between the cell and its environment is achieved and maintained, the cell is said to be in a *steady state*

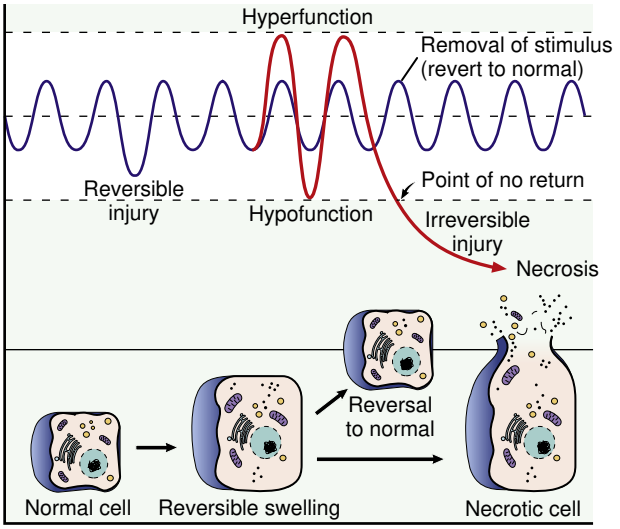


FIG. 1.6 Steady state. The range of the steady state is determined by the reactivity of each cell and the ability of the cell to respond to increased demands or stimuli. The increased or decreased functional adaptations are reversible. However, once response passes the point of no return, the cell injury becomes irreversible.

(Fig. 1.6). If external demands increase, the cell may shift its metabolism to a higher level, achieving a new steady state; similarly, the cell may shift to a lower steady state if external demands decrease. In both instances, the adaptation is temporary, and the cell may revert to the original steady state after external demands cease. However, if external demands exceed the capacity of the cell to adapt, a permanent disequilibrium may ensue. Cell that has passed the critical *point of no return* becomes irreparably damaged and dies. Cell death is called *necrosis.*

Reversible Cell Injury

If the adverse environmental influences evoke a cellular response that remains within the range of homeostasis, the changes produced are called *reversible cell injury.* Cessation of injury results in the return of the cell to its original steady state.

Reversible cell injury is typically mild or short lived. It can be induced by exposure to toxins in low concentrations. Brief *hypoxia* or *anoxia,* such as a decrease in oxygen supply or complete deprivation of oxygen, respectively, can induce the same changes and are best described as swelling of the cytoplasm and cytoplasmic organelles (Fig. 1.7).

Cellular swelling, known as *vacuolar* or **hydropic change**, reflects increased influx of water into the cytoplasm. The water crosses the plasma membrane, enters the hyaloplasm, and accumulates within the mitochondria ("mitochondrial swelling") and membrane-bound vacuoles formed by the invagination of the plasma membrane and the endoplasmic reticulum. This vacuolization of the cytoplasm is best appreciated with electron microscopy. When the insult is over, the cell recovers by pumping out the water, thereby reverting to its original steady state.

The pathogenesis of cellular swelling is relatively easy to explain in terms of altered permeability of the plasma

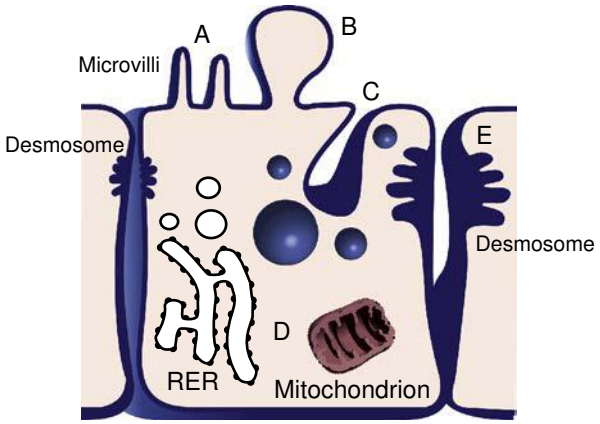


FIG. 1.7 Cellular swelling. ***A,*** Normal microvilli. ***B,*** Swollen microvilli are the consequence of an influx of water in the cytoplasm. ***C,*** Invagination of the cell membrane gives rise to fluid-filled cytoplasmic vacuoles that account, in part, for the changes known as *vacuolar* or *hydropic*. ***D,*** Swollen mitochondria and dilated rough endoplasmic reticulum (RER) are also a part of vacuolar degeneration. ***E,*** Swollen cells lose contact with adjacent cells at the site of cell-to-cell junctions, such as desmosomes.

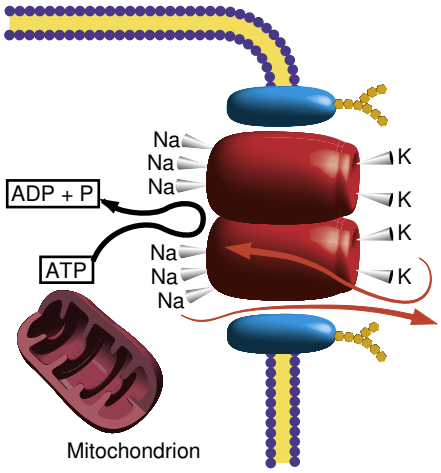


FIG. 1.8 Plasma membrane semipermeability is a function of the Na^+/K^+–ATPase pump. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *P,* phosphorus.

membrane. The plasma membrane is selectively permeable and maintains a concentration gradient of minerals—primarily sodium (Na^+), potassium (K^+), and chloride (Cl^-)—inside and outside of the cell. This is achieved through the function of the Na^+/K^+ adenosine triphosphatase (ATPase) pump, which constantly pumps Na^+ ions from the cytoplasm into the extracellular space (Fig. 1.8). The pump keeps the intracellular concentration of potassium high. Cl^- generally follows the Na^+ ions and, accordingly, the concentration of Na^+ and Cl^- is higher in the extracellular space than in the cytoplasm, whereas the concentration of K^+ is higher inside than outside of the cell. Because the ATPase is fueled by high-energy compounds, such as ATP, anoxia or any other form of energy deprivation causes dysfunction of this enzyme. Without a functioning ATPase, the cell membrane loses its capacity to maintain the gradient of intracellular and extracellular minerals. A high concentration of sodium in the extracellular space results in an influx of sodium and chloride into the cell. This is followed by an influx of water and concomitant cellular swelling. After ATPase function is restored, the sodium and the water are pumped out of the cell and the swelling disappears.

Reversible cell injury is associated with many functional changes, ultimately leading to hydropic change and cell swelling (Fig. 1.9).The most important changes are as follows:

- *Reduced energy production.* Swollen mitochondria generate less energy. Instead of oxidative ATP production, the cell reverts to the less efficient anaerobic glycolysis, which also results in excessive production of lactic acid and a drop in cytosolic pH.
- *Decreased protein synthesis and enzyme activity.* The pH of the cell becomes acidic, further slowing down the entire cell metabolism. The consequent dilation and fragmentation of the RER and the loss of membrane-attached ribosomes ("degranulation of the RER") result in decreased protein synthesis.
- *Increased autophagocytosis.* Damaged organelles and their fragments are removed into lysosomes, which act as autodigestive vacuoles. Hydrolytic lysosomal enzymes may leak into the cytoplasm, contributing to the damage of other cellular components, which are then taken up into the lysosomes and digested.

Irreversible Cell Injury

Cells exposed to heavy doses of toxins, anoxia, severe or prolonged hypoxia, or other overwhelming insults cannot recover, hence the term *irreversible cell injury.* Morphologically, irreversible cell injury may be recognized by typical changes in the nucleus or by a loss of cell integrity and rupture of the cell membrane. Functional tests will show that the nuclear function has been disrupted, that the energy production within mitochondria has fallen below the essential minimum and cannot be restored, and that plasma membrane function is irrevocably lost.

Irreversible cell injury is characterized by typical ultrastructural changes, many of which can be recognized with light microscopy. The most characteristic are *nuclear changes;* clearly, without a viable nucleus, the cell cannot survive. Microscopically, damage to the nucleus can appear in three forms:

- *Pyknosis,* marked by condensation of the chromatin
- *Karyorrhexis,* characterized by fragmentation into smaller particles, colloquially called *nuclear dust*
- *Karyolysis,* involves dissolution of nuclear structure and lysis of chromatin by enzymes such as deoxynuclease (DNase) and ribonuclease (RNase) (Fig. 1.10)

Dead cells release their contents into the extracellular fluid, whereby they reach the circulation. Cytoplasmic enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or lactate dehydrogenase (LDH), which are released from damaged cells, can be measured in blood and are clinically useful signs of cell injury. Levels of AST, ALT, and LDH are typically elevated in the serum of patients with myocardial infarct or viral hepatitis. These enzymes are widely

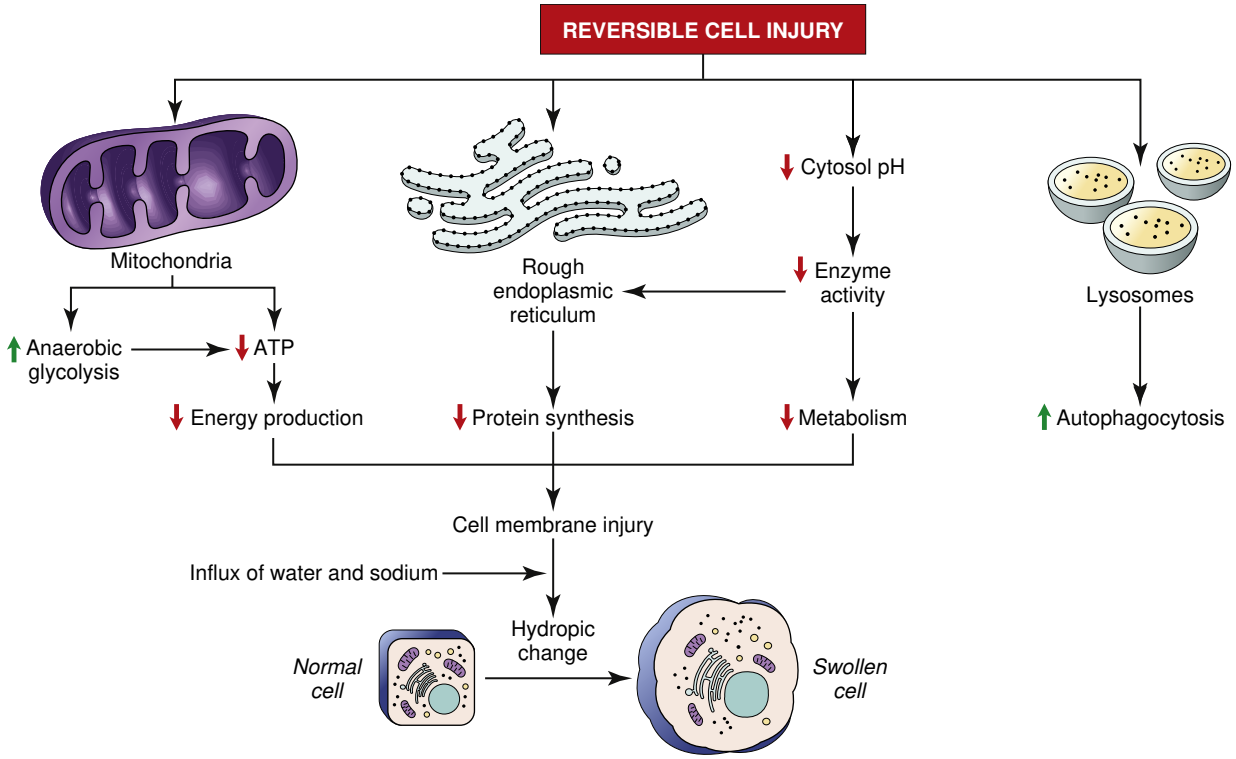


FIG. 1.9 Cytoplasmic changes during reversible cell injury. *ATP,* Adenosine triphosphate.

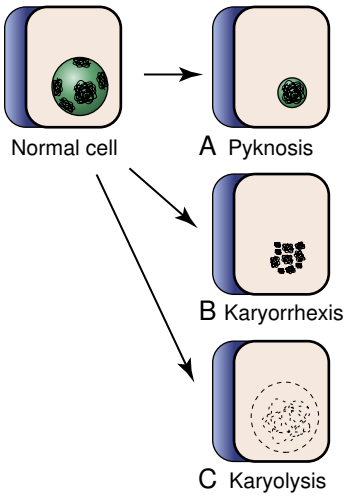


FIG. 1.10 Nuclear changes during irreversible cell injury. *A,* Pyknosis (condensation of chromatin). *B,* Karyorrhexis (fragmentation of nucleus). *C,* Karyolysis (lysis of chromatin).

used as clinical laboratory evidence of cell injury and cell death.

Causes of Cell Injury

Cell injury may be induced by numerous pathogenetic mechanisms, the most important of which are hypoxia, toxins, microbial pathogens, endogenous mediators of inflammation and immune reactions, and genetic and metabolic disturbances. Depending on the severity of the insult, the cell injury may be reversible or irreversible. The most important causes of cell injury, together with clinical examples, are listed in Table 1.1.

Hypoxia and anoxia. **Hypoxia**, a reduced availability of oxygen, and **anoxia**, the complete lack of oxygen, are among the most important and most common causes of cell injury. Oxygen is essential for cellular respiration, and lack of oxygen results in cessation of energy production. Without energy, the cell cannot survive. Short-term anoxia induces reversible cell injury. However, if the oxygen supply is interrupted for long periods, the injury becomes irreversible.

Some cells are more sensitive to hypoxia and anoxia compared with others. For example, brain cells cannot survive without oxygen for more than a few minutes, heart cells can survive 1 to 2 hours, and kidney cells can survive for several hours. Connective tissue cells are most resistant to anoxia; indeed, viable fibroblasts can be obtained from a cadaver even 1 day after death.

In clinical practice, hypoxia or anoxia may occur under many circumstances, including the following examples (Fig. 1.11):

- Obstruction of the airways (e.g., suffocation by a foreign body in the larynx)
- Impeded passage of oxygen across the respiratory surfaces of the lung (e.g., pneumonia)
- Inadequate transport of oxygen in the blood (e.g., low red blood cell count, "anemia")
- Blockade of cellular respiration and oxidative phosphorylation (e.g., cyanide poisoning)

Short-lived reversible cell injury, secondary to hypoxia, may be repaired completely by reoxygenation. For example, a patient who has a heart block and loses consciousness as a

TABLE 1.1 Major Causes of Cell Injury

Cause	Pathogenesis	Clinical Examples
Hypoxia and anoxia	Circulatory disturbances Inadequate oxygen intake	Myocardial infarction Strangulation
Toxin	Direct toxicity Indirect toxicity	Mercury poisoning Carbon tetrachloride poisoning
Microbes	Bacterial exotoxins Direct (viral) cytopathic effect Indirect (immune-mediated cytotoxicity)	Food poisoning Viral infection
Inflammation and immune reactions	Action of cytokines and complement	Autoimmune diseases
Genetic and metabolic disorders	Disruption of metabolic pathways	Lysosomal storage disease (e.g., Tay-Sachs disease)
	Abnormal metabolism	Diabetes

DID YOU KNOW?

Official US life insurance statistics show that every month, approximately 30 Americans choke to death trying to swallow an incompletely chewed big bite of beef steak. Think of these statistics and chew your steak carefully to avoid this form of death caused by anoxia!

result of brain anoxia can resume a normal life if resuscitation is timely and adequate. Ischemic myocardial injury caused by coronary artery thrombosis can be minimized by rapid coronary catheterization aimed at removing the occluding thrombus. However, reoxygenation of the heart carries an additional risk because oversupply of oxygen may have a deleterious effect on the reversibly damaged cardiac cells (Fig. 1.12). Oxygen toxicity results in such cases from activated **oxygen radicals**. These toxic compounds are formed in tissues as a result of oxygen activated by ionized iron, or by chemical reactions that produce *hydrogen peroxide (H_2O_2), superoxide (O_2^-),* and *hydroxyl radical (OH.)*. Under normal circumstances, these activated oxygen radicals are formed in small amounts and are inactivated by the cellular enzymatic scavenger mechanisms (e.g., *catalase* or *superoxide dismutase*). However, if the function of these scavenger enzyme systems is reduced as a result of hypoxia, excess of oxygen radicals may result in additional cell injury. This happens, for example, in patients who have survived acute anoxia caused by myocardial infarction. If the blood supply to the ischemic myocardium is reestablished by rapid medical intervention, the oversupply of oxygen may cause a *postperfusion myocardial injury.*

Toxic injury. Toxic injury may be induced by substances known for their *direct* toxic effects on cells and by those that are not directly toxic but must be metabolically activated to become toxins *(indirect toxicity)*. Heavy metals, such as mercury, are *directly* toxic because they inactivate cytoplasmic enzymes by disrupting the sulfhydryl (S-S) groups that hold the polypeptide chains of an enzyme together in an active state. Carbon tetrachloride (CCl_4), a component of commercial metal-cleaning solutions (e.g., metal polish), is the best studied *indirect* toxin. Upon ingestion, CCl_4, which is itself not toxic, is metabolized to a toxic derivative, carbon

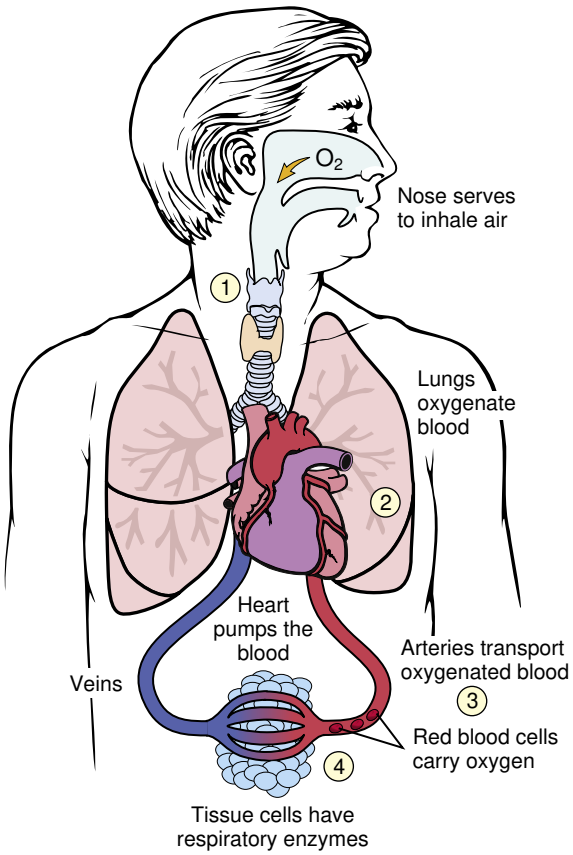


FIG. 1.11 The major causes of hypoxia–anoxia include (1) interruption of the oxygen supply, (2) inhibition of blood oxygenation in the lungs, (3) inadequate transport of oxygen in circulation, and (4) inhibition of cellular respiration.

trichloride (CCl_3). CCl_3 acts as a free radical, damaging cell membranes.

Many drugs and their metabolites cause cell injury, especially if given in large amounts. The mechanism of cell injury varies from one drug to another. Because various drugs affect different organs, the clinical presentations vary considerably. The effect of drugs is also dose dependent; in large amounts, most drugs may be toxic, and many are even lethal.

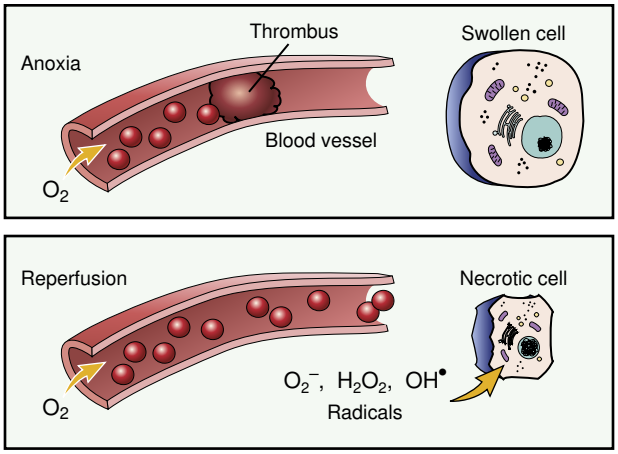


FIG. 1.12 Postperfusion injury by oxygen radicals.

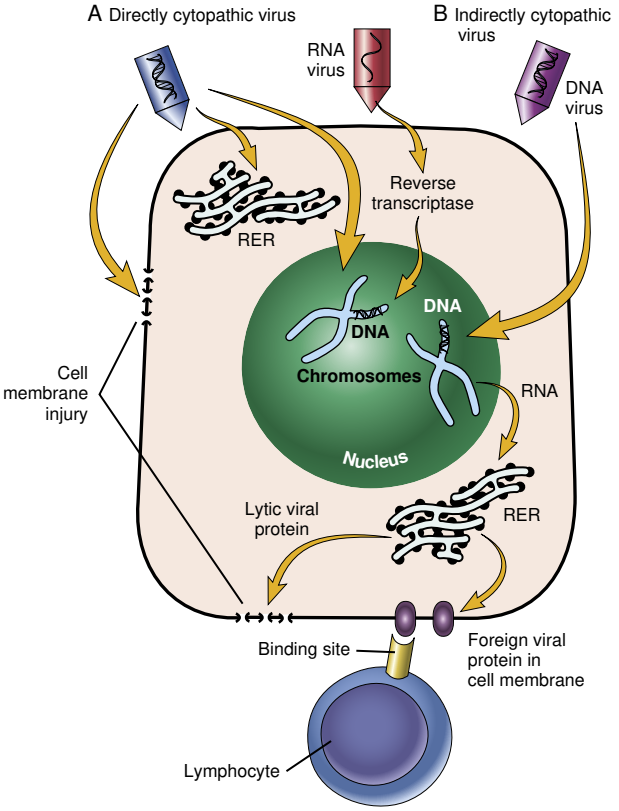


FIG. 1.13 Viral cell injury. *A,* Direct cytopathic effect. *B,* Indirect cytopathic effect mediated by immune mechanisms. *RER,* Rough endoplasmic reticulum.

DID YOU KNOW?

Potassium cyanide is a potent toxin that can be used as a poison. In Germany during World War II, many high-ranking Nazi officials carried a capsule of cyanide placed into a hole in their teeth that could be used for suicide in case they were captured by Allied soldiers.

Small amounts of cyanide are also found naturally in apricot pits. These seeds were used by quack physicians to produce *laetrile,* a presumptive miracle anticancer drug. Laetrile did not cure any cancers, but nobody knows how many patients developed cyanide toxicity from this so-called cancer treatment.

Microbial pathogens. Microbial pathogens cause cell injury in several ways. *Bacteria* most often produce *toxins,* which may inhibit various cell functions, such as respiration or protein synthesis. For example, food poisoning from spoiled, unrefrigerated leftover food is caused by *exotoxins,* which are released by bacteria growing on contaminated food. Ingestion of these exotoxins produces nausea, vomiting, and diarrhea. All these symptoms are a consequence of "cell poisoning"—that is, the adverse effects of bacterial exotoxins on the gastrointestinal cells.

Viruses that are directly cytopathic invade cells and "kill from within" by disturbing various cellular processes or by disrupting the integrity of the nucleus or plasma membrane (Fig. 1.13). Other viruses that are not directly cytopathic integrate themselves into the cellular genome. The genetic material of these viruses encodes the production of foreign proteins, which are mixed with the cell's own proteins and incorporated into the cell's membrane. The body's immune system will recognize the foreign viral proteins in the cell membrane and attack them. By attacking the foreign protein, the immune system will also damage and ultimately kill the virus-infected cell.

Genetic and metabolic disturbances. Genetic and metabolic disturbances are important causes of cell injury. Many genetic diseases adversely affect the normal intermediate metabolism with subsequent accumulation of toxic metabolites in the cells. These diseases will be discussed in greater detail in Chapter 5.

Metabolic disturbances during adulthood also may cause various forms of cell injury. In some instances, the injury affects the cells directly, whereas in others the injury is indirect. For example, *diabetes mellitus,* a disease caused by insulin deficiency, is characterized by hyperglycemia (excess of glucose in blood), which alters the metabolism of major organs, such as the liver or kidneys. At the same time, diabetes produces pathologic changes in small blood vessels, which impede microcirculation and cause pathologic tissue changes related to chronic hypoxia.

CELL ADAPTATIONS

Prolonged exposure of cells to adverse or exaggerated normal stimuli evokes various **adaptations** at the level of individual cells, tissues, or organs. After the cause is removed, most cells that have adapted to chronic stimulation revert to normalcy again. However, some forms of adaptation, especially those associated with cell loss (e.g., bone loss in osteoporosis), are irreversible.

Atrophy

Atrophy denotes a decrease in the size of a cell, tissue, organ, or the entire body. *Atrophy* can refer to the reduced size of individual cells, reduced number of cells in a tissue or organ, or a combination of these two processes. Like all adaptations, atrophy can be classified as physiologic or pathologic.

Physiologic atrophy occurs with age and involves essentially the entire body. For example, in the brain, a certain number of cells are lost every day from birth on; over the years, this results in a decrease in overall brain size. An atrophic brain has narrow

gyri, widened sulci, and dilated lateral ventricles (Fig. 1.14). The atrophic bones of older people are thin and are thus more prone to fracture; their muscles are atrophic and weak.

Physiologic atrophy is not limited to very old age. The thymus undergoes physiologic atrophy during childhood, and only traces of thymic tissue are found after puberty. The ovaries, uterus, and breasts undergo atrophy after menopause.

Pathologic atrophy typically occurs as a result of inadequate nutrition, oxygen supply, or hormonal stimulation. Ischemic organs are typically small, such as kidneys affected by atherosclerosis. Denervated muscles (e.g., leg muscles after spinal cord injury) are atrophic and flaccid. General body wasting (*cachexia*), caused by cancer or malnutrition, is marked by weakness as a result of loss of muscle, which appears microscopically as atrophy of numerous muscle fibers.

Atrophy of individual cells is associated with an obvious reduction in cell size and reduced metabolism. The cytoplasm of atrophic cells contains fewer mitochondria and endoplasmic reticulum. Effete, aging, and damaged organelles are taken up by autophagosomes and degraded. Undigested residues remain in the cytoplasm in the form of lipid-rich brown pigment residues (*lipofuscin*), which impart a brown coloration on the atrophic organs of older persons (e.g., old age *brown atrophy* of the heart or *brown atrophy* of the testis).

Proteins released from damaged organelles and those that are no longer needed in the cytoplasm of atrophic cells are bound to a scavenger protein, called *ubiquitin*. Ubiquitin marks them for destruction in *proteasomes,* large protease complexes specializing in degradation of effete proteins.

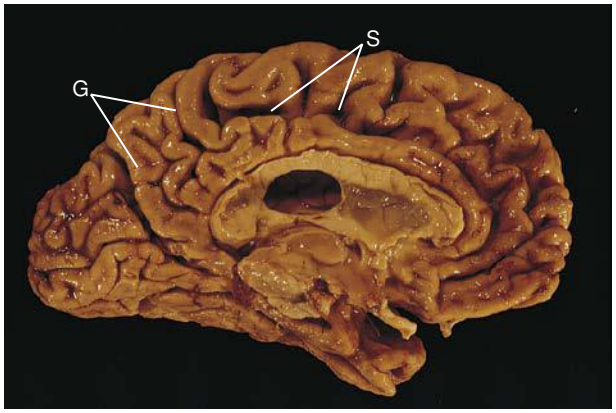


FIG. 1.14 Atrophic brain. The gyri (G) are narrow, and the sulci (S) are wide.

Hypertrophy and Hyperplasia

Hypertrophy refers to an increase in the size of tissues or organs caused by enlargement of individual cells. Etymologically, the term is related to the Greek word *trophe,* meaning "food," and thus actually means enlargement of "overfed" cells. By contrast, **hyperplasia** refers to an increase in the size of tissues and organs caused by an increased number of cells (Fig. 1.15). Hypertrophy and hyperplasia often occur in combination. Pure hypertrophy occurs only in the heart and striated muscles because these organs consist of cells that cannot divide.

Hypertrophy of the heart is a common pathologic finding that occurs as an adaptation of the heart muscle to an increased workload (Fig. 1.16). Hypertrophy of the left ventricle of the heart is a typical complication of hypertension. The increased pressure in the outflow side of the left ventricle requires more force to be overcome, and this is achieved by hypertrophy of muscle fibers. Hypertrophic heart cells increase in size. Such cells contain more myofilaments, which allow them to contract more efficiently. *Hypertrophy of skeletal muscles* is commonly induced by exercise and is typically found in bodybuilders.

Hypertrophy combined with hyperplasia occurs under a variety of conditions. For example, smooth muscle cells in the wall

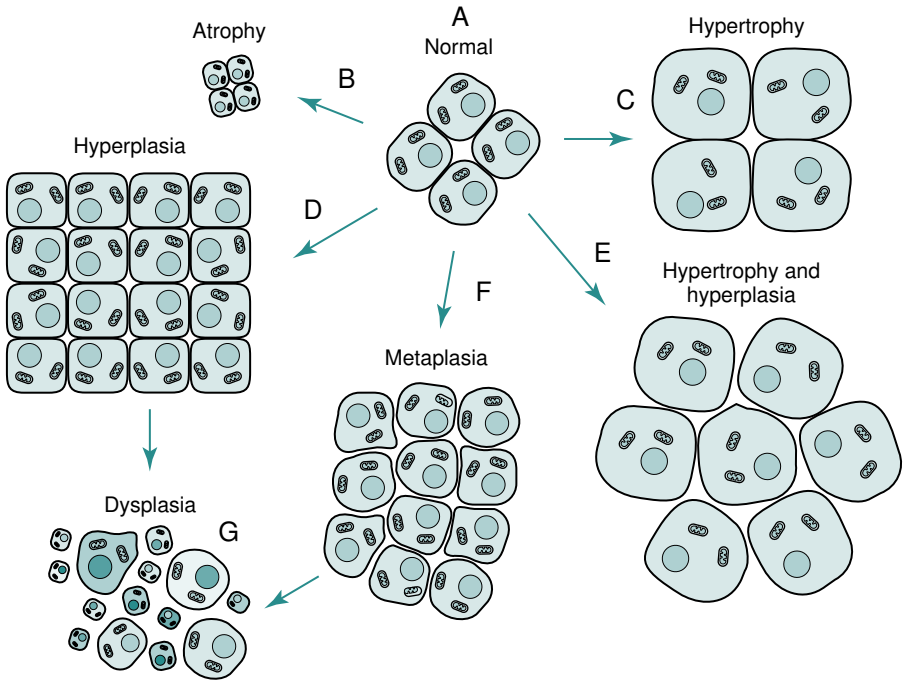


FIG. 1.15 Cell adaptations. A, Normal. B, Atrophy. C, Hypertrophy. D, Hyperplasia. E, Hypertrophy and hyperplasia. F, Metaplasia. G, Dysplasia.

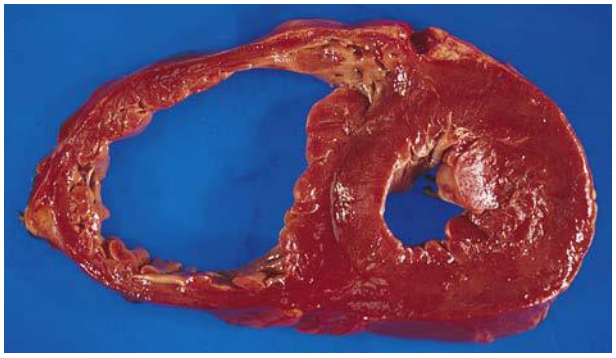


FIG. 1.16 Hypertrophy of the left ventricle of the heart caused by hypertension.

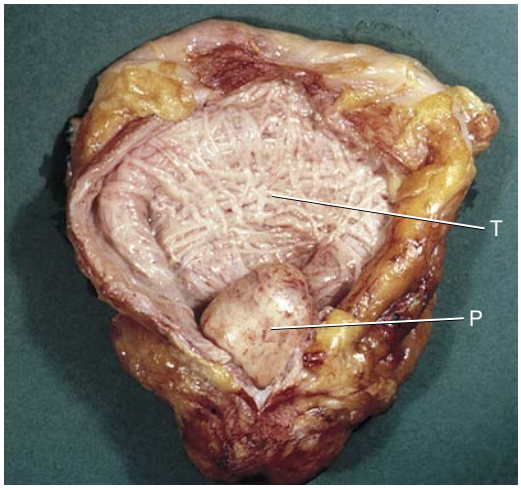


FIG. 1.17 Hyperplasia of the prostate with secondary thickening of the obstructed urinary bladder. The enlarged prostate (P) is seen protruding into the lumen of the bladder, which appears trabeculated (T). These "trabeculae" result from hypertrophy and hyperplasia of smooth muscle cells that occurs in response to increased intravesical pressure caused by urinary obstruction.

of the urinary bladder, when obstructed by a hyperplastic prostate, increase in size and number. This contributes to thickening of the wall of the urinary bladder (Fig. 1.17). Physiologic hypertrophy of uterine smooth muscle cells during pregnancy is also accompanied by hyperplasia.

Pure hyperplasia typically occurs as a result of hormonal stimulation. For example, when continuously stimulated by estrogen, the endometrium may become very thick *(endometrial hyperplasia)*. Microscopic examination reveals an increased number of glandular cells. In benign prostatic hyperplasia (a common cause of prostatic enlargement in older individuals, which is also hormonally induced), hyperplasia of epithelial and stromal cells leads to the formation of grossly visible nodules (see Fig. 1.17).

Hyperplasia may also occur in response to chronic injury, and in some cases, the cause is obvious. For example, tight shoes may cause chronic irritation of the skin. In such cases, the epidermal cells undergo hyperplasia and form a callus or corn. However, some hyperplastic lesions, such as *hyperplastic polyps* of the large intestine, have no obvious cause and probably represent early neoplasia. Some forms of endometrial hyperplasia caused by estrogen may undergo additional genetic changes and, if left untreated, may progress to neoplasia.

Metaplasia

Metaplasia is a form of adaptation characterized by the change of one cell type into another. The best example is squamous metaplasia of the bronchial mucosa seen in smokers. It results from prolonged cigarette smoke irritation, which transforms the normal ciliated columnar bronchial epithelium into squamous epithelium.

Metaplasia is a reversible change. If the smoker stops smoking, the squamous epithelium will revert to ciliated columnar epithelium. If the stimulus that has induced squamous metaplasia persists (i.e., if the smoker does not stop smoking), squamous metaplasia may progress to *dysplasia*. In contrast to the regular layering of normal squamous cells that is typical of metaplasia, dysplasia is characterized by a disorderly arrangement of cells and nuclear atypia. Dysplasia may still be reversible if the stimulus is discontinued, but more often than not, it progresses to *neoplasia* (discussed in Chapter 4; also see Chapter 8 for content on lung carcinoma in smokers).

Intracellular Accumulations

Intracellular accumulations may result from an overload of various metabolites or exogenous materials, or they may be attributable to metabolic disturbances that prevent excretion of metabolic byproducts or normal secretions from cells. In most instances, the underlying mechanisms are complex and involve both an overload and underutilization or reduced excretion.

Anthracosis

Anthracosis (accumulation of coal particles) is the best example of exogenous material accumulation. The term is derived from the Greek word *anthrax,* meaning "carbon." Severe anthracosis is seen in the lungs and bronchial lymph nodes of people who work in coal mines. Coal particles are released into the air from chimneys; in essence, any air pollution could cause anthracosis. Pulmonary anthracosis is prominent in cigarette smokers.

Hemosiderosis

Hemosiderosis is an accumulation of blood-derived brown pigment called **hemosiderin**. Hemosiderin is usually derived from hemolyzed blood. As you may recall, red blood cells (RBCs) contain iron-rich hemoglobin, which disintegrate during hemolysis into globin and heme. Heme gives rise to micelles of ferritin, which aggregates into hemosiderin. Iron in hemosiderin can be demonstrated in tissues with the so-called Prussian blue reaction. Hemosiderosis of the liver develops in people who have received many blood transfusions and in those with hemolytic anemia. It is also a constant feature of a genetic disorder of iron absorption from food, called *hereditary hemochromatosis* (Fig. 1.18). Accumulation of iron pigment in hereditary hemochromatosis causes liver damage and may also lead to cirrhosis (i.e., end-stage liver disease).

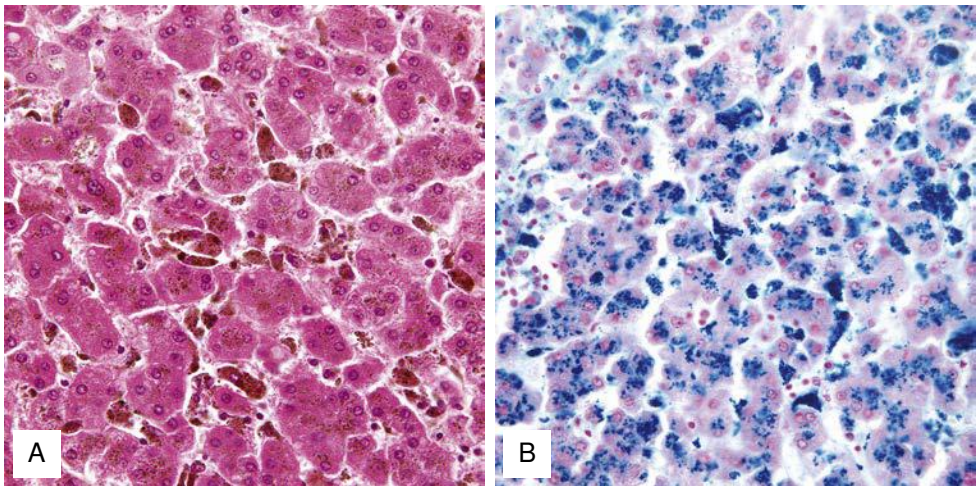


FIG. 1.18 Hereditary hemochromatosis. ***A,*** The disease is characterized by an accumulation of hemosiderin, an iron-rich brown pigment, in liver and Kupffer cells. ***B,*** The so-called Prussian blue reaction gives hemosiderin a blue hue.

Lipid Accumulation

Lipid accumulation in the liver is an example of intracellular accumulation of intermediate metabolites. Fat is normally stored in liver cells in the form of triglycerides. Obese people have fatty livers because of an overload of fat. Fat accumulation in the liver, also known as *steatosis,* is a typical finding in persons with chronic alcohol abuse or from diabetes mellitus.

As shown in Fig. 1.19, alcohol stimulates accumulation of fat in the liver through several mechanisms. The fat is derived, in part, from free fatty acids mobilized from peripheral stores at an accelerated rate. Alcohol has a high caloric content and serves as a substrate for new fat formation in liver cells *(neolipogenesis).* It also inhibits several hepatic lipolytic enzymes and thus impedes utilization of intrahepatic fat. Finally, alcohol inhibits apoprotein synthesis and the export of fat from the liver in the form of lipoproteins.

The clinical consequences of cytoplasmic lipid accumulation in the liver are variable. For example, fatty change in liver cells of most obese persons may be fully reversible if the affected person loses weight by eliminating excessive fat from the body. Conversely, in some individuals with diabetes or chronic drinkers of alcohol, fatty liver may progress to steatohepatitis, a serious disease that can lead to liver failure and end-stage liver disease, called *cirrhosis.*

Aging

The **aging** of cells includes many complex adaptations and, unfortunately, many cellular events that are irreversible. Aging cannot be avoided or prevented; the best we can do is to retard it or minimize its adverse effects on the body.

The process of aging is poorly understood. There are many theories of aging, none of which explain in full the essence of this complex biologic phenomenon. Everybody is aware of the remarkable differences between an old person and a young

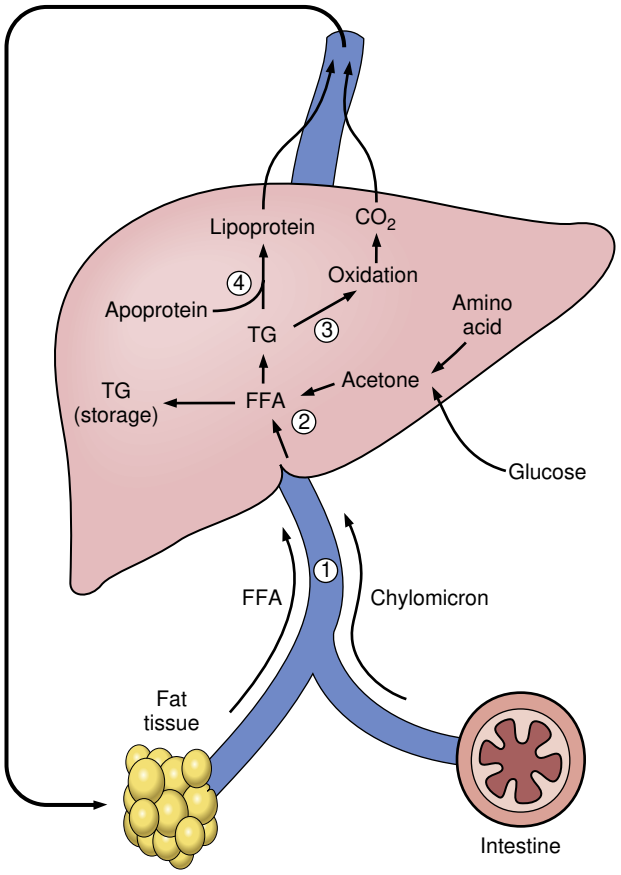


FIG. 1.19 Pathogenesis of alcoholic fatty liver. Triglycerides (TG) in the liver cell are formed through several mechanisms, all of which contribute to the accumulation of fat: (1) increased influx of free fatty acids (FFAs) from peripheral stores; (2) increased neolipogenesis from glucose, amino acids, and alcohol; (3) decreased utilization of triglycerides because of the inhibition of enzymes; and (4) decreased synthesis of apoprotein, which is essential for the formation of lipoproteins, reduces export of lipids from the liver.

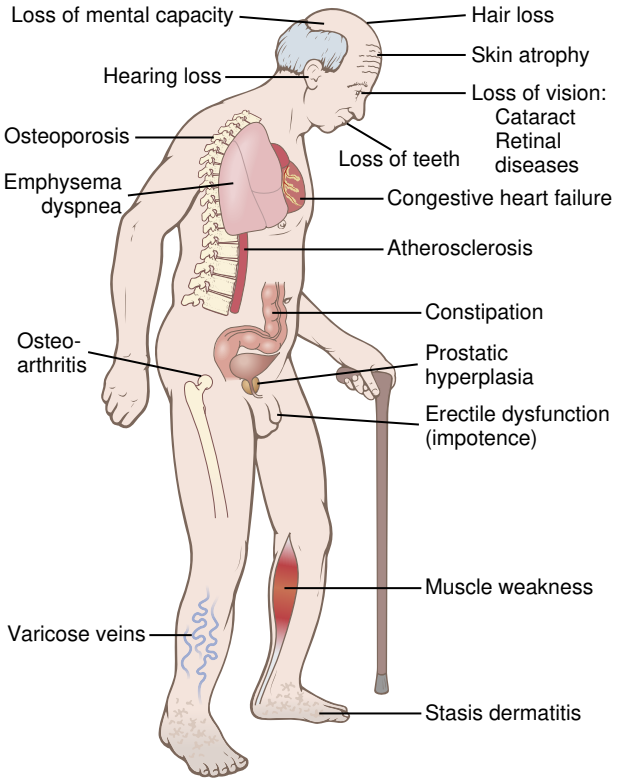


FIG. 1.20 Common pathologic changes in older adults.

person, but our understanding of these differences is still fragmentary.

Scientists studying old age (gerontologists) favor two major hypotheses as an explanation for aging: the *wear-and-tear hypothesis* and the *genetic hypothesis*. Because cells represent the basic living units of all tissues and organs, it is thought that cellular aging represents the critical event in the aging of the organism. Furthermore, the decline of complex integrative and specialized functions of the body results from dysfunctions at the cellular level. In organs composed of cells that cannot regenerate, such as the brain and the heart, the wear-and-tear hypothesis accounts, to a great extent, for the decline in the functioning of these organs. However, because not everyone loses brain cells at the same speed, the genetic theory of aging also has merit. This hypothesis asserts that aging is a genetically predetermined process. Hormonal, immune, and neural theories blame all the calamities of aging on the dysfunction of these integrative processes.

Pathologic changes associated with aging vary from one individual to another. Overall, most organs undergo atrophy and have a reduced functional reserve. Resistance to infection declines with advancing age. Conversely, the incidence of cardiovascular diseases and cancer is increased. Typical pathologic changes encountered in older adults are illustrated in Fig. 1.20.

DEATH

Death, even more so than aging, is an inevitable feature of life. All the cells in the human body have a finite life span, and when that life span comes to an end, cells die. Some of the cells may be replaced by stem cells in that tissue, whereas others are irreplaceable. Heart cells belong to the latter category. However, even if all heart cells die, the life of a person can now be extended with heart transplantation. If the neural cells of the vital centers of the brain die, death is inevitable. Thus, we use the term *brain death,* which, for legal purposes, means cessation of vital brain functions and absence of electrical activity in the brain, as detected by electroencephalography. In practical terms, the noncerebral body functions of a "brain dead" person cannot be maintained on their own and typically require medical support, including mechanical ventilation, assisted feeding, and special long-term care.

Cell Death

Cell death occurs in several forms. We have already mentioned that the irreversible cell injury caused by anoxia or toxins leads to cell death with typical nuclear changes (pyknosis, karyorrhexis, and karyolysis); rupture of the cell membrane; and cessation of cellular respiration. This form of exogenously induced cell death is called *necrosis*. By contrast, *apoptosis* refers to endogenously programmed cell death. Necrosis and apoptosis represent the death of single cells or groups of cells within a living organism. Death of cells and tissues in a dead organism that occur as a result of cessation of respiration and heartbeat is called *autolysis*.

DID YOU KNOW?

The Greek word *necros,* meaning "dead" or "corpse," is also used to construct many other medical words. For example, the postmortem examination of human or animal bodies performed by pathologists is called a *necropsy.* However, the same linguistic root can also be found in other words. According to Greek mythology, *nectar,* the sweet juice consumed by the Greek gods, could bestow immortality. Nectarines, although good for our health, are unfortunately not a remedy for our mortality.

Necrosis

In contrast to autolysis, a postmortem event and therefore of little significance to clinicians, **necrosis** is clinically important. It occurs in several forms: coagulative, liquefactive, caseous, and enzymatic fat necrosis.

Coagulative necrosis. *Coagulative necrosis* is the most common form of necrosis. It is marked by rapid inactivation of cytoplasmic hydrolytic enzymes. This prevents the lysis of tissues, which retain their original form and firm consistency. Coagulative necrosis typically involves solid internal organs, such as the heart, liver, or kidneys (Fig. 1.21), and is most often caused by anoxia (e.g., myocardial infarction).

Liquefactive necrosis. *Liquefactive necrosis* is characterized by the dissolution of tissues, which become soft and diffluent. It occurs most often in the brain, where cells lose their contours and are "liquefied" (i.e., transformed into semifluid mush). Liquefactive necrosis is typical of a brain infarct, usually soft, but ultimately transformed into a fluid-filled cavity (Fig. 1.22).

Coagulative necrosis may liquefy, usually through the action of leukocytes that invade the necrotic tissue to remove the dead cells. Leukocytes release lytic enzymes, which, in turn,

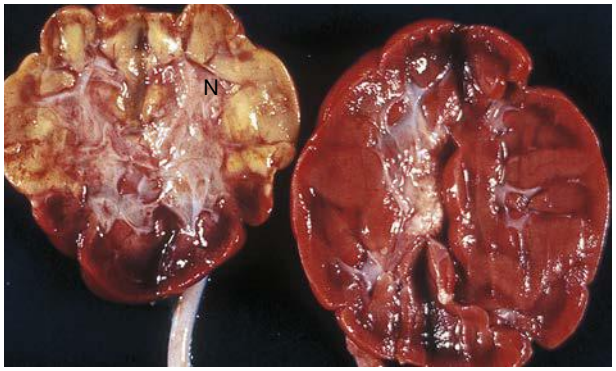


FIG. 1.21 Coagulative necrosis of the kidney of an infant caused by ischemia. The necrotic area (N) is pale yellow in color, in contrast to the normally perfused parenchyma of the kidney on the right, which is reddish brown in color.

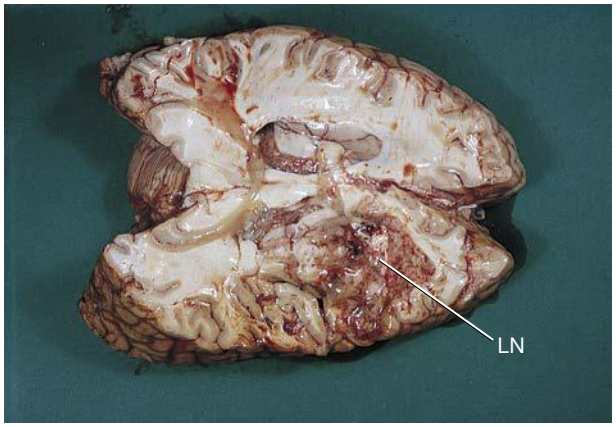


FIG. 1.22 Cerebral infarct. The area of infarction is softened as a result of liquefactive necrosis (LN).

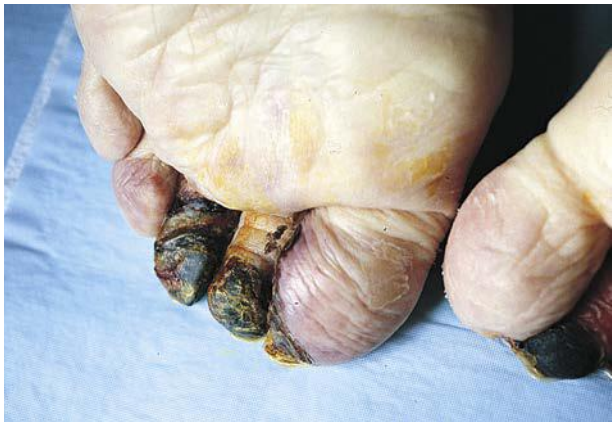


FIG. 1.23 Dry gangrene involving several toes, which appear black.

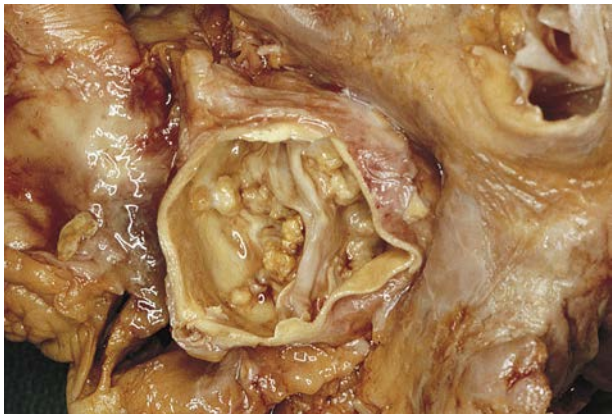


FIG. 1.24 Calcified aortic valve. Nodules on the valves are examples of dystrophic calcification.

transform the solid tissue into liquid pus. Pus is a viscous yellow fluid composed of dead and dying leukocytes and cell debris. Myocardial infarcts that initially show coagulative necrosis are invaded by leukocytes and undergo *secondary liquefaction* usually 4 to 6 days after occlusion of a blood vessel. Softened myocardium may cause rupture of the heart and cardiac death.

Caseous necrosis. *Caseous necrosis,* typically found in patients with tuberculosis, is a special form of coagulative necrosis with limited liquefaction. The center of a tuberculous granuloma becomes necrotic and the cells fall apart. The tissue is yellow-white and "cheesy" in appearance, hence the name caseous necrosis. Caseous necrosis is not unique to tuberculosis; it may also be found in fungal infections, such as histoplasmosis.

Enzymatic fat necrosis. *Enzymatic fat necrosis* is a special form of liquefactive necrosis caused by the action of lipolytic enzymes. It is limited to fat tissue, usually around the pancreas. Pancreatic enzymes released into the adjacent fat tissue (e.g., after rupture of the pancreas caused by seat belt trauma in a traffic accident) degrade the fat into glycerol and free fatty acids. The free fatty acids rapidly bind calcium, forming calcium soaps. Therefore, the area of fat necrosis appears as liquefied fat with whitish specks of calcium soap scattered throughout.

Necrotic tissue, especially found on the extremities, may undergo secondary changes that produce specific morphologic features. Bacterial infection of coagulated tissue leads to inflammation and a secondary liquefaction, which is clinically known as *wet gangrene.* If the necrotic tissue dries out, it becomes dark black and mummified, just as the ancient Egyptian mummies dried in the hot air of the desert. Such lesions are called *dry gangrene* (Fig. 1.23). Both forms of **gangrene** are most often seen on the toes and lower extremities and are usually caused by peripheral vascular disease (atherosclerosis). Gangrene of the toes or the entire foot is especially common in patients with diabetes.

Necrotic tissue attracts calcium salts and often undergoes **calcification**. Calcification of necrotic tissue is called *dystrophic calcification,* in contrast to *metastatic calcification,* which is typically a consequence of hypercalcemia. Dystrophic calcification can be seen in atherosclerotic arteries, damaged heart valves (Fig. 1.24), or necrotic tumors. Metastatic calcification is a feature of metabolic hypercalcemia secondary to hyperparathyroidism or vitamin D toxicity. It most often involves the kidneys, presumably because the fluctuating pH levels in the renal parenchyma and the high concentration of calcium predispose the individual to deposition of calcium salts in this tissue.

Apoptosis

Apoptosis is an "active" form of *cell death.* Because it is energy dependent and requires activation of a specific set of genes and

enzymes, it is also known as *programmed cell death*. The genes activated during apoptosis are popularly known as *suicide genes*, and accordingly, apoptosis is best compared to a suicide. The initial event could be *endogenous* or *exogenous*. In cellular terms, this could mean a long-lasting viral infection (exogenous; e.g., chronic viral hepatitis C) or a lack of necessary growth factors in a brain cell (endogenous). Like a person who has decided to die rather than live, the cell entering the apoptosis pathway will use its "brain" (i.e., its nucleus) and "decide" how to activate a certain set of killer genes and how to inactivate other life-sustaining genes. Continuing with the analogy to suicide, the cell also chooses the tools for its suicide; that is, it synthesizes specific killer enzymes that attack the cell's vital structures, such as the nucleus and the mitochondria.

Apoptosis is a form of cell death that typically affects single cells (Figs. 1.25 and 1.26). During apoptosis, an energy-requiring

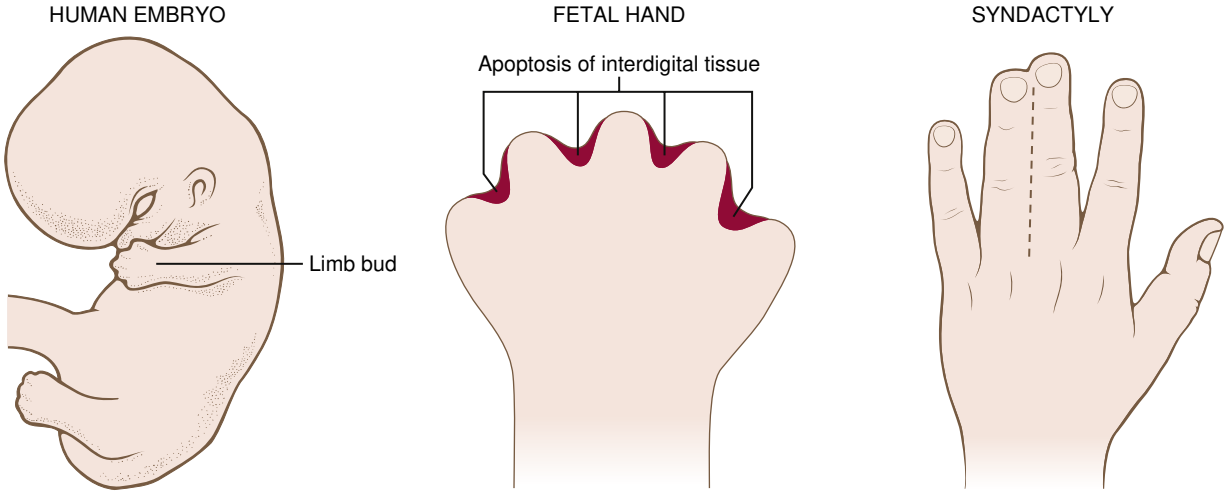


FIG. 1.25 Apoptosis in the fetal limb bud. Apoptosis is important for the formation of fingers. Incomplete or defective apoptosis cause syndactyly.

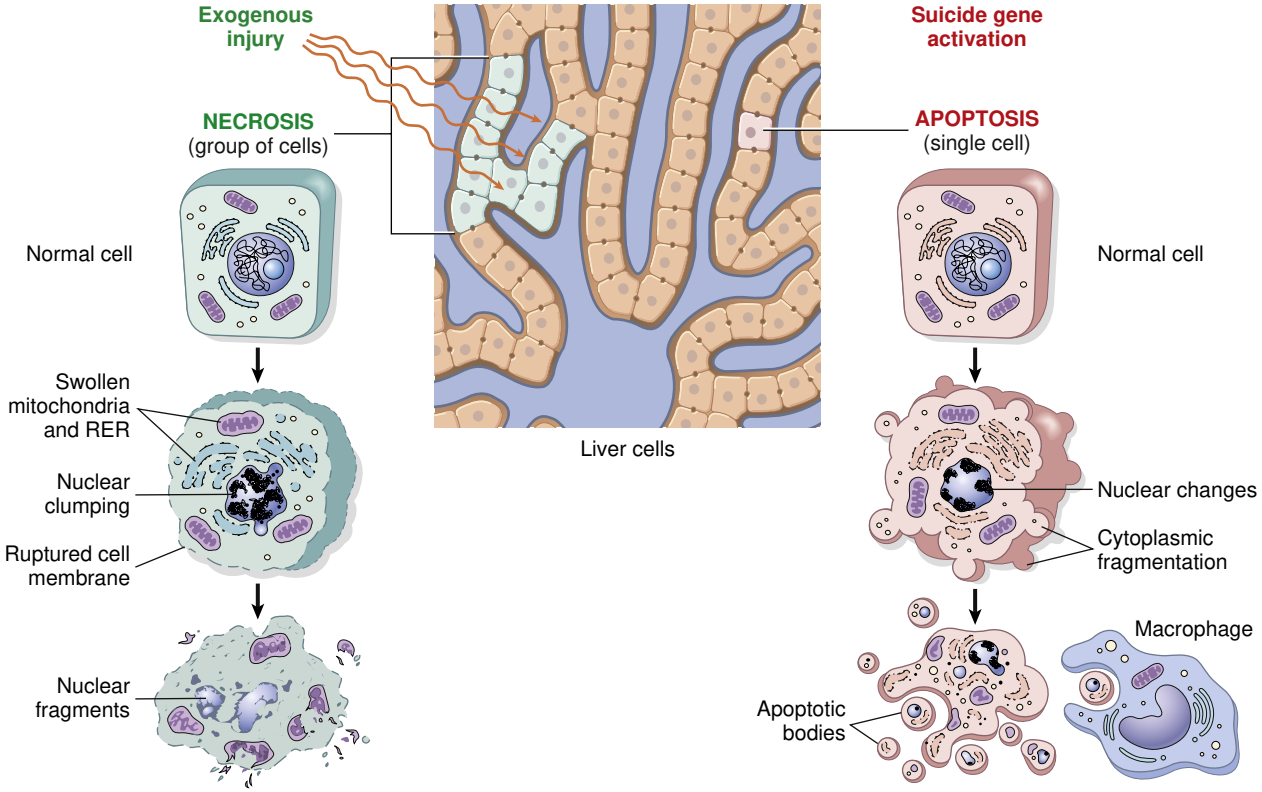


FIG. 1.26 Necrosis and apoptosis in the liver. Necrosis is caused by exogenous injury and involves groups of cells. Necrotic cells are swollen, show nuclear changes, and have ruptured cell membranes. Apoptosis presents as single cell death. It is genetically programmed and energy dependent. The cell fragments ("apoptotic bodies") containing parts of the nucleus and functioning cytoplasmic organelles are ultimately taken up by macrophages or adjacent parenchymal cells. *RER,* Rough endoplasmic reticulum.

TABLE 1.2 Comparison of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cause	Exogenous injury	May be exogenous or endogenous
Mechanisms	Vital processes inhibited	Energy dependent, vital processes active
Cells affected	Multiple	Single
Cell morphology	Swollen, ruptured	Rounded up, fragmented (apoptotic bodies)
Cell membrane	Ruptured	Functionally intact
Outcome	Phagocytosis by neutrophils	Phagocytosis by macrophages and "nonprofessional macrophages"

process, active transcription and translation of genetic material is ongoing, so the enzyme activity in the cytoplasm remains high. The cell subdivides into smaller apoptotic bodies containing fragments of the nucleus, metabolically active mitochondria, and other organelles. Ultimately, these fragments are taken up by macrophages or cells in the adjacent tissue, which act as "nonprofessional phagocytes." In contrast to apoptosis, necrosis affects groups of cells or an entire organ. Toxic stimuli, or ischemia, causing necrosis leads to the inhibition of vital processes, such as gene activity and cellular respiration. The nucleus disintegrates or undergoes lysis, the cytoplasm swells, and the cell membrane ruptures. The fragments are typically taken up by polymorphonuclear neutrophils. The main differences between apoptosis and necrosis are listed in Table 1.2.

Like all other cellular functions, apoptosis is a highly regulated process. Life and death are intricately interconnected; certain cells must die so that others can live. Accordingly, apoptosis occurs during the entire human life span, from the early embryonic stages to old age. Apoptosis can also be induced by adverse exogenous events, and accordingly, it is customary to classify apoptosis as physiologic or pathologic.

Physiologic apoptosis plays an important role in the formation of many, if not all, body parts. For example, in the fetal limb buds, apoptosis of the soft tissues between the primordia of the digits ensures that the fingers and toes are normally formed (see Fig. 1.25). Without apoptosis, such limbs will be abnormally shaped—for example, the digits may be fused together (*syndactyly*). If apoptosis does not occur during the formation of the esophagus or the intestines, there will be no lumen and these organs will show incomplete formation of their central lumen (*atresia*).

Pathologic apoptosis may be a consequence of endogenous intracellular events, or it may be caused by adverse exogenous stimuli. For example, in muscular dystrophy, a group of genetic diseases characterized by a deficiency of specific cell components, the skeletal muscle cells that lack those proteins undergo apoptosis. Organs transplanted from one person to another show signs of apoptosis because the transplanted cells are attacked by the host's immune cells. Liver cells infected with hepatitis viruses also undergo apoptosis (see Fig. 1.26).

Lack of apoptosis can also cause pathologic changes. As mentioned previously, congenital intestinal atresia and syndactyly are salient examples of how lack of apoptosis can cause pathologic changes. Follicular lymphoma, a malignancy of mature B lymphocytes, is related to lack of apoptosis. In this disease, a mutation of the proapoptotic gene (known as *Bcl-2*) adversely affects the lymphocytes, making them "forget to die." Because lymphocytes do not die at their normal rate, they remain in the lymph nodes, causing lymph node enlargement, ultimately overwhelming the organism, and slowly killing the host 5 to 7 years after the diagnosis.

REVIEW QUESTIONS

1. What are the main components of the nucleus and the cytoplasm?
2. Which cell components and organelles contain ribonucleic acid (RNA)?
3. What are the differences between mitochondria and the endoplasmic reticulum?
4. What are the differences among primary and secondary lysosomes, autophagosomes, and heterophagosomes?
5. What are the differences among intermediate filaments, microfilaments, and microtubules?
6. What are the differences in the stimulation of autocrine, paracrine, and endocrine cells?
7. What is homeostasis?
8. How is cellular steady state maintained, and what does a cell reaching the point of no return mean?
9. How does hydropic change develop, and what is the role of Na^+/K^+–ATPase in cellular swelling?
10. What are the microscopic signs of irreversible cell injury?
11. How does hypoxia develop?
12. What are oxygen radicals, and how do they damage cells?
13. How do toxins, microbes, and chemical mediators of inflammation kill cells?
14. What are the main differences among atrophy, hypertrophy, and hyperplasia?
15. What is metaplasia?
16. What are anthracosis and hemosiderosis?
17. How does alcohol cause fatty liver?
18. How does aging occur?
19. What is meant by the term *brain death*?
20. What are the clinicopathologic features of various forms of necrosis?
21. What is the difference between dry gangrene and wet gangrene?
22. What is the difference between metastatic calcification and dystrophic calcification?
23. What is apoptosis?
24. What are the main differences between physiologic apoptosis and pathologic apoptosis?
25. How does apoptosis differ from necrosis?

2

Inflammation

OUTLINE

LEARNING OBJECTIVES

After reading this chapter, the student should be able to:

1. Define inflammation.
2. List the main components of acute inflammation.
3. Describe the vascular changes in acute inflammation.
4. Describe the cellular events in acute inflammation.
5. Define the following terms pertaining to leukocytes involved in an inflammatory response: *margination, diapedesis, emigration, exudation, chemotaxis, phagocytosis,* and *microbicidal substances.*
6. List two cell-derived and three plasma-derived mediators of inflammation.
7. Explain the function of proteins of the complement system and the clotting system in inflammation.
8. Explain the role of arachidonic acid metabolites in inflammation.
9. Explain the main functions of cytokines released in inflammation.
10. Describe possible outcomes of acute inflammation.
11. Describe three pathogenetic pathways leading to chronic inflammation.
12. List the principal cells of acute and chronic inflammation.
13. Describe the formation of a granuloma.
14. Describe the typical complications of granulomatous inflammation.
15. Define the following pathologic terms: *serous inflammation, fibrinous inflammation, purulent inflammation, abscess, ulcer, wound, scar,* and *keloid.*
16. Describe the typical local and systemic symptoms of inflammation.
17. Explain the pathogenesis of fever.
18. Describe wound healing and repair.
19. List three factors that may delay healing and repair.
20. List two complications of wound healing.

KEY TERMS AND CONCEPTS

Abscess
Acute inflammation
Angioblasts
Arachidonic acid
Bacteremia
Basophils
Bradykinin
Chemotaxis
Chronic inflammation
Complement proteins
Cytokines
Eosinophils
Exudate
Fever
Fibrinous inflammation
Fibroblasts
Fibrosis
Granulation tissue
Granulomas
Histamine
Leukocytes
Leukocytosis

Lymphocytes
Macrophages
Mast cells
Monocytes
Myofibroblasts
Phagocytosis
Plasma cells
Platelets
Polymorphonuclear neutrophils (PMNs)
Pseudomembranous inflammation
Purulent inflammation
Scarring
Serous inflammation
Ulcer
Wound healing

Inflammation is a nonspecific, but predictable, response in living tissues and the body to injury. The injury may be caused by chemical agents, physical forces, living microbes, or many other physiologic or pathologic (exogenous or endogenous) stimuli that disturb the normal steady state.

Before discussing the main events that occur during inflammation, it is important to note the following key points pertaining inflammation:

- Inflammation includes a series of interconnected events in response to an injury. It involves a coordinated reaction of cells, tissues, and organs, or the entire human body, in which vessels, blood cells, nerves, and soluble mediators of inflammation are all involved.
- Inflammation is a dynamic process, evolving through several phases that can last a few minutes to a few days or months to years. Inflammation of sudden onset and short duration is characterized as *acute inflammation,* in contrast to *chronic inflammation,* which lasts a long time.
- Inflammation usually ends by healing, but sometimes healing may last longer than the inflammation itself, or in some instances, it may never occur.
- Inflammation has an overall protective role and is generally beneficial to the body. However, it may have adverse side effects. For example, fever, which is initially beneficial, may be so high that it causes death. Sometimes the process may become uncontrollable, producing more harm than good. Inflammation occurs only in living tissues.
- From a forensic point of view, inflammation is considered a *vital reaction.* If histologic signs of inflammation are found in tissues recovered at autopsy, one may be sure that inflammation occurred before death.

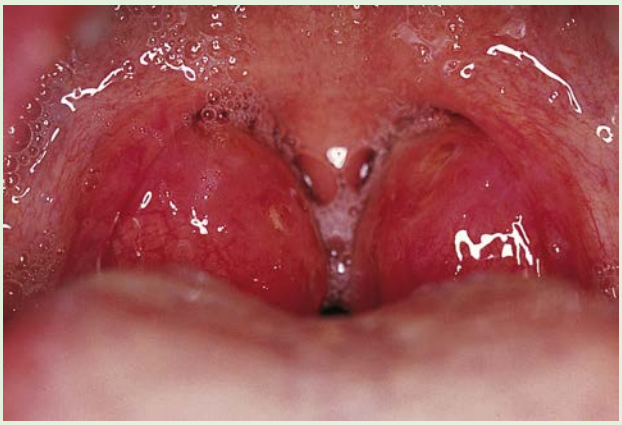
SIGNS OF INFLAMMATION

The Roman physician Celsus (circa 30 BCE–38 CE) described the *four cardinal signs of inflammation: calor* (heat), *rubor* (redness), *tumor* (swelling), and *dolor* (pain) (Fig. 2.1). Rudolf Virchow (1821–1902), the father of modern pathology, is credited with adding *functio laesa,* or *disturbed function,* as the fifth classic symptom of inflammation. However, the pathology of inflammation remained poorly understood until the scientific advances of the nineteenth century made microscopic studies of inflamed tissues possible.

Microscopic studies during the nineteenth century have been supplemented and expanded by biochemical and molecular biology investigations performed during the twentieth century and the current century. Today, we know that

DID YOU KNOW?

Acute tonsillitis shows all the classical signs of inflammation. The tonsils are obviously swollen and red and are probably warm and painful. The patient cannot swallow easily. Most of you have had bouts of acute tonsillitis, and thus you can relate to these symptoms and signs of acute inflammation. (From Stevens A, Lowe J, Scott I: *Core Pathology,* 3rd edition. London, Mosby Elsevier,2008.)



inflammation is a complex process that includes the following key components:

- *Circulatory changes* involving the blood flow through the inflamed tissue
- *Vascular changes* involving the physical, biochemical, and biologic changes in the endothelial lining, vessel wall, and perivascular tissue of small vessels, such as arterioles, capillaries, and venules
- *Humoral response,* that is, release and action of soluble mediators produced by inflammatory cells and various organs in response to injury
- *Cellular response,* including primarily circulating platelets and white blood cells (WBCs) but also important cells in the perivascular tissue

PATHOGENESIS OF INFLAMMATION

Circulatory Changes

Hemodynamic (vascular) changes—that is, changes in blood flow—represent the body's first response to injury. The redness and swelling of the skin that occur after a gentle slap on the arm or the face are typical of such a vascular response. The

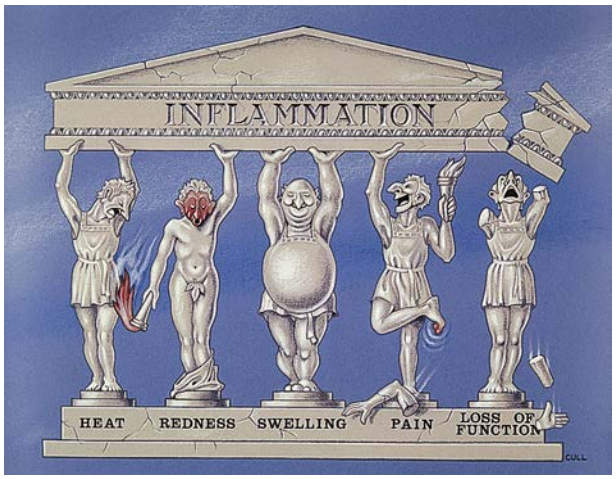


FIG. 2.1 The cardinal signs of inflammation were described in Roman times. (Reprinted with permission from Professor Peter Cull, London University, London, United Kingdom.)

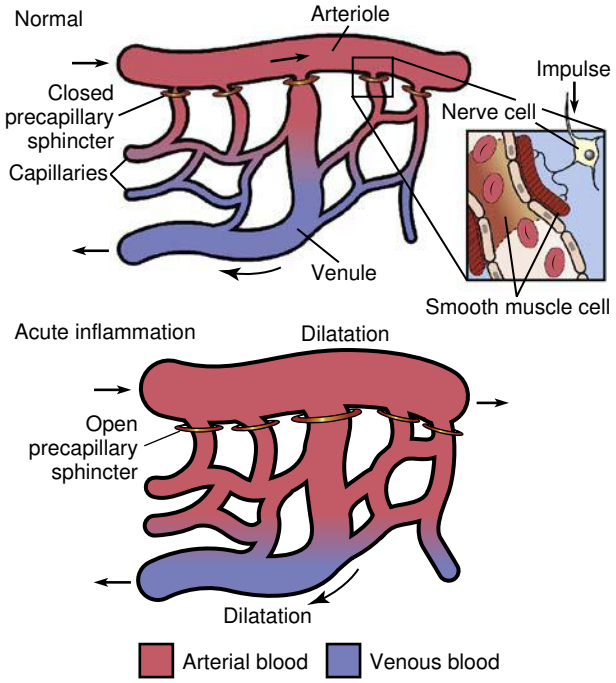


FIG. 2.2 Circulatory changes in inflammation. Relaxation of the precapillary sphincter in the arterioles results in flooding of the capillary network and dilation of capillaries and postcapillary venules.

mechanical stimulus fuels the nerves that transmit signals to the smooth muscle cells of the precapillary arterioles. The smooth muscle cells in the arterioles act as sphincters, regulating the inflow of blood into the capillaries (Fig. 2.2).

Relaxation of smooth muscle cells allows blood to rush into the capillaries, and this accounts for the redness, swelling, and warmth of the tissue. The first response of the arterioles to an injurious stimulus is *vasoconstriction,* which lasts only a few seconds. This is followed by *vasodilation* (i.e., relaxation of the precapillary sphincter), resulting in the flooding of the capillary network with arterial blood, manifesting as redness and mild swelling of the tissue engorged by blood. Arterial blood is

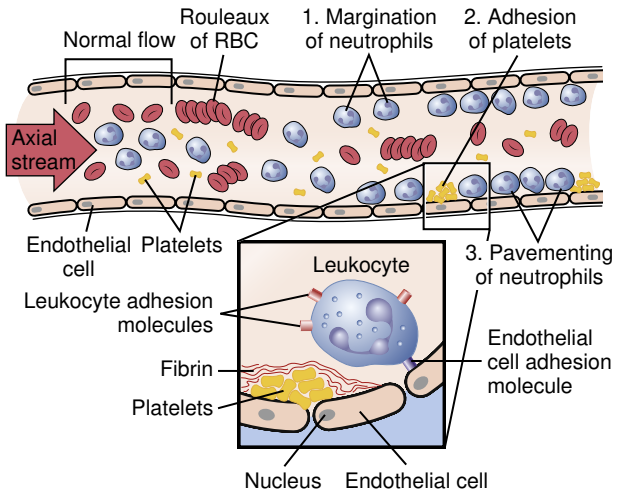


FIG. 2.3 Cellular changes in inflammation. (1) Margination of neutrophils brings the inflammatory cells in close contact with the endothelium. (2) Adhesion of platelets results in the release of mediators of inflammation and coagulation. Fibrin strands are the first signs of clot formation. (3) Pavementing of neutrophils is mediated by adhesion molecules activated by the mediators of inflammation released from platelets and leukocytes. *RBC,* Red blood cell.

warm, and because it is pumped into the area in large quantities, the inflamed tissue also becomes warm. Influx of blood into inflamed areas is called *active hyperemia.*

Engorged capillaries consist only of endothelial cells and a basement membrane and thus cannot contract, but they dilate in response to increased intraluminal blood pressure. From the capillaries, the pressure is transmitted to the venules, which also do not have the capacity to contract. Increased pressure in the capillaries and the venules promotes plasma filtration through the walls of these vessels, leading to inflammatory edema.

Blood flow in the dilated capillaries and venules is relatively slow, and this leads to a redistribution of the red blood cells (RBCs) and WBCs in the bloodstream. In the central part of the stream, the erythrocytes form stacks, called *rouleaux,* which impede the circulation even more, contributing to the turbulent flow of the blood (Fig. 2.3). *Margination* of ***leukocytes***, which are pushed to the marginal part of the bloodstream, leads to *pavementing* (i.e., their attachment to the endothelial cells lining the inside of the blood vessels). At the same time, leukocytes undergo *activation* and develop elongated protrusions from their surface cytoplasm, become sticky, and adhere to the endothelial cells lining the capillaries, particularly those of the postcapillary venules.

The adhesion of neutrophils to endothelial cells is accomplished by surface *adhesion molecules,* such as *selectins* and *integrins.* These molecules are normally present on leukocytes and endothelial cells in their inactive forms but are activated during inflammation. Adhesion molecules are activated through the action of soluble mediators of inflammation called **cytokines**, such as *interleukins* (ILs) or *tumor necrosis factor* (TNF). Small amounts of ILs and TNF are normally present in blood. However, their concentration is increased at the site of inflammation as they are released from endothelial cells, leukocytes, platelets, and macrophages in the adjacent connective tissue.

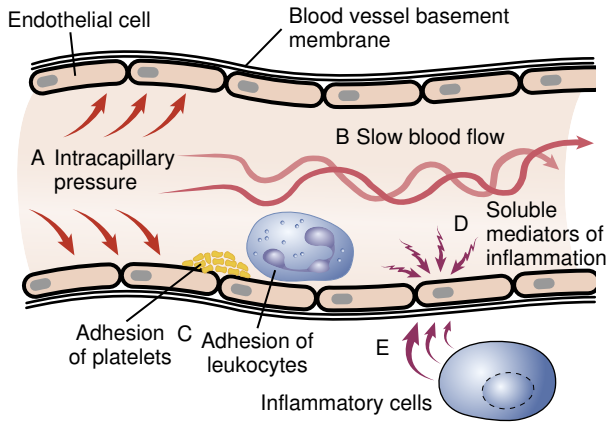


FIG. 2.4 Increased permeability of blood vessels, the most important causes of which are increased intracapillary pressure *(A),* relative hypoxia secondary to slow blood flow *(B),* adhesion of leukocytes and platelets to endothelial cells *(C),* the action of soluble mediators of inflammation in the plasma *(D),* and mediators of inflammation released from inflammatory cells in the tissue surrounding the blood vessel *(E).*

These cytokines play a major role in maintaining and amplifying inflammation.

Vascular Changes

The permeability of the vessel wall of capillaries and postcapillary venules changes, however, in response to inflammation as a result of several features of inflammation, most importantly because of the following (Fig. 2.4):

- Increased hydrostatic pressure inside the congested blood vessels
- Slowing down of the circulation, which reduces the supply of oxygen and nutrients to endothelial cells
- Adhesion of leukocytes and platelets to endothelial cells
- Release of soluble mediators of inflammation from WBCs, platelets, and endothelial cells; and from the biochemical changes of mediators already present in plasma

Mediators of Inflammation

The most important features of chemical mediators of inflammation are summarized as follows:

- Mediators of inflammation belong to two classes: (1) plasma-derived and (2) cell-derived substances. *Plasma-derived mediators* circulate in an inactive form and must be transformed into an active form by an activator. All activators have natural inactivators keeping them in balance. *Cell-derived mediators* may be preformed and stored in granules of platelets and leukocytes, or they may be synthesized de novo on demand. Preformed mediators (e.g., histamine stored in basophils) are released quickly and act immediately. Other mediators, such as prostaglandins, require time to be produced from their precursor, the arachidonic acid.
- Mediators of inflammation are multifunctional and thus have numerous effects on blood vessels, inflammatory cells, and other cells in the body. The most important effects relevant to an understanding of inflammation are vasodilation or vasoconstriction, altered vascular permeability, activation of inflammatory cells, chemotaxis, cytotoxicity, degradation of tissue, pain, and fever.
- Mediators of inflammation are biochemically heterogeneous. The most important are biogenic amines (e.g., histamine), proteins (e.g., complement proteins), and lipids (e.g., arachidonic acid derivatives, such as prostaglandins and leukotrienes) as discussed in the text below.

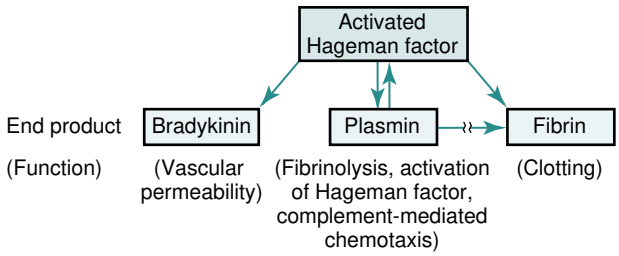


FIG. 2.5 Activation of Hageman factor leads to synthesis of bradykinin, plasmin, and fibrin, resulting in increased vascular permeability, thrombolysis, complement activation, and clotting, respectively.

Histamine. This low-molecular-weight bioamine is stored in the cytoplasmic granules of platelets, basophils, and mast cells. **Histamine** acts on the endothelial cells of venules increasing their permeability and thus allowing the exit of fluid from the intravascular into the interstitial space. Edema forms quickly but lasts less than half an hour because histamine is rapidly inactivated by histaminase. It is therefore called an *immediate transient reaction.*

Bradykinin. This protein acts on blood vessels in a manner similar to histamine but much slower. **Bradykinin** is activated in plasma from its precursor kininogen through the action of an enzyme called *kallikrein,* which, in turn, has to be activated by Hageman factor, also known as *coagulation factor XII*. Because Hageman factor simultaneously activates the clotting and complement systems, fibrinolysis, and chemotaxis, bradykinin is obviously a part of a very complex inflammatory reaction (Fig. 2.5). Finally, it should be added that bradykinin can incite pain and is one of the mediators of inflammation, accounting for dolor, the fourth cardinal sign of inflammation.

Complement proteins. **Complement proteins** are part of a system and are activated in a cascade, acting one on another. These complement proteins are numbered from 1 to 9 (e.g., C1, C5, C9). Activation of the complement cascade can occur through three pathways:

- *Classical pathway,* which is typically activated by antigen–antibody complexes formed in immune reactions. It is called *classical* because it was first discovered during the study of classic immune reactions. However, we now know that other stimuli can also initiate it. For example, proteolytic enzymes released from leukocytes or uric acid deposited in the tissue during an attack of gout also can activate complement through this pathway.
- *Alternative pathway,* originally named so by the immunologist who discovered it because it has nothing to do with the

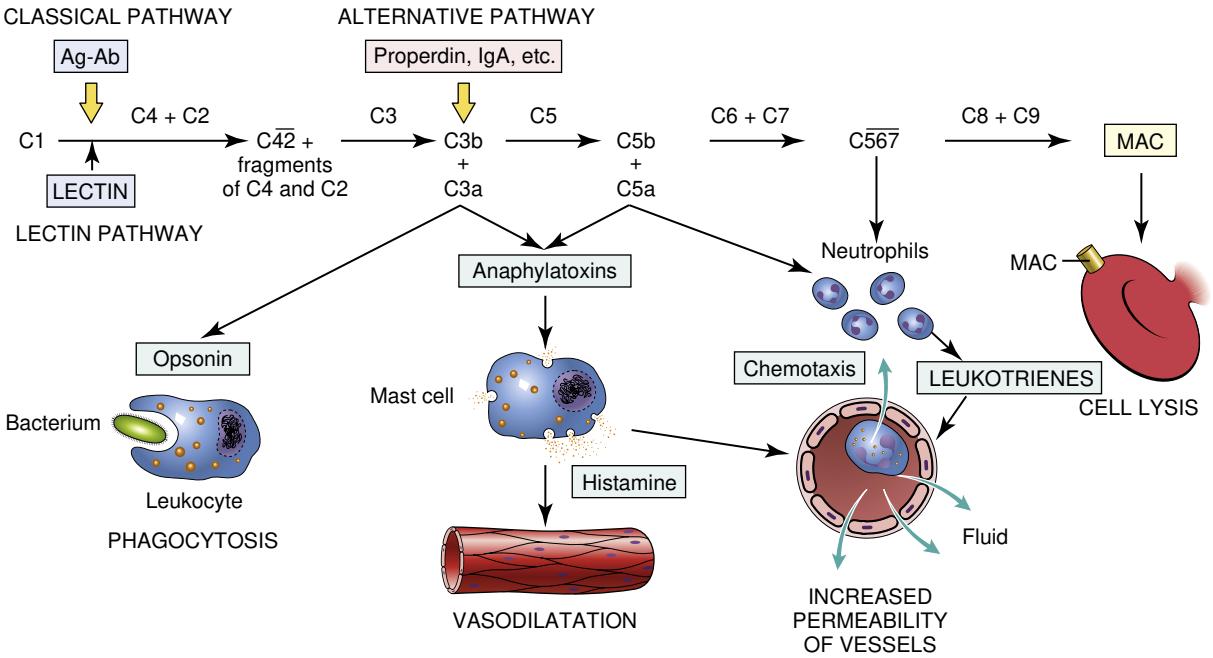


FIG. 2.6 Complement activation. Activation of the classical (antigen [Ag] and antibody [Ab] mediated), alternative, or lectin pathway leads to a common terminal pathway from C5 to C9. These complement components form the final membrane attack complex (MAC). Other intermediate complexes and fragments are also biologically active: opsonins facilitate phagocytosis; anaphylatoxins act on mast cells and mediate a release of histamine, which acts on blood vessels; and chemotactic fragments and intermediate complexes attract leukocytes to the site of inflammation. Activated neutrophils secrete other mediators, such as leukotrienes, which amplify the inflammatory response.

immune reactions and is activated by bacterial endotoxins, fungi, snake venom, and other substances.

- *Lectin pathway,* which is activated by the binding of plasma mannose-binding lectin (i.e., a carbohydrate-binding protein) to surface carbohydrates on bacteria.

All three pathways converge on a common terminal pathway (Fig. 2.6), which finally leads to the formation of the *membrane attack complex (MAC).* The MAC is enzymatically active and destroys cells by literally boring holes in their membranes. For example, in hemolytic anemia, the MAC perforates the cell membrane of RBCs and causes their lysis. Other biologically active complexes are formed along the common terminal pathway of the complement cascade. Furthermore, the activated complement components are cleaved into fragments (e.g., labeled C3a or C5b), which are also biologically active. Intermediate complement complexes and fragments act on leukocytes and endothelial cells directly or by activating other mediators of inflammation (e.g., C3b binds to the surface of bacteria, where it acts as *opsonin,* facilitating phagocytosis). Some complement fragments are considered *anaphylatoxins* because they mediate the release of histamine from mast cells, thus causing vasodilation and increased vascular permeability. Complement fragments promote *chemotaxis* of neutrophils and also activate these cells. Activating neutrophils produces leukotrienes from arachidonic acid, thus contributing to the propagation of inflammation. These main aspects of complement activation are illustrated in Fig. 2.6.

Arachidonic acid derivatives. **Arachidonic acid** is derived from phospholipids of cell membranes through the action of phospholipases. Once formed, it is further metabolized through one of two possible metabolic pathways: lipoxygenase and cyclooxygenase pathway (Fig. 2.7).

The *lipoxygenase* pathway leads to the formation of several leukotrienes (LTs) and lipoxins (LXs). *Leukotrienes* promote chemotaxis and increase vascular permeability, as typically found in *anaphylactic shock.* They also cause bronchospasm in asthma by contracting the smooth muscle in the bronchi. *Lipoxins* inhibit chemotaxis of leukocytes and apparently serve as negative regulators of leukotriene-mediated reactions.

The *cyclooxygenase* pathway leads to formation of several *prostaglandins* (PGs), and *thromboxane.* PGs , which belong to several classes (e.g., PGD_2, PGE_2, PGI_2) cause vasodilatation and increased vascular permeability and mediate pain and fever. Thromboxane promotes platelet aggregation, thrombosis, and vasoconstriction, whereas PGI_2 (also known as *prostacyclin*) counteracts these effects.

The synthesis of arachidonic acid and its derivatives can be inhibited by several drugs and/or hormones. For example, corticosteroid hormones have an inhibitory effect on *phospholipase,* which is involved in generating arachidonic acid from cell membrane phospholipids. Cyclooxygenase can be inhibited by aspirin, a drug known to have antiinflammatory and antipyretic effects. Newer selective inhibitors of cyclooxygenase and lipoxygenase have been synthesized and are used for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis and asthma.

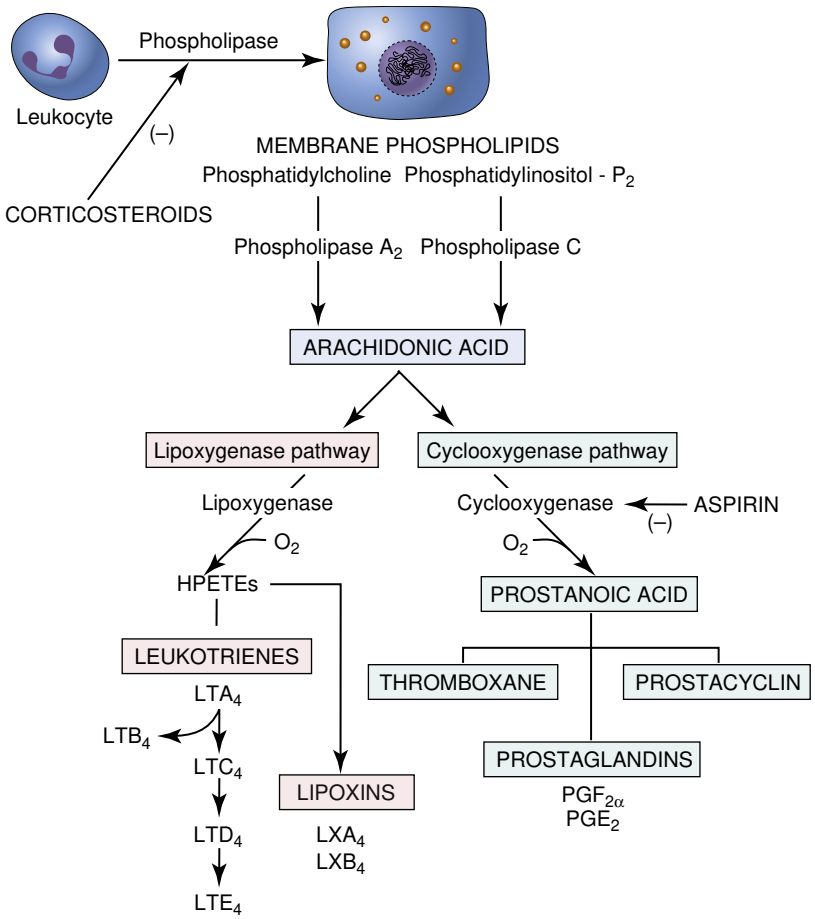


FIG. 2.7 Arachidonic acid metabolism. Phospholipases from leukocytes acts on the phospholipids in cell membranes, forming the arachidonic acid pool. The cyclooxygenase and lipoxygenase pathway metabolites actively mediate all aspects of inflammation. *HPETEs,* Hydroperoxyeicosatetraenoic acid compounds; *LT (A4-E4),* leukotrienes; *LX (A4, B4),* lipoxins; *PGF2$_\alpha$, PGE2,* prostaglandins F_{2a} and E_2.

CELLULAR EVENTS IN INFLAMMATION

Emigration of Leukocytes

The increased permeability of the vessel walls of the postcapillary venules and capillaries persists for several hours to several days and is usually accompanied by leakage of fluid into the interstitial space. This process is called *transudation,* and it typically accounts for the formation of the initial *inflammatory edema,* which is rich in proteins but contains few cells. Emigration of cells across the vascular wall leads to the formation of **exudate**. Exudate contains much more protein compared with transudate and, in addition, contains inflammatory WBCs. In acute inflammation, most of the cells involved are **polymorphonuclear neutrophils (PMNs)**, called so because their nucleus has a variable number of segments.

The inflammation begins with an emigration of PMNs through the vessel wall. This process sequentially in several phases: (1) adhesion of PMNs to the endothelial cells, (2) insertion of cytoplasmic pseudopods between the junctions of endothelial cells, (3) passage through the basement membrane, and (4) amoeboid movement away from the vessel toward the cause of inflammation (e.g., bacteria) (Fig. 2.8).

DID YOU KNOW?

Did the ancient Greeks use aspirin? Aspirin is a drug that was introduced in the nineteenth century. It contains acetylsalicylic acid (an inhibitor of cyclooxygenase), which has antiinflammatory properties.

Today, aspirin is used to treat headaches and fever. The ancient Greeks did not have the necessary technology to produce acetylsalicylic acid. However, they used the bark of the willow tree, which contains the same chemical, for medicinal purposes. Aspirin could therefore be considered one of the oldest medicinal substances still in use.

Active movement of PMNs along a concentration gradient is called **chemotaxis**. *Chemoattractants* (i.e., the chemicals that mediate chemotaxis) are derived from bacteria or tissues destroyed by inflammation or from activated complement. Chemotactic substances stimulate PMNs to move along a chemical concentration gradient until they reach its source or the site that has the highest concentration. In this respect, the migration of PMNs toward the chemoattractant resembles the movement of bees toward a flower or the pheromone-mediated movement of male insects toward receptive females of the same species.

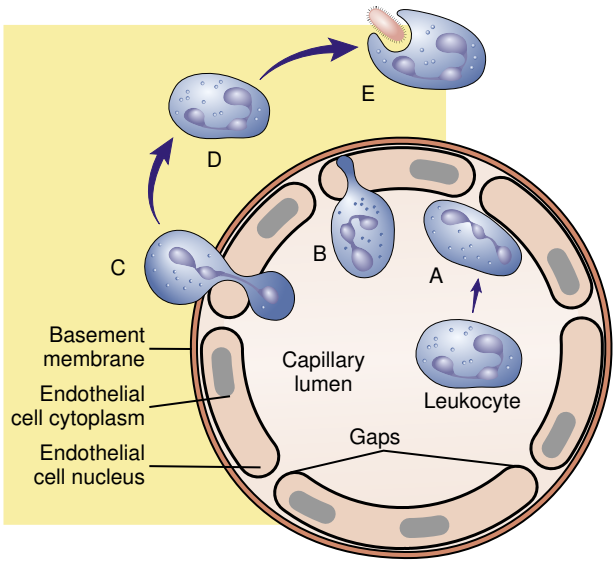


FIG. 2.8 The emigration of leukocytes from blood vessels comprises several steps: adhesion *(A),* insertion of pseudopods between the endothelial cells *(B),* passage through the basement membrane *(C),* ameboid movement toward the source of chemotactic stimuli *(D),* and phagocytosis of bacteria that were the source of chemotactic stimuli *(E).*

RBCs do not migrate actively like neutrophils. Nevertheless, if the vascular wall defect is large enough, RBCs will be carried through and into the interstitial space. This process is called diapedesis.

Phagocytosis

PMNs that reach bacteria or other sources of chemotactic substances lose their mobility and begin acting as scavengers. This is accomplished through **phagocytosis** or active ingestion of bacteria, similar to the uptake of particulate matter into lysosomes as described in Chapter 1.

To illustrate phagocytosis, let us assume that a PMN has encountered a bacterium (Fig. 2.9). The bacterium is recognized as a foreign particulate material by the pseudopods extending from the surface of the PMN. This recognition is followed by attachment of the cell membrane of the PMN to the bacterial cell wall. The attachment can be facilitated by immunoglobulin or complement, which may act like *opsonins,* that is, substances mediating the uptake of bacteria into PMNs. Many leukocytes have receptors for the C3 complement and the Fc portion of an immunoglobulin, and these receptors mediate the contact between bacteria and leukocytes.

DID YOU KNOW?

Most of the scientific terms for various aspects of inflammation were made up from Greek and Latin words by nineteenth century European physician-scientists. Many of these pertain to food consumption. For example, the term *phagocytosis* is derived from the Greek word for "eating." The term for opsonin was derived from the Greek word for "food catering." Opsonins coat bacteria like butter on a sandwich bun, making them ready for catering to the phagocytic neutrophils.

Engulfment of the bacterium is a process by which the cytoplasm of the PMN surrounds the foreign particle and encloses it into an invagination of the cell membrane. Inside the nascent vacuole, the bacterium is killed by bactericidal substances

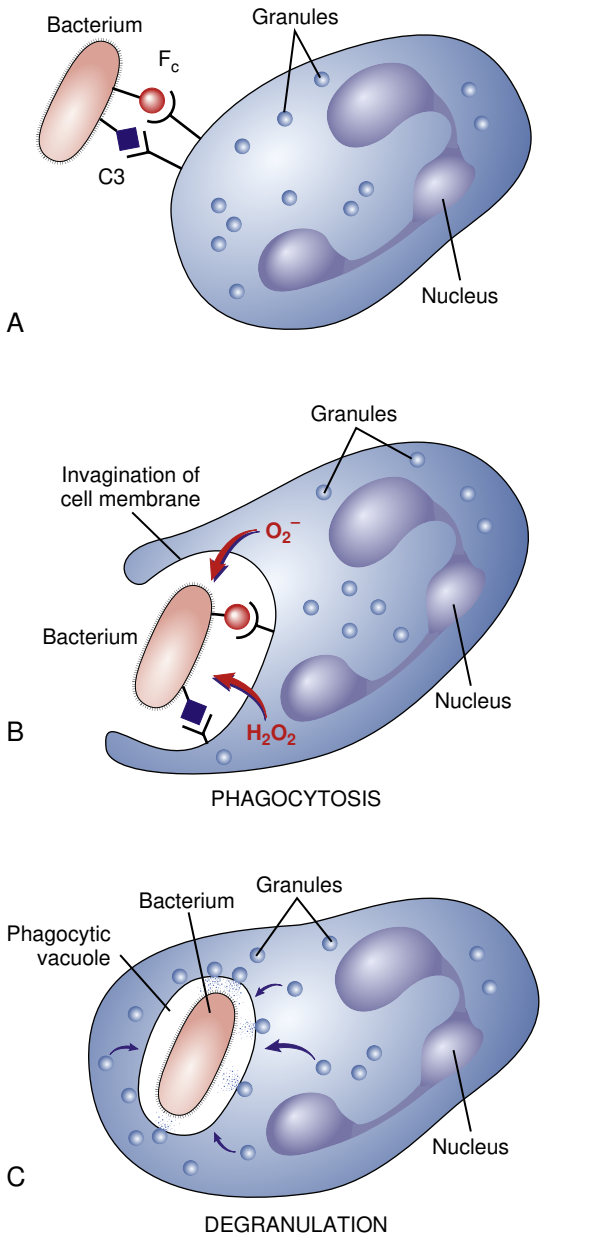


FIG. 2.9 Phagocytosis of bacteria. ***A,*** The bacterium that was opsonized (i.e., coated with immunoglobulin G [IgG] and complement [C3]) binds to the F_c and complement receptors on the surface of the leukocytes. ***B,*** Engulfment of the bacterium into an invagination of surface membrane is associated with an oxygen burst and formation of oxygen radicals that are bactericidal and thus kill the bacterium. ***C,*** Inclusion of the bacterium into a phagocytic vacuole is associated with the fusion of the vacuole with lysosomes and specific granules of the leukocyte. The contents of the lysosomes and specific granules are bactericidal and contribute to final inactivation and degradation of the bacterium in the heterophagosome. The cytoplasm of the leukocyte is therefore devoid of granules ("degranulation of leukocytes").

released from the cytoplasm of the PMN. The bacterium is internalized into a *phagocytic vacuole,* which then fuses with lysosomes. The contents of specific leukocytic granules and lysosomes are discharged into the lumen of this phagocytic vacuole. This degranulation of the PMN is the final step in the fight against bacteria. Lysosomal enzymes digest bacteria and dissolve them into harmless elementary components.

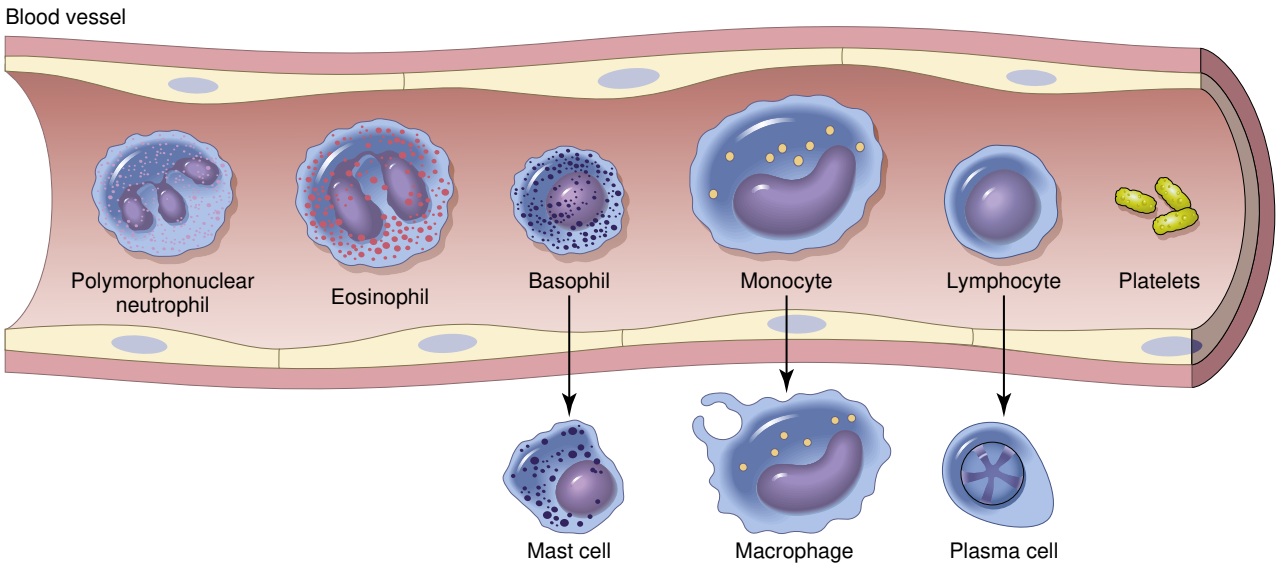


FIG. 2.10 Inflammatory cells. Inflammatory cells are white blood cells found inside the blood vessels and tissue cells found outside the blood vessels. This schematic drawing illustrates the typical features of polymorphonuclear neutrophils (PMNs), eosinophils, basophils, monocytes, and lymphocytes (found inside the blood vessels) and their descendants in tissues (mast cells, macrophages, and plasma cells).

Many PMNs die in their fight with bacteria. Dead and dying leukocytes, admixed with tissue debris and lytic enzymes released from their granules, form a viscous yellow fluid known as *pus*. Inflammation dominated by pus formation is called *purulent inflammation*.

Cells of Inflammation

PMNs are the primary cells that respond to bacterial infection. Platelets are also present from the earliest stages of inflammation and other cells are recruited shortly thereafter. These latecomers include eosinophils, basophils, monocytes, and lymphocytes. In tissue spaces, basophils transform into mast cells, monocytes transform into macrophages, and lymphocytes differentiate into plasma cells (Fig. 2.10).

Polymorphonuclear Neutrophils

PMNs are the most abundant WBCs in the circulating blood, accounting for 60% to 70% of all WBCs. They are the first cells to appear in acute inflammation. PMNs have a segmented nucleus and a well-developed cytoplasm filled with granules. The term is based on the fact that the nucleus may have one to five segments—that is, it is polymorphic (variably shaped). Because the granules of PMNs stain with both hematoxylin and eosin (H&E), they are considered "neutral" and known as *neutrophilic granulocytes* or simply *neutrophils*.

The most important features of PMNs include the following:

- *Mobility.* PMNs are highly mobile and are therefore the first cells to reach the site of inflammation in response to chemotactic substances.
- *Phagocytosis.* PMNs are scavenger cells capable of ingesting bacteria and other cellular debris.
- *Bactericidal activity.* Granules in the cytoplasm of PMNs contain substances that kill bacteria. Toxic oxygen radicals generated during the activation of PMNs are also *bactericidal* (i.e., they kill bacteria).
- *Cytokine production.* PMNs secrete and release various mediators of inflammation. These biologically active substances promote inflammation, recruit new leukocytes, and cause systemic symptoms. For example, IL-1 released from PMNs serves as an endogenous *pyrogen,* acting on the hypothalamic thermoregulatory center and thus causing fever.

Eosinophils

Eosinophils, or eosinophilic leukocytes, account for 2% to 3% of all circulating WBC. In the zone of inflammation, eosinophils appear 2 to 3 days after the PMNs. This is, in part, because of their slower mobility and their comparatively slower reaction to chemotactic stimuli.

The term *eosinophil* is based on the staining property of cytoplasmic granules, which bind eosin and appear pink in routine H&E–stained slides. Like PMNs, they are mobile, phagocytic, and bactericidal. In contrast to a PMN, however, an eosinophil has a single nucleus, which is usually divided into two lobes located at opposite sides of the cytoplasm.

Eosinophils interact with basophils and are prominent in *allergic reactions,* such as hay fever and asthma. They also participate in the inflammatory response to *parasitic infections.* Eosinophils live longer than PMNs and therefore may be seen in chronic inflammation.

Basophils

Basophilic leukocytes account for less than 1% of circulating WBCs. Nevertheless, these cells are important participants in inflammatory reactions and are most prominent in *allergic reactions* mediated by immunoglobulin E (IgE). **Basophils** have a bean-shaped single nucleus and are somewhat larger than PMNs. Their cytoplasm contains granules rich in vasoactive substances, such as histamine. Basophils are precursors of **mast cells**, which have similar functions and are considered *tissue-based basophils.*

Macrophages

Macrophages (also known as *histiocytes*) are tissue-based mononuclear cells derived from blood **monocytes**. They have a bean-shaped nucleus and are larger than PMNs. Macrophages appear at the site of inflammation 3 to 4 days after the onset of infection or tissue destruction. Macrophages are long-lived cells and therefore are typically present in chronic inflammation.

Macrophages, as their name implies, are capable of phagocytosis and are active in bacterial killing, albeit not as efficiently as the PMNs. Macrophages also secrete numerous mediators of inflammation (*cytokines*) that act both locally and on the body as a whole.

Platelets

Platelets (*thrombocytes*) are fragments of the cytoplasm released from megakaryocytes in bone marrow. They do not have a nucleus, and their cytoplasm contains vacuoles and membrane-bound granules. These granules contain various biologically active substances, such as histamine; coagulation proteins; cytokines; and growth factors, such as *platelet-derived growth factor* (PDGF).

Platelets release their granules upon contact with the extracellular matrix, endothelial cells, or thrombin formed by early thrombi. The release of histamine increases vascular permeability in the early stages of inflammation. Other substances released upon degranulation promote blood clotting, as described in greater detail in Chapters 6 and 9. PDGF promotes the proliferation of connective tissue cells and is important in the healing of inflammation.

Other Cells

Lymphocytes and **plasma cells** are components of chronic inflammation. However, because these cells have immune functions, they are described in greater detail in Chapter 3. Fibroblasts and angioblasts participate in chronic inflammation and healing and are described later in this chapter.

CLASSIFICATION OF INFLAMMATION

Inflammation can be classified in clinical practice according to four parameters. These include duration, etiology, location, and morphology or pathologic characteristics.

Duration

Inflammation can be classified according to its duration: either acute or chronic. **Acute inflammation** usually has a sudden onset and lasts from a few hours to a few days; for example, inflammation of the nasal mucosa *(acute rhinitis)* that occurs with the common cold is acute. **Chronic inflammation** lasts longer, usually weeks to months or even years.

Chronic inflammation is usually related to acute and represents one of the following events:

- Extension of acute inflammation
- Prolonged healing of acute inflammation
- Persistence of causative agent(s) that initiated the acute inflammation

Some types of chronic inflammation evolve without a typical acute phase and represent a slow-smoldering process from their onset. This type of inflammation is classified as *primary chronic inflammation* to distinguish it from inflammation that is preceded by an acute phase, called *secondary chronic inflammation.* For example, tuberculosis is a chronic disease with an imperceptible acute phase and is classified as primary chronic inflammation. Typically, the initial symptoms are nonspecific, and most patients complain only of fatigue and low-grade fever and are not able to pinpoint the exact time of onset of their symptoms. Conversely, acute viral hepatitis B is usually associated with a sudden onset of jaundice. In most instances, the process heals without consequence. However, in a small number of patients, the infection persists, with consequent chronic hepatitis, which may progress to cirrhosis of the liver. In such cases, the chronic inflammation is considered to be secondary to an acute infection.

Chronic inflammation also develops in response to foreign particular matter. For instance, a foreign body granuloma will develop around thorns in subcutaneous tissue. Likewise, persons exposed to dust containing silica particles develop chronic lung silicosis, which does not have a recognizable acute phase.

Autoimmune diseases, such as rheumatoid arthritis, also are characterized by a chronic course, although these diseases tend to have periodic flare-ups (called *exacerbations*). Some autoimmune diseases, such as autoimmune hepatitis and systemic lupus erythematosus, respond well to medical treatment. However, if the treatment is interrupted, symptoms may reappear (called *recurrence).*

Etiology

Inflammation is caused by infectious pathogens or by chemical and physical factors, foreign bodies, and immune mechanisms briefly described as follows:

- *Infections* are caused by living pathogens and are classified as bacterial, viral, protozoal, fungal, or helminthic.
- *Chemical causes* can be classified as organic or inorganic, industrial or medicinal, and exogenous or endogenous.
- *Physical causes* of inflammation, which act on the tissue by transmitting upon them measurable energy, including heat, irradiation, and trauma.
- *Foreign bodies* also may cause acute or chronic inflammation, which is typically seen around a thorn wedged into the skin or in the subcutaneous tissue around surgical sutures.
- *Immune causes* of inflammation are related to antibody or cell-mediated hypersensitivity reactions (discussed in Chapter 3).

Location

Inflammation may be *localized* or *widespread (systemic).* For example, a boil or a furuncle is a localized skin infection. Disseminated boils, a condition termed *furunculosis,* occurs in people with a reduced resistance to bacterial infections. From the furuncles, bacteria may enter the bloodstream and cause a systemic infection, which is called **bacteremia**. Symptomatic bacterial infection with the appearance of bacterial toxins in blood (*toxemia*), followed by systemic inflammatory response syndrome (SIRS), mostly mediated by cytokines released in response to infection, is called *sepsis.* It is a life-threatening clinical condition, which may be complicated by dysfunction of major organs and even septic shock and circulatory failure.

DID YOU KNOW?

The Bible mentions Job as a pious man whose body was covered with boils by Satan. In reference to this Biblical story, physicians have named a hereditary susceptibility to bacterial infections as "Job syndrome." Children affected by this disease typically have numerous skin furuncles, which are often complicated by pneumonia and infections of other internal organs. Scientists have isolated the gene that accounts for the defective defense against bacterial infections in this syndrome.

PATHOLOGY OF INFLAMMATION

Several forms of inflammation can be recognized on gross examination of the affected tissues. These changes are readily seen in clinical practice. Physical examination of the patient may reveal typical signs of inflammation on the skin, eyes, oral mucosa, or genital organs. During surgery, it is possible to see the inflamed internal organs. These organs can also be visualized without surgery by using a fiberoptic instrument, such as a *laparoscope,* which is used to inspect the abdominal cavity.

The terms used for the various forms of inflammation are usually descriptive. Most terms are formed by adding a suffix—*itis*—to the Latin or Greek name for various organs. For example, *hepatitis* denotes inflammation of the liver, and *appendicitis* signifies inflammation of the appendix. Additional terms are used for greater precision. For example, *posttransfusion viral hepatitis B* indicates that the disease was acquired by transfusion and was as a result of hepatitis B virus.

Serous Inflammation

Serous inflammation, considered the mildest form of inflammation, is characterized by the *exudation of serum,* that is, the acellular clear fluid remaining in a tube after the blood coagulum has formed. Serous inflammation occurs in the early stages of most inflammation. For example, in the early stages of bacterial or viral pneumonia, it can be recognized by x-ray examination and microscopically as a protein-rich material inside the alveolar space, which contains only a few inflammatory cells.

Serous inflammation is typical of many viral infections. The skin vesicles caused by herpesvirus are perhaps the best example of serous inflammation (Fig. 2.11). These vesicles are filled with protein-rich fluid similar to serum in the blood vessels.

Autoimmune diseases affecting serosal surfaces, such as the peritoneum, pleura, or pericardium, also present as serous inflammation. Depending on the anatomic location, serous pericarditis, pleuritis, and peritonitis are all characterized by accumulation of a clear, yellowish fluid in these body cavities. Joint swelling, secondary to intraarticular fluid accumulation, is typical of rheumatoid arthritis, clinically the most common autoimmune disorder.

Joint swelling and accumulation of serous fluid may occur as a result of joint trauma, in which case, it is obviously caused by a physical agent. Blisters of the skin caused by second-degree burns are yet another example of serous inflammation, in this case caused by a physical agent.

In most of these forms of serous inflammation, the serous fluid is readily reabsorbed, and if the cause of the inflammation is eliminated, these lesions heal without any permanent consequences.

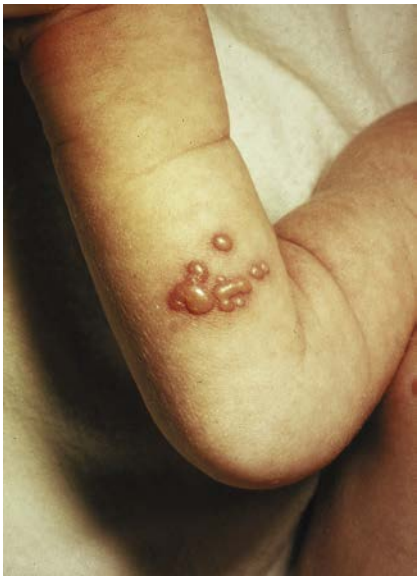


FIG. 2.11 Serous inflammation. Herpes infections manifest as vesicles filled with serous fluid.

Fibrinous Inflammation

Fibrinous inflammation is characterized by an exudate that is rich in fibrin. Fibrin is formed from long strands of polymerized fibrinogen, one of the largest plasma proteins. In contrast to serous exudate, which contains predominantly albumin and immunoglobulins that have leaked from intact, but permeable, blood vessels or through small vascular defects, extravasation of fibrin occurs only through larger defects of the vessel wall. Fibrinous exudate is therefore indicative of severe inflammation.

Fibrinous inflammation is seen in many bacterial infections, such as "strep throat" or bacterial pneumonia. In bacterial pericarditis, the surface of the heart is covered with shaggy, yellowish layers of fibrin (Fig. 2.12).

Fibrinous exudate does not resolve as easily as serous exudate does. Macrophages that invade the exudate have the capacity to lyse fibrin and thrombi. Blood vessels grow into the exudate, probably to provide a route for scavenger cells and for the removal of the debris. These blood vessels fill the space occupied by fibrin and further obliterate it, a process termed *organization of the exudate.* Macrophages in the exudate also stimulate the ingrowth of fibroblasts, contributing further to the formation of fibrous tissue and obliteration of the tissue space (e.g., organizing pneumonia).

Purulent Inflammation

Purulent inflammation is typically caused by pus-forming bacteria, such as streptococci and staphylococci. Pus is viscous yellow fluid composed of dead and dying PMNs and necrotic tissue debris. It is rich in lytic enzymes released from leukocytes, destroyed cells, and bacteria. Purulent exudate, also rich in fibrin, is said to be *fibrinopurulent.*

Pus may accumulate on the mucosa, skin, or internal organs (Fig. 2.13). A localized cavitary purulent inflammation with

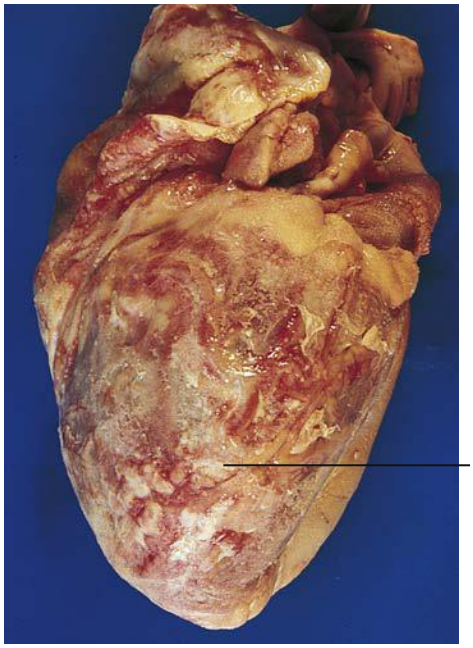


FIG. 2.12 Fibrinous pericarditis. The epicardial surface of the heart is covered with a shaggy layer of fibrin.

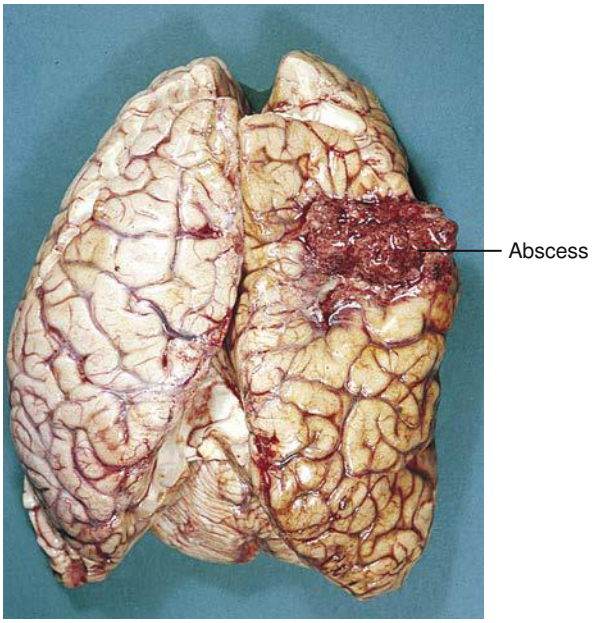


FIG. 2.14 Brain abscess. The localized lesion in the right hemisphere consists of pus admixed with mushy brain tissue.

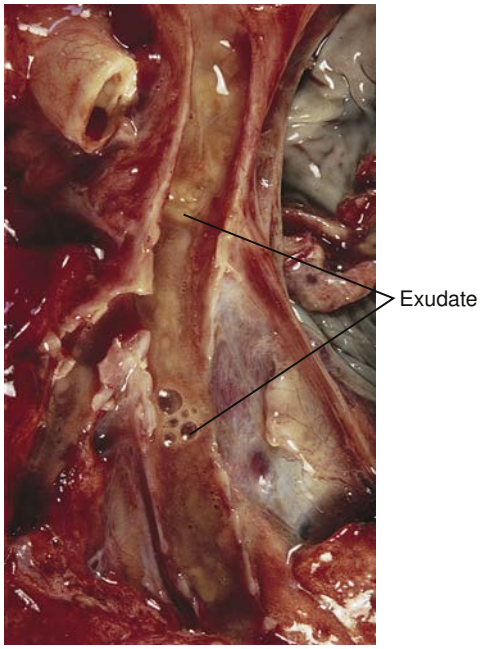


FIG. 2.13 Purulent tracheobronchitis. The trachea is filled with pus, which appears as a turbid yellow exudate.

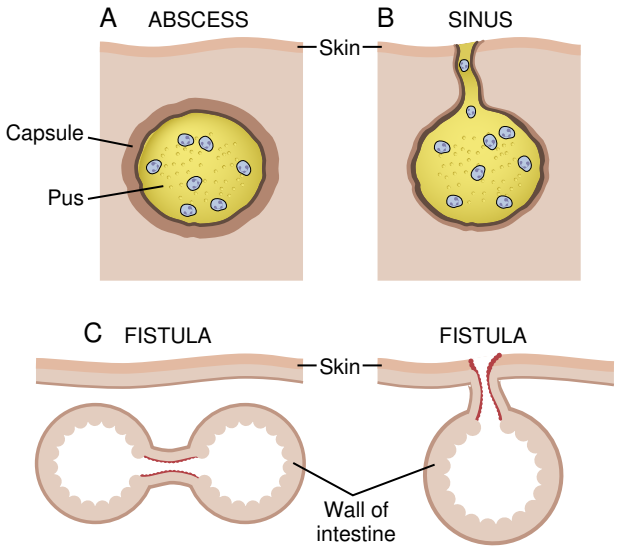


FIG. 2.15 Diagram of an abscess, sinus, and fistula. ***A,*** An abscess is a localized, purulent inflammation. Older abscesses are surrounded by a capsule that consists of granulation tissue. ***B,*** A sinus forms a tract connecting the abscess with the skin. This allows the drainage of pus outside the body. ***C,*** A fistula is an inflammatory tract that connects either two hollow organs or a hollow organ with the skin.

accumulation of pus in the newly formed tissue space is called an **abscess** (Fig. 2.14). In chronic abscesses, the wall of the cavity is composed of a capsule, which consists of fibrotic granulation tissue. Abscesses do not heal spontaneously and must be evacuated surgically.

Large abscesses tend to rupture, forming a sinus or fistula (Fig. 2.15). A *sinus* is a cavity usually at the site of a previous abscess, which drains through a tract to the surface of the body. A *fistula* (Latin, meaning "tube") is a similar channel formed between two preexisting cavities, hollow organs, or between a hollow organ or preexisting cavity and the surface of the body. A fistula may be formed, for example, between two loops of intestine that have been fused together by inflammation, as we will see in the discussion of Crohn disease in Chapter 10. Accumulation of pus in a preexisting cavity is called *empyema.* For example, empyema of the gallbladder occurs when drainage of pus from the gallbladder is obstructed by an impacted gallstone. Thoracic empyema denotes accumulation of pus in the pleural cavity.

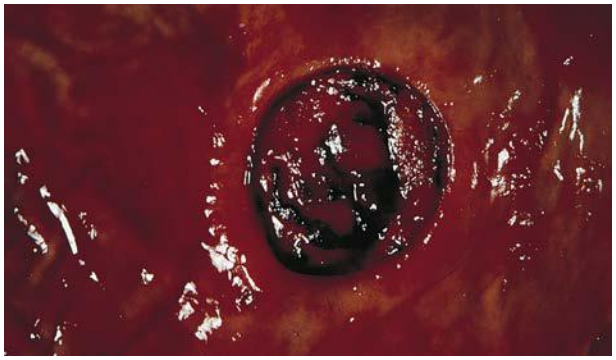


FIG. 2.16 Peptic ulcer. An ulcer represents a defect of the gastric mucosal lining.

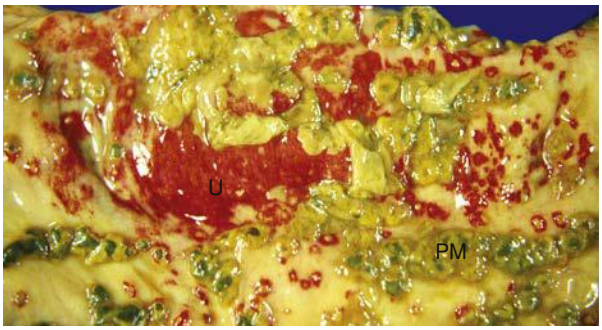


FIG. 2.17 Pseudomembranous inflammation. The mucosa of the large intestine is partially ulcerated and red (U), but in other parts it is covered with greenish-yellow material corresponding to the pseudomembranes (PM).

Ulcerative Inflammation

Ulcerative inflammation is characterized by formation of an **ulcer** of the skin or mucosa of hollow organs (e.g., stomach or intestines). An ulcer is defined as a defect involving the epithelium, but it may extend into the deeper connective tissue as well. A typical example is the peptic ulcer of the stomach or duodenum (Fig. 2.16).

Pseudomembranous Inflammation

Pseudomembranous inflammation is a form of ulcerative inflammation that is combined with fibrinopurulent exudation. The exudate of fibrin, pus, cellular debris, and mucus forms a pseudomembrane on the surface of the ulcers (Fig. 2.17). For example, *Clostridioides difficile* (a bacterium commonly known as *C. diff.*) causes pseudomembranous colitis in persons who have been taking broad-spectrum antibiotics. These drugs eliminate the normal intestinal flora and allow an overgrowth of *C. diff.*, which secrete exotoxin, killing intestinal cells, causing ulceration and exudation in form of pseudomembranes. Similar pseudomembranes can also form in the throat affected by diphtheria, a previously lethal childhood infection that has been almost completely eradicated in the Western world through childhood immunization.

Chronic Inflammation

Chronic inflammation is best defined on the basis of its duration—it lasts a long time. Because of its prolonged duration, such an inflammation produces more extensive tissue destruction, heals less readily, and is associated with more serious functional deficiencies compared with acute inflammation.

Chronic infections are marked by an exudate composed of lymphocytes, macrophages, and plasma cells. The secretory products of chronic inflammatory cells stimulate proliferation of fibroblasts and perpetuate the inflammation by constantly recruiting new inflammatory cells. Thus loss of parenchymal cells is accompanied by **scarring** (i.e., the replacement of normal cells with fibroblasts and collagen), which may distort the organs involved. For example, fallopian tubes affected by chronic pelvic inflammatory disease (PID) are twisted and obliterated. Kidneys affected by chronic glomerulonephritis are small and shrunken and do not function properly, accounting for the clinical symptoms of uremia, also known as *end-stage kidney disease.*

The functional consequences of chronic inflammation cause many clinical symptoms. For example, the **fibrosis** (hardening of tissue) associated with chronic lung disease causes thickening of the alveolar walls, which impairs the passage of oxygen from air into blood and causes *dyspnea* (shortness of breath). Constrictive pericarditis prevents dilation of the heart during diastole and adversely affects the pumping function of the heart. Chronic myocarditis with scarring may prevent the normal transmission of electrical signals through the heart muscle and also weakens the contractile strength of the myocardium, leading to heart failure. Loss of pancreatic parenchyma in chronic pancreatitis causes severe digestive problems because of the resultant deficiency of pancreatic enzymes.

Granulomatous Inflammation

Granulomatous inflammation is characterized by formation of **granulomas**. Granulomas, named so because on gross examination, they often resemble small granules, are formed by T lymphocytes, macrophages, and multinucleated giant cells. They may be caused by antigens that evoke a cell-mediated hypersensitivity reaction or by antigens that persist at the site of inflammation. Granulomas are typically formed in tuberculosis but are also found in tissues infected by fungi, such as *Histoplasma capsulatum* and *Blastomyces dermatitidis.*

Macrophages and T lymphocytes form granulomas and are part of a hypersensitivity reaction, which is discussed in greater detail in Chapter 3. Suffice it to say here that T lymphocytes respond to injury by accumulating in the tissue and secreting cytokines, which attract macrophages. Under the influence of cytokines secreted by lymphocytes, the macrophages transform into the so-called *epithelioid cells,* which adhere to each other and form a nodule. Epithelioid cells may fuse and thus form *multinucleated giant cells* (Fig. 2.18).

Granulomas of tuberculosis and other infectious granulomas are often associated with central caseous necrosis. In the lungs, confluent necrotizing granulomas may cause cavities, erode the blood vessels, and ultimately destroy the entire lung. In contrast, immunologically mediated granulomas of *sarcoidosis,* a disease of unknown origin, do not show central caseating necrosis (hence called *noncaseating granulomas*) and are less destructive.

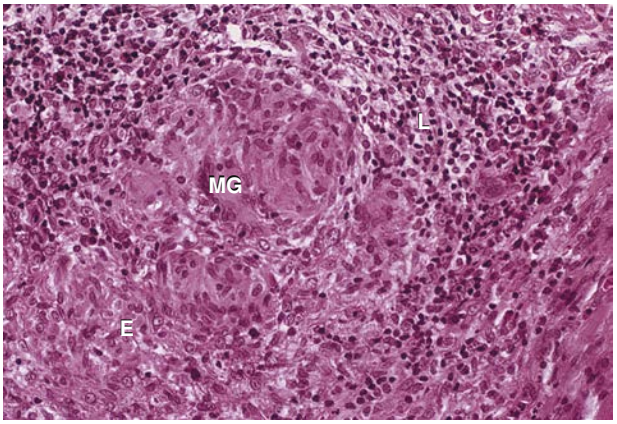


FIG. 2.18 Granulomatous reaction. The lesion is composed of epithelioid cells (E), lymphocytes (L), and multinucleated giant cells (MG).

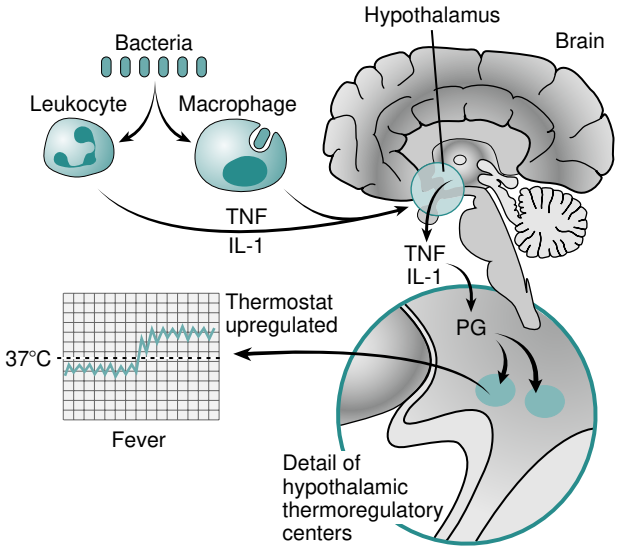


FIG. 2.19 Pathogenesis of fever. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are endogenous pyrogens released from leukocytes or macrophages during inflammation. The action of IL-1 and TNF on the thermoregulatory centers in the hypothalamus is mediated by prostaglandins (PGs). This can be inhibited by aspirin, which blocks prostaglandin synthesis by inhibiting cyclooxygenase.

CLINICOPATHOLOGIC CORRELATIONS

The classic symptoms of inflammation are still the most important local findings and most useful indicators in the diagnosis of inflammation. For example, acute inflammation of the nail fold *(paronychia)* occurs with symptoms of redness *(rubor),* swelling *(tumor),* warmth *(calor),* and pain *(dolor).* Movement and the normal function of the finger may also be limited by pain *(functio laesa).*

Similar symptoms could characterize an acute attack of appendicitis, but the appendix is hidden from sight, so all the symptoms cannot be recognized immediately. The swollen hyperemic appendix may produce pain, or the pain may be elicited by the physician palpating the abdominal wall in the right lower quadrant. Clearly, one cannot see the appendix through the skin; thus, the other signs of inflammation do not become evident until the surgeon intervenes and removes the affected organ. At the time of the operation, the appendix is typically swollen, red, and warm.

Localized inflammation like appendicitis typically produces two important systemic findings: fever and leukocytosis. **Fever**—an elevation in body temperature that exceeds 37°C—is a typical response to acute inflammation caused by *endogenous pyrogens.* These substances—primarily IL-1 and TNF—act on the thermoregulator centers of the hypothalamus, which serves as a thermostat (Fig. 2.19). If the threshold of the thermostat (like the heating sensor in a house) is raised, the temperature of the body rises.

Fever is mediated by prostaglandins that are released by pyrogens in the hypothalamic center. Prostaglandin synthesis can be inhibited by antipyretic drugs, such as aspirin. However, in most cases, the fever will abate on its own as soon as the inflammation resolves. Prolonged or uncontrolled fever may cause hypermetabolism and increased energy depletion resulting in fatigue and exhaustion.

Leukocytosis, an increase in the number of leukocytes in blood, is another important sign of inflammation. Normal blood has 4500 to 11,000 WBCs/ μL. Mediators of inflammation act on the bone marrow and stimulate a rapid release of leukocytes, resulting in leukocytosis (i.e., leukocytes in the blood exceed 11,000/ μL). Leukocytosis is usually transient except in certain forms of chronic inflammation, in which it may be prolonged.

Other symptoms of inflammation are mostly nonspecific and are called *constitutional.* These include fatigue, weakness, depression, lack of appetite, generalized pain, and exhaustion. The pathogenesis of these symptoms is not understood but could be related to the action of mediators of inflammation, such as IL-1 or TNF. These cytokines act on the liver and induce the production of several plasma proteins, such as *cross-reactive protein* (*CRP)* and others, known collectively as *acute phase reactants.* Acute phase reactants cause an increase in the *erythrocyte sedimentation rate (ESR),* which may be used as a laboratory test for detecting inflammation.

HEALING AND REPAIR

Acute inflammation may heal without any consequences *(sequelae),* or it may progress to chronic inflammation. Mild inflammation usually resolves spontaneously after the inciting stimuli have disappeared and the mediators of inflammation are no longer being secreted. However, if the inflammation was accompanied by considerable destruction of tissue, complete healing may be delayed or never accomplished.

Tissue loss has different consequences in different organs and tissues, depending primarily on the nature of the cells forming those tissues. In general, cells can be classified into three groups, according to their capacity to proliferate (Fig. 2.20):

- *Continuously dividing* or *mitotic cells* (also known as *labile cells*) are cells that divide through their entire life span. Such cells are typically known as *tissue stem cells* and are found in the basal layer of the skin or in the mucosa of internal organs. These cells divide at a regular rate and give rise to more differentiated cells. Their descendants replace the superficial

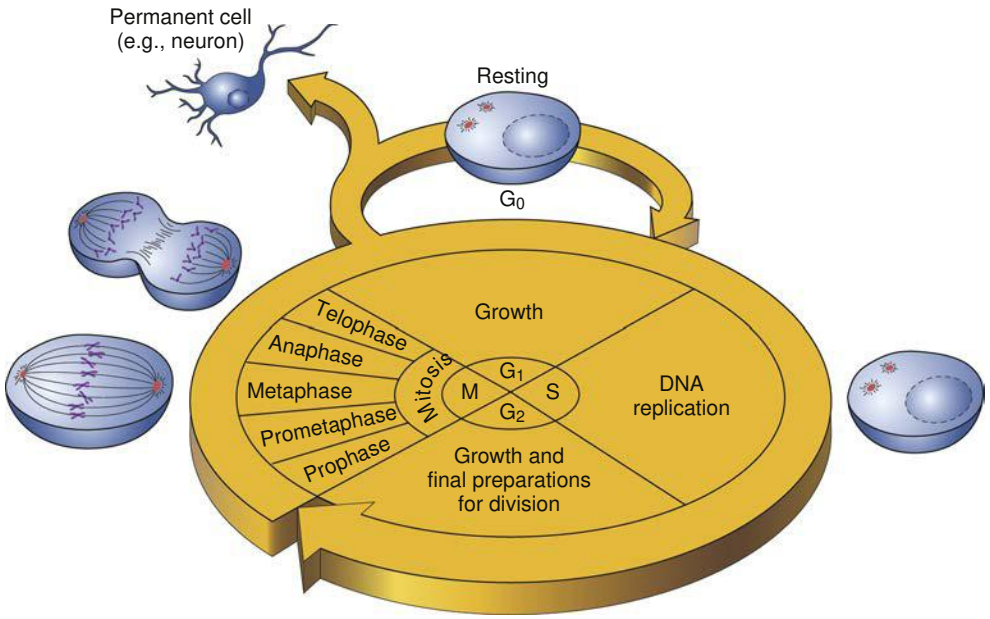


FIG. 2.20 Three cell types in relation to the mitotic cell cycle. Mitotic cells may be in any of the four phases of the normal mitotic cycle. Facultative mitotic cells are arrested in the G_0 (resting) phase but can enter the cycle, if necessary. Postmitotic cells have left the mitotic cycle and cannot reenter it. Mitosis is a relatively short phase of the mitotic cycle. After mitosis, the mitotic cells enter the G_1 (gap) phase, which is of variable duration. The facultative mitotic cells enter a G_0 phase, during which they perform various specialized functions. The G_1 phase is followed by the deoxyribonucleic acid (DNA) synthetic phase (S) and a second gap phase (G_2).

epithelial cells that have been shed after having reached the end of their predetermined life span.

- *Quiescent, facultative mitotic cells* (also known as *stable cells*) do not divide regularly but can be stimulated to divide, if necessary. Such cells form the parenchymal organs (e.g., the liver or kidney). Loss of liver parenchyma after partial hepatectomy stimulates the remaining liver cells to enter *mitosis* and, by dividing, to replace the loss. When the liver has regenerated, the cells become quiescent again and do not proliferate.
- *Nondividing, postmitotic cells* (also known as *permanent cells*) do not have the capacity to proliferate under any circumstances. This category includes neurons and myocardial cells. Loss of postmitotic myocardial cells cannot be compensated; instead, the defect is repaired by fibrous scarring. Loss of brain cells is also irreversible.

Continuously dividing cells can thus easily repair a defect in the epithelial covering. Likewise, skin *wounds* or *mucosal ulcers* heal readily under appropriate conditions as the superficial layers are replenished from the descendants of cycling stem cells in the basal layer or the intestinal crypts. Loss of liver or kidney tubular cells may be replenished by regeneration to complete the healing. However, necrosis of heart muscle or brain cells leads to permanent defects that cannot be corrected by the proliferation of equivalent, highly specialized cells.

Wound Healing

Wound healing is an important event that takes place at many anatomic sites. It is perhaps best illustrated by the sequence of events that occur after skin incision. Similar changes occur during the healing of internal wounds, at the site of internal surgical incisions, and after surgical removal of organs or tumors.

Cells Participating in Healing

The most important cells that are involved in wound healing are leukocytes, macrophages, various connective tissue cells, and epithelial cells. PMNs play a brief role in scavenging the initial site of injury; however, *macrophages* are much more important. Macrophages are stay long at the site of healing and produce many cytokines, growth factors, and mediators that act on other connective tissue cells, most notably *myofibroblasts, angioblasts,* and *fibroblasts* to form *granulation tissue.*

Myofibroblasts. As their name implies, **myofibroblasts** have hybrid properties of smooth muscle cells and fibroblasts. This enables them to contract, similar to muscle cells, and secrete matrix substances, such as fibroblasts. The contraction of myofibroblasts that occurs within the first few days of healing reduces the defect and holds the margins of tissue in close approximation. This enables the proliferating epithelial cells to cover the surface defect and to restore the integrity of the epithelium.

Angioblasts. **Angioblasts** are precursors of blood vessels. They proliferate like sprouts from the several small blood vessels at the margins of the wound. These appear 2 to 3 days after incision, and by the fifth or sixth day, the entire field is permeated with newly formed blood vessels that serve two functions: (1) to provide a route for the scavenger cells to remove the scab and tissue debris and (2) to allow the influx of blood and its accompanying oxygen and nutrients.

Fibroblasts. **Fibroblasts** are connective tissue cells that produce most of the extracellular matrix. Of the numerous matrix components, the most important are fibronectin and several forms of collagen.

- *Fibronectin* is a protein found in blood and connective tissues. It has numerous functions in wound healing, the most

important of which are the formation of a scaffold, the provision of tensile strength, and the ability to "glue" other substances and cells together.

- *Collagens* are predominantly fibrillar proteins found in the intercellular (interstitial) spaces of most organs. Some 30 different collagens have been isolated and characterized thus far, and it is likely that several others will be identified in the near future. Collagen type I is the most abundant protein in the human body, forming the bony skeleton and essentially all connective tissues in various organs. Collagen type III is important and is mentioned here because it forms thin fibers that are first to appear in the process of wound healing.

The secretion of collagen is rather complex and requires several essential elements, such as zinc, copper, and vitamin C (*ascorbic acid*). Furthermore, collagen does not acquire its full strength until it is laid down in the extracellular spaces. This occurs several weeks after injury, when the collagen fibers are cross-linked with each other to form a dense meshwork.

DID YOU KNOW?

Vitamin C is called *ascorbic acid,* which, in Latin, means that it prevents scurvy. Today, we all know that scurvy is a sequela of vitamin C deficiency. However, it took many years for this fact to become well known. It all began some 250 years ago, when the Scottish captain James Lind forced his sailors to take a spoonful of citrus juice daily during long sea voyages. Thereafter, he wrote a book on how lemon can prevent scurvy. Before Lind's discovery, scurvy was a deadly disease that claimed the lives of millions of sailors on transoceanic voyages. Today, vitamin C is routinely added to many commercial foods; it not only prevents scurvy but also helps with wound healing.

Clinical Wound Healing

Healing of sterile surgical wounds occurs by *first intention* (Fig. 2.21). The incision site initially contains coagulated blood that forms a scab. The scab is invaded by PMNs, whose function is to scavenge debris. These are replaced 2 to 4 days later by macrophages. The cytokines and growth factors secreted by macrophages promote the ingrowth of myofibroblasts, angioblasts, and fibroblasts.

The vascularized connective tissue that is rich in macrophages, myofibroblasts, angioblasts, and fibroblasts is called **granulation tissue** (Fig. 2.22). Granulation tissue represents a temporary, makeshift structure that changes over time. Initially, it contains many myofibroblasts, which contract the wound and then disappear. Macrophages also become less prominent, and the blood vessels that are initially prominent slowly collapse. As a result, if everything goes well, the wound becomes less inflamed and, by the second week, starts blanching. The interstitial spaces that were initially filled with extravasated blood become edematous and finally are filled with matrix. With time, the composition of this matrix changes from fibronectin and fibrin to type III collagen and, finally, to predominantly type I collagen, resulting in the formation of a *scar.*

Changes in the dermis are accompanied by a proliferation of epithelial cells from the margins of the wound. These cells cover the defect within 3 to 7 days. Under ideal circumstances, the granulation tissue filling the skin defect in the wound is transformed into a scar within 3 to 6 weeks. The scar is then remodeled, and most of the disorderly formed collagen is replaced with cross-linked collagen type I, which is indistinguishable from that in the normal skin.

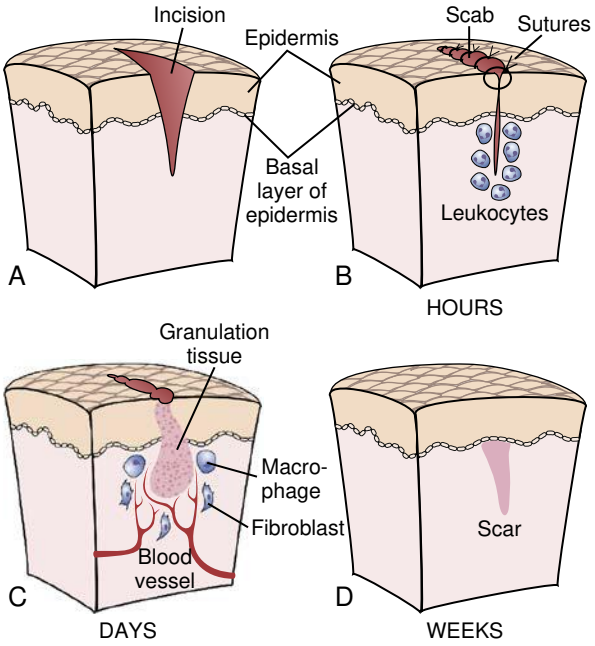


FIG. 2.21 Wound healing by first intention. The sequence of events includes formation of a scab *(A)* and scavenger action of polymorphonuclear leukocytes *(B),* formation of the granulation tissue *(C),* and scarring *(D).*

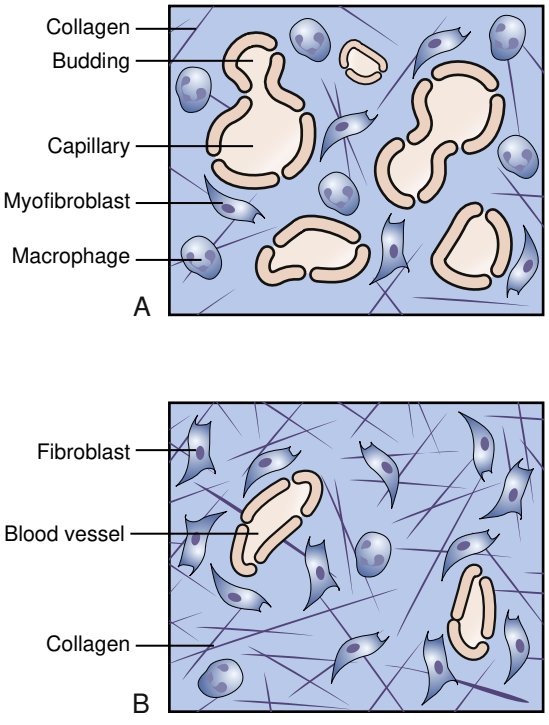


FIG. 2.22 Diagram of the histologic appearance of granulation tissue. *A,* In the early stages, it contains numerous macrophages, myofibroblasts, and blood vessels. *B,* In the late stages, granulation tissue is less vascular. Moreover, it contains more matrix and fibroblasts and only scattered macrophages.

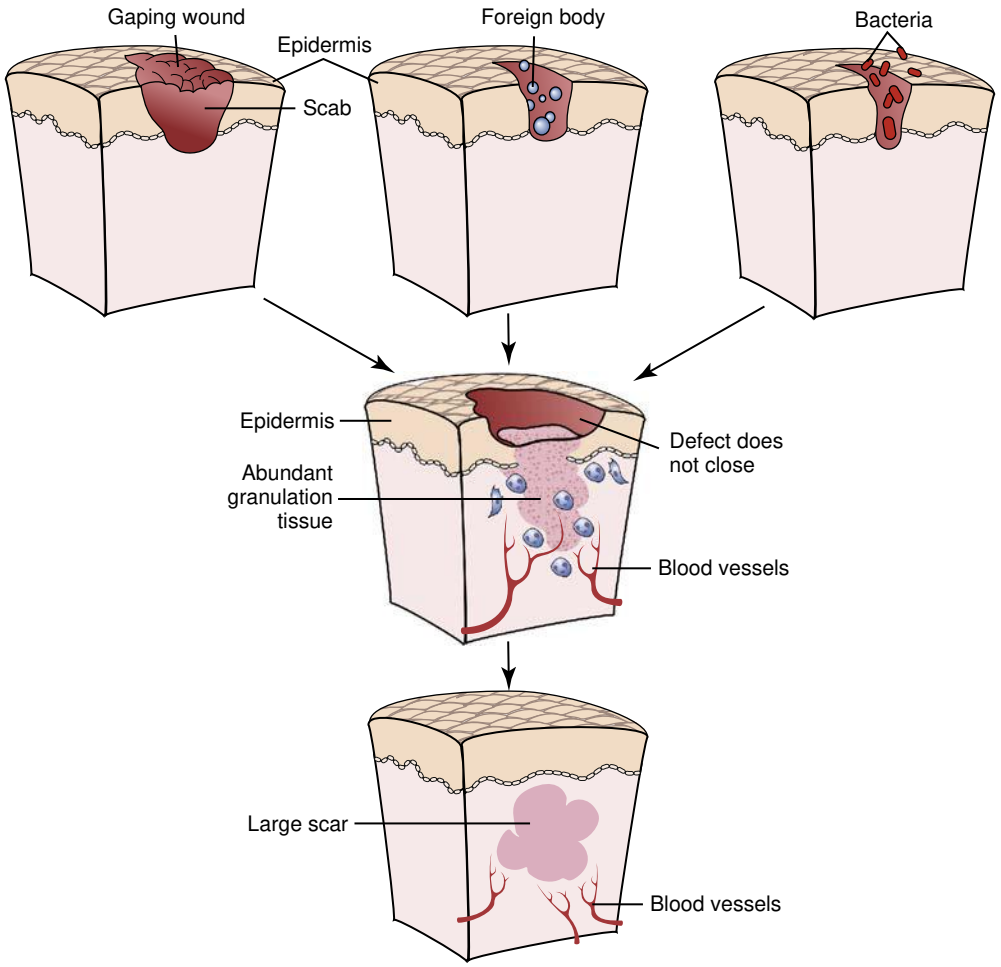


FIG. 2.23 Wound healing by secondary intention occurs in wounds that are marked by a large defect of tissue that contain foreign material or that are infected. The healing is slower because the epithelial cells proliferating from the wound margin take longer to cover the defect. Granulation tissue is more abundant; consequently, scarring is more prominent.

In contrast to the orderly sequence of events that characterizes the healing of sharp, sterile, surgical wounds by first intention (primary union), large defects and essentially all infected wounds heal by *secondary intention* (Fig. 2.23). Large defects cannot readily be bridged, and the surgeon cannot juxtapose the gaping tissue margins. Wound contraction cannot be accomplished by myofibroblasts in such cases, and the granulation tissue remains exposed to the external world. Wound healing by secondary intention is usually prolonged, and some wounds never heal completely.

Delayed Wound Healing

Wound healing may be complicated by local or systemic influences. Overall, the most important determinants of wound healing are as follows:

1. *Site of the wound.* Skin wounds heal well, whereas brain wounds do not heal at all.
2. *Mechanical factors.* Wounds heal faster if the margins can be juxtaposed neatly by a surgeon and the field can be kept immobile. Tension at the wound margins, if the skin had to be stretched to cover the gap, will impede healing. Movement may slow down healing, which is why patients are confined to the bed for some time after surgery. Foreign particles in the wound also retard healing.
3. *Size of the wound.* Small wounds heal faster than large ones.
4. *Presence or absence of infection.* Sterile wounds heal faster than those that are infected. Unfortunately, infections are sometimes inevitable. Indeed, wound infections develop in approximately 5% of hospitalized patients postoperatively.
5. *Circulatory status.* Wounds involving ischemic tissues heal poorly. Heart failure and advanced atherosclerosis found in older adults are associated with poor wound healing.
6. *Nutritional and metabolic factors.* Proteins are essential for wound healing; thus malnutrition delays wound healing, as does vitamin C deficiency. Metabolic disturbances, such as those caused by diabetes mellitus or prolonged corticosteroid therapy, also cause delayed wound healing.

Complications of Wound Healing

Wound healing may be less than optimal as a result of the factors just discussed. In general, these complications may lead to the following:

- *Deficient scar formation.* Sluggish formation of granulation tissue occurs in patients with diabetes, partly as a result of

the ischemia caused by diabetic microangiopathy and partly because of the metabolic disturbances of diabetes. Inadequate collagen production is a complication of prolonged therapy with corticosteroid hormones. Scars in such patients lack tensile strength, and *wound dehiscence* (i.e., separation of tissue margins) may occur.

- *Excess scar formation.* Excessive scarring leads to the formation of *keloids,* hypertrophic scars, which may cause disfigurement of extremities or parts of the body (Fig. 2.24). Large scars, especially those caused by skin burns, tend to be irregularly shaped, which can give rise to *contractures* (an exaggeration of wound contraction). Contractures over the joints may impede movement and may even completely immobilize an extremity.

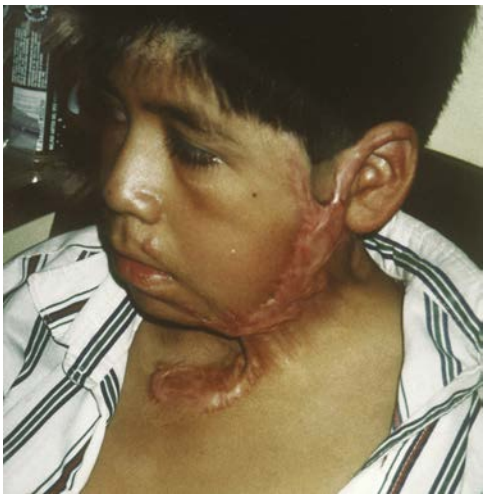


FIG. 2.24 Keloid. Healing of a deep skin burn is characterized by formation of an irregular and hypertrophic scar.

REVIEW QUESTIONS

1. What are the cardinal signs of inflammation?
2. What happens to the leukocytes inside the blood vessels in inflamed tissue?
3. Why does the permeability of blood vessels increase during acute inflammation?
4. Why are some complement fragments called *opsonins, anaphylatoxins,* or *chemotactic factors*?
5. How is the membrane attack complex (MAC) formed, and how does it damage red blood cells?
6. How are leukotrienes and prostaglandins formed, and what are their functions in acute inflammation?
7. How do polymorphonuclear neutrophils emigrate from blood vessels toward bacteria in the tissue, and how do they kill bacteria?
8. What are the main functions of polymorphonuclear neutrophils, eosinophils, and basophils?
9. What are the main functions of macrophages?
10. How do platelets differ from other white blood cells?
11. How does cellular inflammatory response to a viral infection differ from that to a bacterial infection?
12. What are the main causes of inflammation?
13. How does serous inflammation differ from fibrinous and purulent inflammation?
14. What is the difference between an abscess and empyema?
15. What is the difference between ulcerative and pseudomembranous inflammation?
16. Which cells participate in chronic inflammation?
17. What are the main clinicopathologic features of granulomatous inflammation?
18. What is the pathogenesis of fever and leukocytosis in acute inflammation?
19. What are the differences among continuously dividing, quiescent, and nondividing cells?
20. Which cells participate in the formation of granulation tissue during wound healing?
21. What is granulation tissue, and how does it evolve during wound healing?
22. What is the difference of wound healing by first and secondary intentions?
23. How does granulation tissue transform into a scar?
24. Which adverse factors could delay wound healing?
25. How does wound dehiscence differ from keloid formation?

3

Immunopathology

OUTLINE

LEARNING OBJECTIVES

After reading this chapter, the student should be able to:

1. Define and distinguish between innate and acquired immunity.
2. List the main organs and cells that participate in the immune response.
3. Describe the main differences between subsets of lymphocytes: B cells, T cells, and natural killer cells.
4. Describe the basic features of immunoglobulins and their reactions with antigens.
5. Describe the role of major histocompatibility complex in antigen presentation.
6. List four mechanisms of hypersensitivity reactions.
7. Describe type I hypersensitivity reaction and how it induces hay fever and asthma.
8. Describe type II hypersensitivity reaction and how it induces hemolytic anemia, myasthenia gravis, and Graves disease.
9. Describe type III hypersensitivity reaction and how it induces vascular and tissue changes.
10. Describe the cell-mediated hypersensitivity reaction and how it induces granuloma formation.
11. Describe the main forms of transplants: homograft, isograft, autograft, and xenograft.
12. Discuss the medical uses of transplantation and give three examples.
13. Discuss the principles of blood transfusion.
14. Describe Rh incompatibility between the mother and the fetus.
15. Discuss the pathogenesis of autoimmune diseases.
16. Discuss common congenital immunodeficiency diseases and acquired immunodeficiency states.
17. Explain the pathogenesis of acquired immunodeficiency syndrome (AIDS) and list its most important complications.
18. List the most common forms of amyloid and relate them to clinical presentations of amyloidosis.

KEY TERMS AND CONCEPTS

Acquired immunodeficiency syndrome (AIDS)
Amyloidosis
Anaphylactic shock
Antibodies
Antigen
Asthma
Autoimmune diseases
B-lymphocytes
Contact dermatitis
Cytokines
Glomerulonephritis
Goodpasture syndrome
Graft-versus-host (GVH) reaction
Graves disease

Hay fever
Hemolytic anemia
Human immunodeficiency viruses (HIVs)
Hypersensitivity reaction
Immunity
Immunodeficiency
Immunohistochemistry
Immunoglobulins
Kaposi sarcoma
Maternal–fetal RH incompatibility
Myasthenia gravis
Natural killer (NK) cells
Opportunistic infections
Plasma cells
Serum sickness
Systemic lupus erythematosus (SLE)
T lymphocytes
Transplant rejection

Immunity, derived from the Latin term meaning "exemption from duty" (*munus,* meaning "duty" or "service"), was originally defined as resistance to infections. Immune persons would be "exempt from suffering" inflicted by infectious diseases. Subsequently, it became apparent that immune reactions were not only elicited by various living pathogens but also by many other substances (e.g., snake poison) if they were perceived as foreign by the immune system. Furthermore, we have learned that these reactions occur in many forms and that immunity not only provides protection but also can cause disease.

Immunologic techniques are useful in research and are also used daily in clinical laboratories. This applied immunology forms the basis for immunodiagnostics. Finally, immunotherapy should be mentioned because it provides new modalities for the treatment of diseases. Immunopreventive techniques, such as vaccination and active and passive immunizations, have contributed enormously to the fight against diseases in humans and animals. It is fair to say that immunization has probably saved more human lives than all drugs combined.

IMMUNE RESPONSE

The immune response has two different forms: (1) a relatively primitive, nonspecific set of *innate immunity* and (2) a complex system of cellular and humoral reactions that evolve in response to repeated exposures to foreign substances, known as *acquired immunity.* In this chapter, we will mostly deal with the pathology of acquired immunity.

Innate Immunity

Innate protective mechanisms are inherited and operational at the time of birth. They are relatively nonspecific, and in contrast to acquired immunity, these mechanisms rely on antigenic stimulation—that is, they do not depend on previous exposure to foreign substances (Fig. 3.1). These innate defense mechanisms include the following:

- Various mechanical barriers (e.g., the epidermis or the ciliated cells in the mucosa of the nose or the bronchus)
- Phagocytic cells, such as neutrophils, macrophages, and dendritic cells
- Natural killer (NK) cells
- Protective proteins found in tissues and plasma, such as properdin and lysozyme. *Properdin* is a plasma protein that activates the alternative complement pathway (described in Chapter 2). *Lysozyme* is a low-molecular-weight protein found in some body fluids, such as tears and nasal and intestinal secretions. It nonspecifically kills many bacteria.

The innate immune system protects the body principally by three mechanisms: (1) by initiating inflammation, (2) by combating infections, and (3) by mounting a general response to damaged cell products.

Acquired Immunity

Acquired immunity is based on specific responses elicited by substances that act as antigens. An **antigen** is any chemical substance that can induce a specific immune response—that is, a reaction to production of specific antibodies or specifically sensitized immune cells. Acquired immunity is based on the ability of the body's immune system to distinguish *self* from *nonself,* to generate an immunologic memory, and to mount an integrated reaction of various cells. As will be shown later, acquired immunity is based on the reaction of the immune system and involves other cells (auxiliary [helper] cells), such as *macrophages, basophils,* and *eosinophils.*

The body's ability to mount an appropriate immune response is termed *immunocompetence.* Immunocompetence depends on adequate structural and functional development of the immune system and on the coordinated action of its components. A brief description of the organs and cells that constitute the immune system is presented, along with a review of their function. The various pathologic changes mediated by immune mechanisms are then discussed.

CELLS OF THE IMMUNE SYSTEM

All cells of the immune system are descendants of primitive hematopoietic stem cells originally found in bone marrow (Fig. 3.2). The *bone marrow stem cells* give rise to two major cell lineages: *lymphocytes,* also known as *lymphoid cells*, and all other nonlymphoid cells, including polymorphonuclear neutrophils (PMNs), eosinophils, basophils, macrophages, and megakaryocytes. Lymphoid cells are the *primary cells* of the immune system, whereas the other cells may or may not contribute to immune reactions and are in this context considered to be *helper cells.*

Lymphocytes

Lymphocytes are small cells, only slightly larger than erythrocytes. They have a round nucleus and very little cytoplasm. All lymphocytes are derived from bone marrow prelymphoid

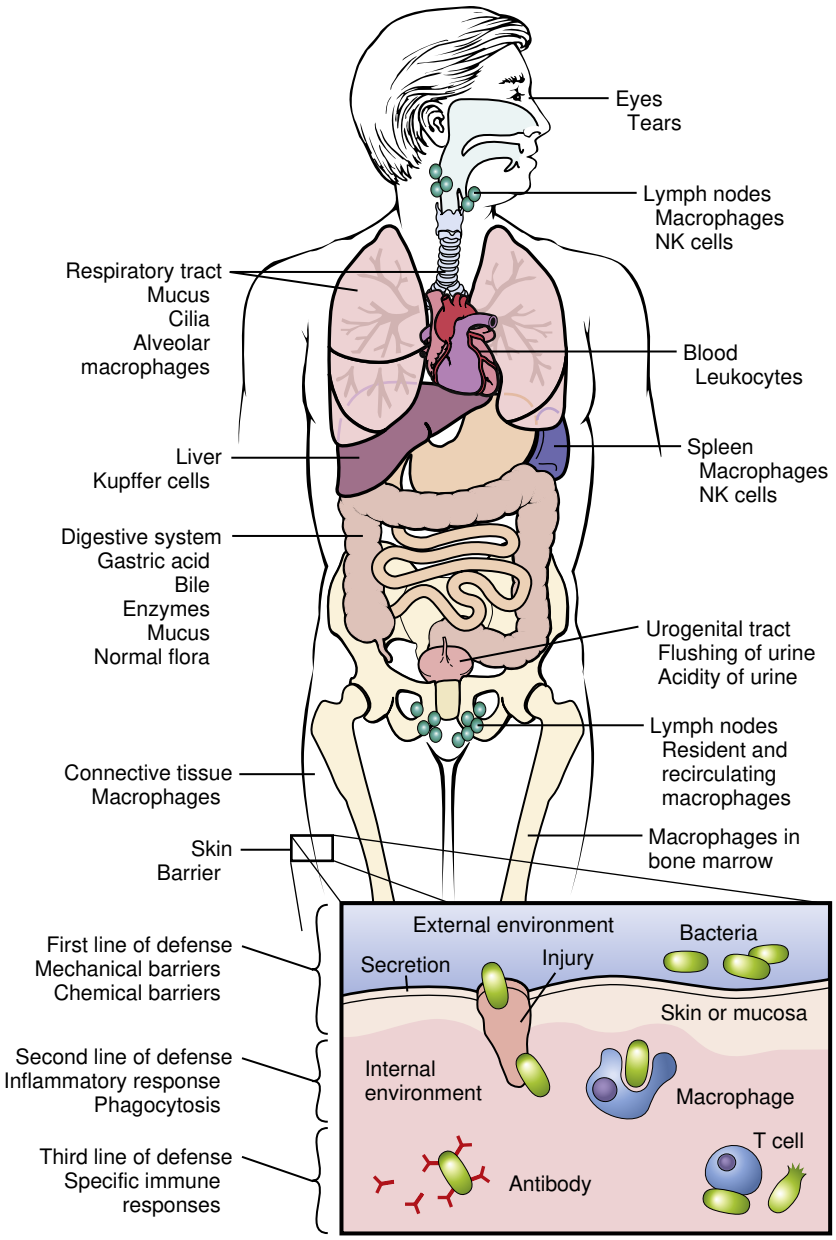


FIG. 3.1 Natural protective mechanisms of the human body. *NK,* Natural killer.

stem cells, which give rise to two distinct cell lineages: (1) **T lymphocytes**, named so because they mature in the *thymus,* and (2) **B lymphocytes**, named after bone marrow in which they primarily reside. Bone marrow and thymus are called *primary lymphoid organs.* From the primary lymphoid organs, T and B lymphocytes enter the blood circulation and colonize various *secondary lymphoid organs.* Among these, the most prominent are the *lymph nodes* and the spleen, in which lymphocytes constitute a significant percentage of the total cell population. Lymphocytes are also present in other organs and are most prominent in the gastrointestinal and bronchial mucosae, where they form the so-called *mucosa-associated lymphoid tissue (MALT).*

T and B lymphocytes have distinct functions, although morphologically, they cannot be distinguished by light or electron microscopy. In practice, this can be done by immunocytochemical staining of tissue sections or cell smears with specific, color-coded antibodies. Antibodies to so-called *cluster differentiation (CD) antigens* have been most useful in this regard. CD antigens are selectively expressed during specific stages of lymphocyte development. Some CD antigens are selectively expressed on T cells, and others are selectively expressed on B cells. Several subsets of T and B lymphocytes and their immature precursors can be recognized by using this approach. With the use of cell sorters, such as the fluorescence-activated cell sorter (FACS), it is possible to distinguish T lymphocytes from B lymphocytes

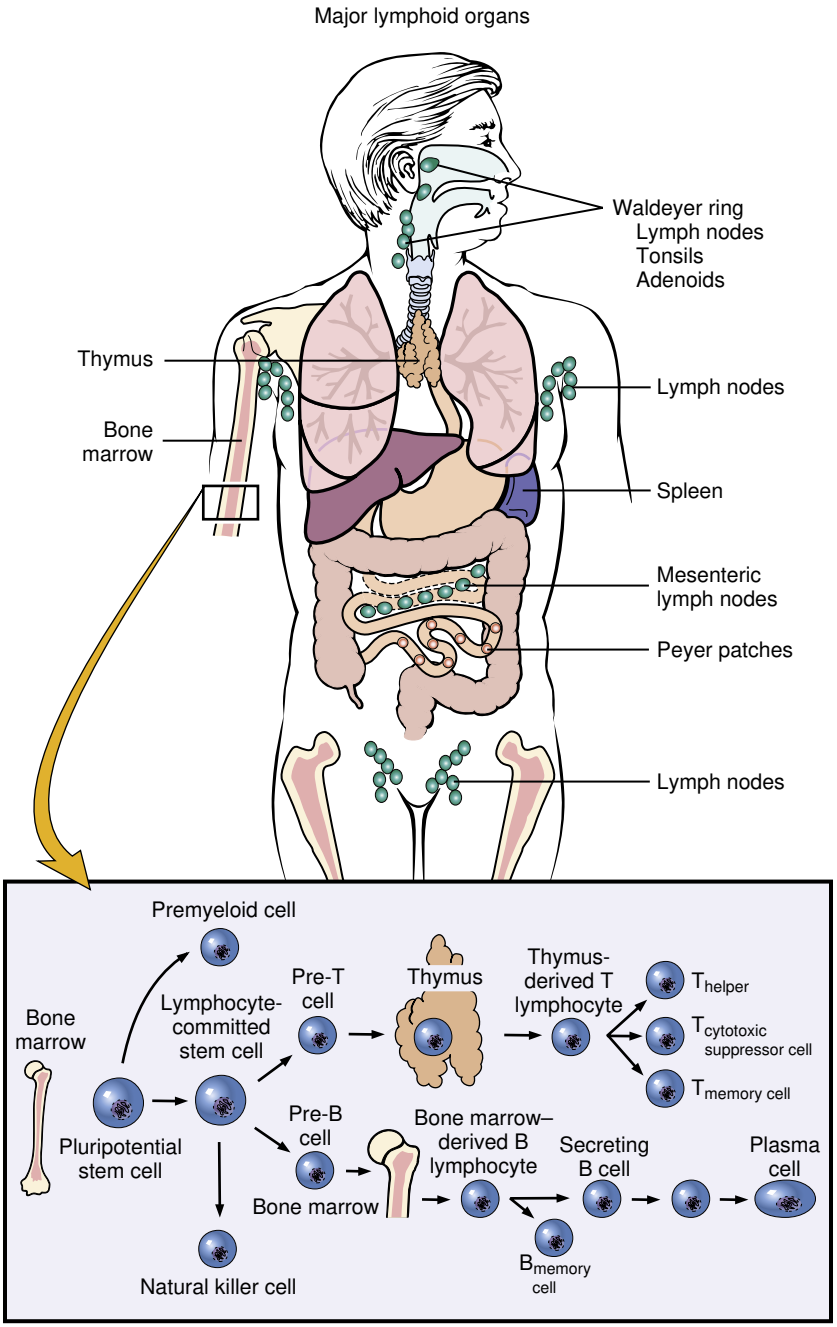


FIG. 3.2 Immune system. Lymphocytes, like all other hematopoietic cells, are derived from a common pluripotent bone marrow stem cell. These stem cells give rise to myeloid cell precursors and are committed to lymphocytic lineages. Three lymphoid cell lineages lead to mature T and B cells (plasma cells), or natural killer cell formation.

and to determine their ratio in the blood circulation or in various lymphoid organs.

T Lymphocytes

T lymphocytes are lymphocytes that have matured in the thymus. They account for two thirds of all lymphocytes in blood and also are found in the paracortical zone of lymph nodes and the periarteriolar sheath of the spleen. There are several subsets of T cells, the most important of which are the *T helper* and *T suppressor/cytotoxic* cells. T helper cells secrete **cytokines** and thus participate in the immune response to antigens and help B cells produce antibodies, as discussed in the next section. T suppressor/cytotoxic cells suppress unwanted antibody production and mediate the killing of virus-infected cells or tumor cells that are recognized by the body as foreign.

Common to all T cells is the surface T-cell receptor (TCR), which is linked to a membrane protein known as *CD3.* T cells use TCR-CD3 for recognition of antigens. Like all other genes inherited from our parents, the gene for TCR is in all the cells of the body but is activated only in T cells. *TCR* gene activation

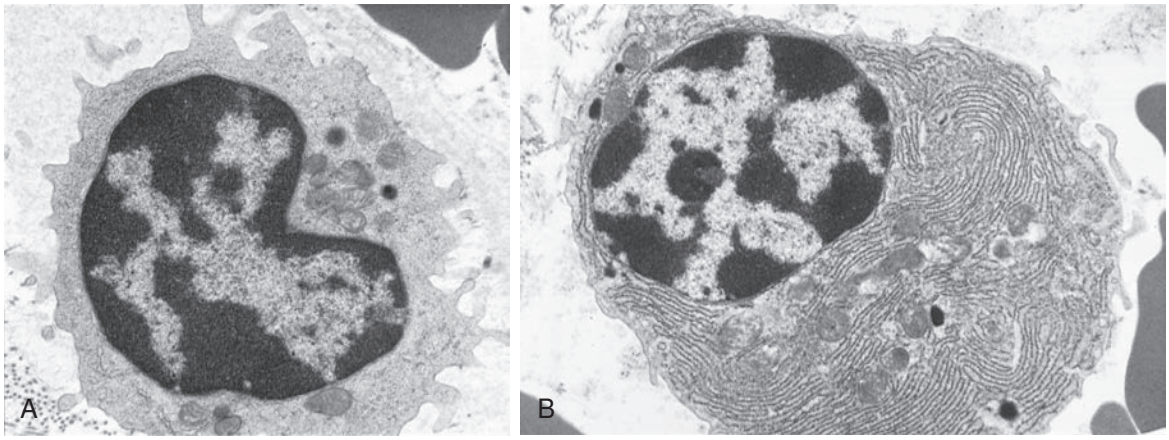


FIG. 3.3 Electron microscopic photograph of a lymphocyte and a plasma cell. ***A,*** The cytoplasm of the lymphocyte is scant and contains few organelles. ***B,*** The cytoplasm of the plasma cell is well developed and contains prominent rough endoplasmic reticulum (RER). The RER serves as the site for production of immunoglobulins.

occurs through rearrangement of parts of the gene. Because this occurs only in T cells, the rearranged *TCR* is a unique genetic marker of T lymphocytes. This is important to note because 10% to 15% of peripheral lymphocytes have the same surface markers as those of T lymphocytes but do not have *TCR* gene rearrangement. These cells are known as **natural killer (NK) cells**. NK cells mediate innate immune reactions and are not involved in T- and B cell–mediated immune reactions. Their function is to react to virus-infected cells and to kill tumor cells and transplanted foreign cells without previous sensitization.

T helper cells express CD4 on their surfaces, whereas the T suppressor/cytotoxic cells express the CD8 antigen. CD4 and CD8 are used as markers for these lymphocytes and for the counting of T helper and T suppressor/cytotoxic cells in blood. In normal blood, CD4-positive cells predominate, and the cell ratio of CD4 to CD8 is approximately 2:1. In individuals with **acquired immunodeficiency syndrome (AIDS)**, CD4 cells are selectively lost, and the cell ratio of CD4:CD8 is less than 1.

B Lymphocytes

B cells are lymphocytes that are essential to produce antibodies. These cells are primed to differentiate into immunoglobulin-producing **plasma cells**. The most important feature of the B-cell lineage is the activation of the *immunoglobulin gene.* The immunoglobulin gene is similar to *TCR,* and its activation also occurs through a rearrangement of parts of the gene. The immunoglobulin gene rearrangement enables B cells to produce immunoglobulins that are incorporated into the B-cell antigen receptor complex on the plasma membrane. Antigen-stimulated B lymphocytes differentiate subsequently into plasma cells.

Plasma Cells

Plasma cells are fully differentiated descendants of B lymphocytes. These cells have an oval shape and an eccentrically located round nucleus. The cytoplasm of plasma cells is basophilic because it contains an abundance of ribosomes. On electron microscopy, their cytoplasm contains numerous stacks of rough endoplasmic reticulum (RER) (Fig. 3.3). The RER is the site of synthesis of **immunoglobulins**, the primary secretory products of plasma cells.

ANTIBODIES

Antibodies are proteins of the immunoglobulin (Ig) class and are secreted by plasma cells. They can be defined operationally as proteins reacting with antigens. Chemically, they can be categorized into five classes: IgG, IgM, IgA, IgE, and IgD.

These immunoglobulins share some common features:

- Immunoglobulins are composed of light and heavy chains (Fig. 3.4), and all the light chains are either kappa (κ) or lambda (λ). A single molecule contains either two κ chains or two λ chains. Heavy chains are immunoglobulin class specific (i.e., unique to each of the five classes).
- Each heavy and light immunoglobulin chain has constant (C_H, C_L) and variable (V_H, V_L) parts, and these portions are important for recognition of antigens.
- Each antibody can be cleaved enzymatically into two fragments: The F_c portion, which contains the constant region, and the F_{ab} fragment, which contains the variable region. F_c binds to specific F_c receptors that are expressed on macrophages, PMNs, and others. F_{ab} serves as the antigen-binding site.

IgM is composed of five basic units and is thus the largest immunoglobulin (*macroglobulin*) held together with a linker J chain. Its function is to neutralize microorganisms. It is an avid complement activator because it has five complement-binding sites. IgM is the first immunoglobulin to appear after immunization, and it is a natural antibody against blood group antigens ABO.

IgG has the smallest molecular weight of all the immunoglobulins, but it is nevertheless the most copious immunoglobulin in blood. It is produced in small amounts upon initial immunization, but its production is boosted by reexposure to the antigen. F_c receptors for IgG exist on macrophages, PMNs, lymphocytes, eosinophils, and platelets and in the placenta. This allows passage of IgG across the placenta to the fetus. IgG acts

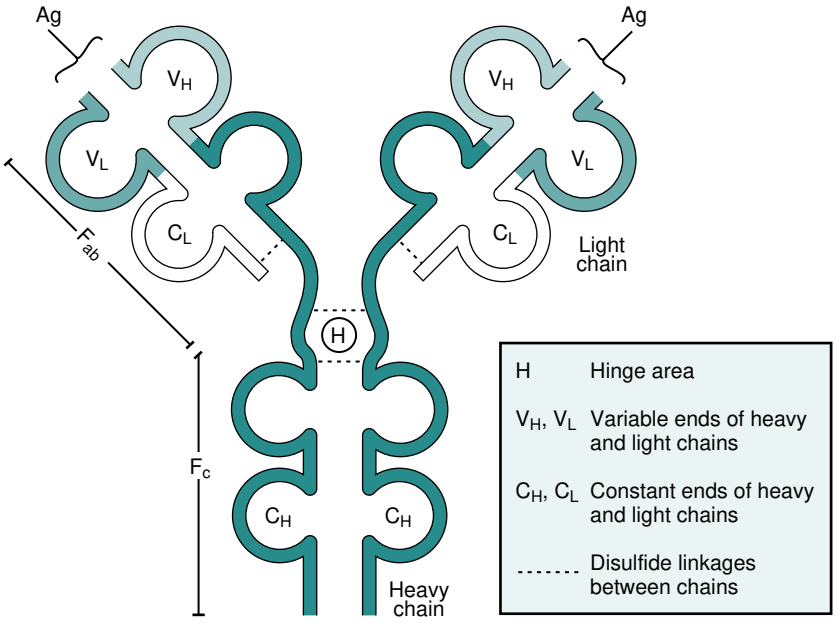


FIG. 3.4 Diagram of an immunoglobulin. The F_{ab} and F_c portions are also indicated. *Ag,* Antigen.

as an *opsonin*—that is, it coats bacteria and thus facilitates their phagocytosis.

IgA is found in blood but is more abundant in mucosal secretions (e.g., tears and nasal mucus), breast milk, and intestinal contents, where it has an important protective function.

IgE is present in trace amounts in serum. This immunoglobulin is secreted by sensitized plasma cells in tissues and is locally attached to mast cells. IgE mediates allergic *type I hypersensitivity reactions,* also known as *atopic* or *anaphylactic reactions*.

IgD is a cell membrane-bound immunoglobulin found exclusively on B cells. It participates in the antigenic activation of B cells, but it is not released into serum or body fluids.

Antibody Production

Antibody production begins with contact between an antigen and the cells of the immune system. All substances identified by the body as foreign may serve as antigens and incite an immune response. This activation of B cells culminates in the production of specific antibodies that can react with the antigens.

To elicit antibody production, the antigen must bind to the B lymphocyte antigen receptor complex. This complex includes IgM or IgD, which binds the antigen, and several membrane molecules that do not participate in antigen binding but are essential for signal transduction and initiation of antibody production. Antibody production requires the support of T helper cells. It is worth noting that B cells can internalize the antigens and thereafter may function as *antigen-presenting cells (APCs),* providing the internalized antigens to T cells.

Major Histocompatibility Complex

All processed antigens are presented to T cells in the context of the major histocompatibility complex (MHC) proteins expressed on the surfaces of APCs. These MHC proteins, first identified on leukocytes, are also known as *human leukocyte antigens* (HLAs), although they are expressed on other nucleated cells in the body. A unique set of MHC antigens determines the individuality of each person. Only identical twins have the same MHC antigens. In immune reactions, the MHC regulates the cell-to-cell contact during antigen presentation.

Human MHC antigens belong to two groups. Type I MHC proteins, found on all nucleated cells of the body, serve as the receptors for CD8, thus linking macrophages to cytotoxic T lymphocytes. By binding to type I MHC, cytotoxic T lymphocytes kill virus-infected cells and transplanted foreign cells, or tumor cells. Type II MHC molecules react with CD4, mediating the attachment of macrophages to helper T lymphocytes. Type II molecules serve in the presentation of exogenous antigens (e.g., bacteria) that are first internalized and processed before presentation to T cells.

The main function of the MHC is presentation of antigens to T cells. It is worth remembering that T cells can react only to membrane-bound antigens; thus without the APC, there is no T-cell reaction to antigens. The MHC is also important for organ transplantation, and most transplant rejection reactions result from the HLA incompatibility of the host and the donor.

Antigen–Antibody Reaction

Most antigens have more than one antigenic site, or *epitope,* which means that they are *multivalent* (i.e., able to bind more than one antibody). Antigens and antibodies are bound to each other by complex physical and chemical bonds, forming *antigen–antibody complexes.* If the antigen is soluble and circulating in blood, the complexes will also circulate in plasma, the fluid portion of blood. However, these complexes tend to enlarge as more and more antibodies and antigen molecules are included

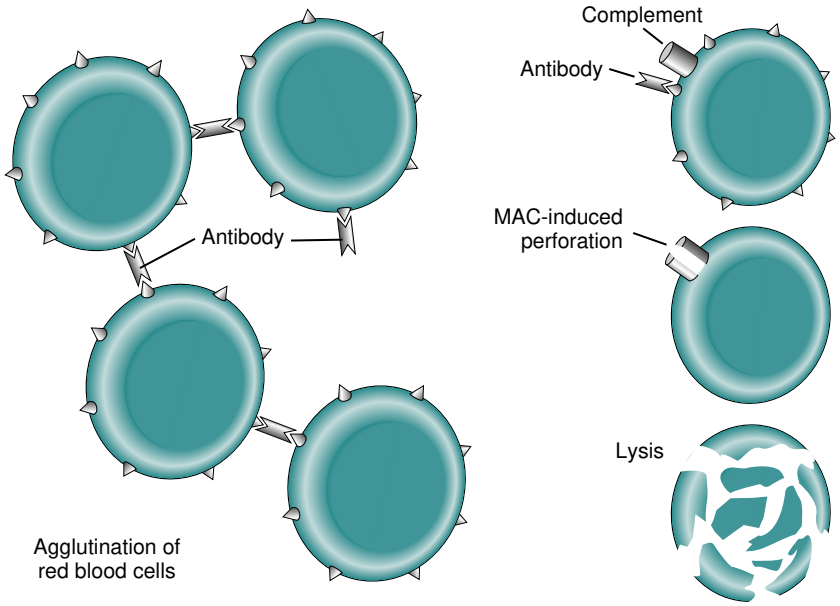


FIG. 3.5 Reaction of antibody with antigen on the surface of red blood cells (RBCs). This could lead to agglutination of RBCs or hemolysis mediated by activated complement. *MAC,* Membrane attack complex.

in the meshwork. Finally, the complexes reach the size of small particles and are phagocytized by fixed macrophages in the spleen and the liver. The smaller complexes may remain in the circulation, depending on their overall solubility, size, and electrical charge. Contingent on these three properties, the immune complexes may remain suspended in circulation for a long time. Alternatively, they may be attached to red blood cells (RBCs) or endothelial cells or filtered through the capillary walls with other proteins.

Antibodies to insoluble antigens, such as cell surface antigens, become fixed to the cell membrane (Fig. 3.5). This is best illustrated by the antibodies against RBCs that typically coat the cell surface. Antibodies bind RBCs to each other, best seen by placing a drop of blood on a glass slide. The antibody-coated RBC clump together on the slide. This process called *agglutination* can be easily recognized because the RBCs that are clumped together will separate from serum and form a dense red dot on the glass.

Another way of recognizing antibodies in the laboratory is to add antibody to blood and induce *hemolysis.* By adding antibody to blood, antibodies are allowed to form antigen–antibody complexes with the surface molecules of RBCs. These complexes activate the complement cascade in blood, leading to the formation of the membrane attack complex (MAC), as described in Chapter 2. The MAC inserts into the membranes of RBCs, causing their rupture, where upon hemoglobin spills out into the fluid.

HYPERSENSITIVITY REACTIONS

An abnormal immune response to exogenous antigens or a reaction to endogenous autoantigens is called a ***hypersensitivity reaction***. Hypersensitivity reactions are the basis of hypersensitivity diseases, including *allergies* and *autoimmune disorders.*

Hypersensitivity diseases are pathogenetically classified into four major groups, each of which is mediated by a distinct mechanism:

Type I—anaphylactic or atopic reaction
Type II—cytotoxic antibody-mediated reaction
Type III—immune complex–mediated reaction
Type IV—cell-mediated, delayed-type reaction

Type I Hypersensitivity

Type I hypersensitivity, also known as *anaphylactic* or *atopic* reaction, is primarily mediated by IgE and mast cells, or basophils. IgE is produced by plasma cells derived from B lymphocytes controlled by T helper cells, which have been sensitized to foreign antigens, such as pollen. Upon second exposure to the same antigen, the primed plasma cells secrete an antibody that diffuses locally toward mast cells and is fixed to the F_c receptors on their surfaces (Fig. 3.6). Subsequent reexposure to the antigen leads to the formation of antigen–antibody complexes on the surface of mast cells. This triggers the release of vasoactive substances stored in mast cell granules. The most important among these is *histamine,* the well-known vasoactive biogenic amine. The release is instantaneous, as any sufferer of hay fever can testify. It is accompanied by increased vascular permeability, edema, and accumulation of inflammatory cells, most notably eosinophils. *Eosinophilia*—an increased number of eosinophils in the blood—is a common systemic feature of type I hypersensitivity reactions.

Type I hypersensitivity reactions also produce a late-phase response that usually occurs 4 to 6 hours after exposure to an allergen. Basophils and mast cells play an important role in this reaction, but other inflammatory cells also participate and are