

I

II

III

Robbins and Cotran PATHOLOGIC BASIS OF DISEASE

Seventh Edition

VINAY KUMAR MBBS, MD, FRCPath

Alice Hogge and Arthur Baer Professor
Chairman,
Department of Pathology
The University of Chicago,
Pritzker School of Medicine
Chicago, Illinois

ABUL K. ABBAS MBBS

Chair,
Department of Pathology
University of California, San Francisco
San Francisco, California

NELSON FAUSTO MD

Chairman,
Department of Pathology
University of Washington School of Medicine
Seattle, Washington

With Illustrations by James A. Perkins, MS, MFA

ELSEVIER
SAUNDERS

IV

ELSEVIER
SAUNDERS
An Imprint of Elsevier

The Curtis Center
170 S Independence Mall W 300E
Philadelphia, Pennsylvania 19106

ROBBINS AND COTRAN PATHOLOGIC BASIS OF DISEASE, 7/E

0-7216-0187-1

International Edition ISBN 0-8089-2302-1

Copyright © 2005, Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Permissions may be sought directly from Elsevier's Health Sciences Rights Department in Philadelphia, PA, USA: phone: (+1) 215 238 7869, fax: (+1) 215 238 2239, e-mail: healthpermissions@elsevier.com. You may also complete your request on-line via the Elsevier homepage (<http://www.elsevier.com>), by selecting 'Customer Support' and then 'Obtaining Permissions'.

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the publisher nor the authors assume any liability for any injury and/or damage to persons or property arising from this publication.

Previous editions copyrighted 1999, 1994, 1989, 1984, 1979, 1974

Library of Congress Cataloging-in-Publication Data

Robbins and Cotran pathologic basis of disease.—7th ed./[edited by]

Vinay Kumar, Abul K. Abbas, Nelson Fausto ; with illustrations by James A. Perkins. p. ; cm.

Rev. ed. of: Robbins pathologic basis of disease, 1999.

ISBN 0-7216-0187-1

1. Pathology.

[DNLM: 1. Pathology. QZ 4 R6354 2004] I. Title: Pathologic basis of disease. II. Kumar, Vinay. III. Abbas, Abul K. IV. Fausto, Nelson. V. Robbins, Stanley L. (Stanley Leonard). VI. Cotran,

Ramzi S. Robbins pathologic basis of disease.

RB111.R62 2004

616.07—dc22

2004046835

Publishing Director: William Schmitt

Managing Editor: Rebecca Gruliow

Design Manager: Ellen Zanolle

Printed in China

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

V

IN MEMORY OF

Dr. Stanley L. Robbins (1915–2003)

and

Dr. Ramzi S. Cotran (1932–2000)

Dear friends, respected colleagues, and dedicated teachers

They leave a legacy of excellence

that will enrich the lives of generations

of future physicians.

VI

VII

Contributors

Charles E. Alpers MD

Professor of Pathology,
Adjunct Professor of Medicine,
University of Washington School of Medicine;
Pathologist,
University of Washington Medical Center,
Seattle, WA
The Kidney

Douglas C. Anthony MD, PhD

Professor and Chair,
Department of Pathology and Anatomical Sciences,
University of Missouri,
Columbia, MO
Peripheral Nerve and Skeletal Muscle;
The Central Nervous System

Jon C. Aster MD, PhD

Associate Professor of Pathology,
Harvard Medical School;
Staff Pathologist,
Brigham and Women's Hospital,
Boston, MA
Red Blood Cell and Bleeding Disorders;
Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus

James M. Crawford MD, PhD

Professor and Chair,
Department of Pathology,
Immunology and Laboratory Medicine,
University of Florida College of Medicine;
Professor and Chair,
Shands Hospital at the University of Florida,
Gainesville, FL

*The Gastrointestinal Tract;
Liver and Biliary Tract*

Christopher P. Crum MD

Professor of Pathology,
Harvard Medical School;
Director,
Women's and Perinatal Pathology,
Brigham and Women's Hospital,
Boston, MA
The Female Genital Tract

Umberto De Girolami MD

Professor of Pathology,
Harvard Medical School, Boston;
Director of Neuropathology,
Brigham and Women's Hospital,
Boston, MA
*Peripheral Nerve and Skeletal Muscle;
The Central Nervous System*

Jonathan I. Epstein MD

Professor of Pathology, Urology, and Oncology;
The Rinehard Professor of Urologic Pathology,
The Johns Hopkins University School of Medicine, Baltimore;
Director of Surgical Pathology,
The Johns Hopkins Hospital,
Baltimore, MD
The Lower Urinary Tract and Male Genital System

Robert Folberg MD

Frances B. Greever Professor and Head,
Department of Pathology,
University of Illinois at Chicago,
Chicago, IL
The Eye

Matthew P. Frosch MD, PhD

Assistant Professor of Pathology,
Harvard Medical School Boston;
Assistant Pathologist,
C.S. Kubik Laboratory for Neuropathology,
Massachusetts General Hospital,
Boston, MA
*Peripheral Nerve and Skeletal Muscle;
The Central Nervous System*

Ralph H. Hruban MD

Professor of Pathology and Oncology,
The Johns Hopkins University School of Medicine;
Attending Pathologist,
The Johns Hopkins Hospital,
Baltimore, MD
The Pancreas

Aliya N. Husain MBBS

Professor,
Department of Pathology,
Pritzker School of Medicine,
University of Chicago,
Chicago, IL
The Lung

Agnes B. Kane MD, PhD

Professor and Chair,
Department of Pathology and Laboratory Medicine,
Brown University Medical School,
Providence, RI
Environmental and Nutritional Pathology

Susan C. Lester MD, PhD

Assistant Professor of Pathology,
Harvard Medical School;
Chief,
Breast Pathology,
Brigham and Women's Hospital,
Boston, MA
The Breast

Mark W. Lingen DDS, PhD

Associate Professor,
Department of Pathology,
University of Chicago,
Chicago, IL
Head and Neck

Chen Liu MD, PhD

Assistant Professor of Pathology,
University of Florida College of Medicine,
Gainesville, FL
The Gastrointestinal Tract

Anirban Maitra MBBS

Assistant Professor,
Department of Pathology,
The Johns Hopkins University School of Medicine;
Pathologist,
The Johns Hopkins Hospital,
Baltimore, MD
Diseases of Infancy and Childhood;
The Endocrine System

Alexander J. McAdam MD, PhD

Assistant Professor of Pathology,
Harvard Medical School;
Medical Director,
Infectious Diseases Diagnostic Laboratory,
Children's Hospital Boston,
Boston, MA
Infectious Diseases

Martin C. Mihm Jr. MD

Clinical Professor of Pathology,
Harvard Medical School;
Pathologist and Associate Dermatologist,
Massachusetts General Hospital,
Boston, MA
The Skin

Richard N. Mitchell MD

Associate Professor,
Department of Pathology,
Harvard Medical School;
Director,
Human Pathology,
Harvard-MIT Division of Health Sciences and Technology,
Harvard Medical School;
Staff Pathologist,
Brigham and Women's Hospital,
Boston, MA
Hemodynamic Disorders, Thromboembolic Disease, and Shock

George F. Murphy MD

Professor of Pathology,
Harvard Medical School;
Director of Dermatopathology,
Brigham and Women's Hospital,
Boston, MA
The Skin

Andrew E. Rosenberg MD

Associate Professor of Pathology,
Harvard Medical School;
Associate Pathologist,
James Homer Wright Laboratories,
Department of Pathology,
Massachusetts General Hospital,
Boston, MA
Bones, Joints, and Soft Tissue Tumors

Frederick J. Schoen MD, PhD

Professor of Pathology and Health Sciences and Technology,

Harvard Medical School;
Director,
Cardiac Pathology and Executive Vice Chairman,
Department of Pathology,
Brigham and Women's Hospital,
Boston, MA
Blood Vessels;
The Heart

Klaus Sellheyer MD

Assistant Professor of Pathology,
Thomas Jefferson University;
Attending Dermatopathologist,
Jefferson Medical College,
Philadelphia, PA
The Skin

Arlene H. Sharpe MD, PhD

Professor of Pathology,
Harvard Medical School;
Chief,
Immunology Research Division,
Department of Pathology,
Brigham and Women's Hospital,
Boston, MA
Infectious Diseases

Robb E. Wilentz MD

Voluntary Faculty,
Department of Dermatology,
University of Miami School of Medicine;
Laboratory Director,
Division of Pathology,
Skin and Cancer Associates,
Miami, FL
The Pancreas

Preface

We launch the seventh edition of *Pathologic Basis of Disease* with mixed emotions, excitement and enthusiasm, as we enter the new millennium, tempered by sadness over the loss of our dear colleagues Drs. Stanley Robbins and Ramzi Cotran. To acknowledge their immeasurable and everlasting contribution to this text, the book is now renamed *Robbins and Cotran Pathologic Basis of Disease*.

This edition, like all previous ones, has been extensively revised, and some areas completely rewritten. Some of the more significant changes are as follows:

- Chapter 1 has been completely reorganized to include the entire spectrum of cellular responses to injury, from adaptations and sublethal injury to cell death. This was accomplished by combining the first two chapters of the sixth edition. We believe that this integrated and extensively revised chapter will allow a better understanding of cell injury, the most fundamental process in disease causation.
- Chapter 3, covering tissue repair and wound healing, has been extensively revised to include new and exciting information in stem cell biology and the emerging field of regenerative medicine.
- Chapter 8, dealing with infectious diseases, has been organized taxonomically with emphasis on mechanisms of tissue injury by different categories of infectious agents. While examples of infections by prototypic microorganisms have been retained, most of the organ-specific infectious diseases have been moved to later chapters where other diseases of the organ are described.
- Discussion of diabetes mellitus has been moved from the chapter on pancreatic diseases to the chapter on endocrine disorders, where it blends more logically with other hormonal diseases.
- Discussions of the lower urinary tract and the male genital system have been combined and grouped into a single chapter in recognition of the fact that there is overlap in diseases and diagnostic considerations.
- A new feature best described as "boxes" has been introduced in selected chapters. For boxes, we have selected topics at the cutting edge of science that are worthy of a more detailed presentation than is essential for a student textbook. In doing so, we hope that we have presented the excitement of the topic without encumbering the body of the text with details that may appear overwhelming to the beginning reader.
- The chapter on ocular diseases has been rewritten and reorganized to facilitate an understanding of ophthalmic pathology by the non-specialist.
- In addition to the revision and reorganization of the text, there have been significant changes in illustrations. Many new photographs and schematics have been added and a large number of the older "gems" have been enhanced by digital technology. Thus we hope that even the veterans of the Robbins Pathology titles who have seen many previous editions of the book will find the color illustrations more sparkling and fresh. Approximately 50 new pages of illustrations have been added.

In the 5 years since the previous edition, spectacular advances, including the completion of the human genome project, have occurred. Whenever appropriate we have blended the new discoveries into the discussion of pathogenesis and pathophysiology, yet never losing sight

that the "state of the art" has little value if it does not enhance the understanding of disease mechanisms. As in the past, we have not avoided discussions of "unsolved" problems because of our belief that many who read the text might be encouraged to embark on a path of discovery.

Despite the changes outlined above and extensive revisions, our goals remain essentially the same.

- To integrate into the discussion of pathologic processes and disorders the newest established information available—morphologic and molecular.
- To organize the presentations into logical and uniform approaches, thereby facilitating readability, comprehension, and learning.
- To maintain a reasonable size of the book, and yet to provide adequate discussion of the significant lesions, processes, and disorders, allotting space in proportion to their clinical and biologic importance.
- To place great emphasis on clarity of writing and good usage of language in the recognition that struggling to comprehend is time-consuming and wearisome and gets in the way of the learning process.
- To make this first and foremost a student text—used by students throughout their 4 years of medical school and into their residencies—but, at the same time, to provide sufficient detail and depth to meet the needs of more advanced readers.

We have been repeatedly told by the readers that one of the features they value most in this book is its up-to-dateness. We have strived to maintain such timeliness by providing references from recent literature, many published in 2003 and some from the early part of 2004. However, older classics have also been retained to provide original source material for advanced readers.

With this edition, we also move into the digital age: the text will be available online to those who own the print version. This online access gives the reader the ability to search across the entire text, bookmark passages, add personal notes, use PubMed to view references, and many other exciting features, including timely updates. In addition, included in the text is a CD-ROM of case studies, previously available separately as the Interactive Case Study Companion developed by one of us (VK) in collaboration with Herb Hagler, PhD, and Nancy Schneider, MD, PhD, at the University of Texas, Southwestern Medical School in Dallas. This will enhance and reinforce learning by challenging students to apply their knowledge in solving clinical cases. A virtual microscope feature enables the viewing of selected images at various powers.

This edition is also marked by the addition of two new "seasoned" coauthors. All three of us have reviewed, critiqued, and edited each chapter to ensure uniformity of style and flow that have been the hallmarks of the text. Together, we hope that we have succeeded in bringing to the reader the excitement of the study of disease mechanisms and the desire to learn more than what can be offered in any textbook.

V K
A K A
N F

Acknowledgments

The authors are grateful to a large number of individuals who have contributed in many ways toward the completion of this textbook.

First and foremost, all three of us offer our tributes and gratitude to two stalwarts of American pathology, Dr. Stanley Robbins and Dr. Ramzi Cotran. Their passion for excellence and uncompromising standards have made this book what it is. While neither of the two will see this edition in its completed form, their stamp on *Pathologic Basis of Disease* is indelible. Second, we thank our contributing authors for their commitment to this textbook. Many are veterans of previous editions; others are new to the seventh edition. All are acknowledged in the Table of Contents. Their names lend authority to this book, for which we are grateful.

Many colleagues have enhanced the text by reading various chapters and providing helpful critiques in their area of expertise. They include (at the University of Chicago): Drs. Todd Kroll,

Michelle LeBeau, Olaf Schneewind, Josephine Morello, Megan Mc Nerney, Fred Wondisford, Aliya Husain, Jonathan Miller, Julian Solway, John Hart, Amy Noffsinger, Thomas Krausz, Raminder Kumar, Joanne Yocum, Christopher Weber, Elizabeth McNally, and Manny Utset; (at the University of California at San Francisco): Drs. Steve Gitelman, Jonathan Lin, David Wofsy, Patrick Treseler, Mark Anderson, and Aaron Tward; (at the University of Washington, Seattle): Drs. Zsolt Argyenyi, Peter Beyers, Ann DeLancey, Charles Murry, Thomas Norwood, Brian Rubin, Paul Swanson, Melissa Upton, and Mathew Yeh. Dr. David Walker, at the University of Texas Medical Branch at Galveston provided a thorough critique of the chapter on infectious disease. Dr. Lora Hendrick Ellenson at Cornell University (Weill Medical College) provided a critique of the chapter on the female genital tract. Dr. Arlene Herzberg and Kelly McGuigan provided help with the chapter on skin diseases.

Special thanks are owed to Dr. Henry Sanchez at the University of California at San Francisco for his painstaking review and revision of the older color illustrations and for his magic touch in enhancing them digitally. Their freshness will be obvious to the readers. Many colleagues provided photographic gems from their collection. They are individually acknowledged in the text.

Our administrative staff needs to be acknowledged since they maintain order in the chaotic lives of the authors and have willingly chipped in when needed for multiple tasks relating to the text. At the University of Chicago, they include Ms. Vera Davis and Ms. Ruthie Cornelius; at The University of California at San Francisco, Ms. Ana Narvaez; and at the University of Washington, Seattle, Ms. Catherine Alexander, Steven Berard, Carlton Kim, Ms. Genevieve Thomas, and Ms. Vicki Tolbert. Ms. Beverly Shackelford at the University of Texas at Dallas, who has helped one of us (VK) for 21 years, deserves special mention since she coordinated the submission of all manuscripts, proofread many of them, and maintained liaison with the contributors and publisher. Without her dedication to this book and her meticulous attention to detail, our task would have been much more difficult. Most of the graphic art in this book was created by Mr. James Perkins, Assistant Professor of Medical Illustration at Rochester Institute of Technology. His ability to convert complex ideas into simple and aesthetically pleasing sketches has considerably enhanced this book.

Many individuals associated with our publisher, Elsevier (under the imprint of W.B. Saunders), need our special thanks. Outstanding among them is Ellen Sklar, Production Editor, supervising the production of this book. Her understanding of the needs of the authors and the complexity of publishing a textbook went a long way in making our lives less complicated.

XII

Mr. William Schmitt, Publishing Director of Medical Textbooks, has always been our cheerleader and is now a dear friend. Our thanks also go to Managing Editor Rebecca Gruliow and Design Manager Ellen Zanolle at Elsevier. Undoubtedly there are many other "heroes" who may have been left out unwittingly—to them we say "thank you" and tender apologies for not acknowledging you individually.

Efforts of this magnitude take a heavy toll on the families of the authors. We thank our spouses Raminder Kumar, Ann Abbas, and Ann DeLancey for their patience, love, and support of this venture, and for their tolerance of our absences.

Finally, Vinay Kumar wishes to express his deep appreciation to Drs. Abul Abbas and Nelson Fausto for joining the team, and together we salute each other for shared vision and dedication to medical education. Despite differences in our vantage points, opinions, and individual styles, our common goal made this an exciting and rewarding partnership.

V K
A A
N F

Section I - General Pathology

2

3

Chapter 1 - Cellular Adaptations, Cell Injury, and Cell Death

4

Introduction to Pathology

Pathology is literally the study (*logos*) of suffering (*pathos*). More specifically, it is an abridging discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie disease. By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a sound foundation for rational clinical care and therapy.

Traditionally, the study of pathology is divided into general pathology and special, or systemic, pathology. The former is concerned with the basic reactions of cells and tissues to abnormal stimuli that underlie all diseases. The latter examines the specific responses of specialized organs and tissues to more or less well-defined stimuli. In this book, we first cover the principles of general pathology and then proceed to specific disease processes as they affect particular organs or systems.

The four aspects of a disease process that form the core of pathology are its cause (*etiology*), the mechanisms of its development (*pathogenesis*), the structural alterations induced in the cells and organs of the body (*morphologic changes*), and the functional consequences of the morphologic changes (*clinical significance*).

Etiology or Cause.

The concept that certain abnormal symptoms or diseases are "caused" is as ancient as recorded history. For the Arcadians (2500 BC), if someone became ill, it was the patient's own fault (for having sinned) or the makings of outside agents, such as bad smells, cold, evil spirits, or gods.^[1] In modern terms, there are two major classes of etiologic factors: intrinsic or genetic, and acquired (e.g., infectious, nutritional, chemical, physical). The concept, however, of one etiologic agent for one disease — developed from the study of infections or single-gene disorders — is no longer sufficient. Genetic factors are clearly involved in some of the common environmentally induced maladies, such as atherosclerosis and cancer, and the environment may also have profound influences on certain genetic diseases. Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, or a treatment developed.

Pathogenesis.

Pathogenesis refers to the sequence of events in the response of cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease. The study of pathogenesis remains one of the main domains of pathology. Even when the initial infectious or molecular cause is known, it is many steps removed from the expression of the disease. For example, to understand cystic fibrosis is to know not only the defective gene and gene product, but also the biochemical, immunologic, and morphologic events leading to the formation of cysts and fibrosis in the lung, pancreas, and other organs. Indeed, as we shall see throughout the book, the molecular revolution has already identified mutant genes underlying a great number of diseases, and the entire human genome has been mapped. Nevertheless, the functions of the encoded proteins and how mutations induce disease are often still obscure. Because of technologic advances, it is becoming increasingly feasible to link specific molecular abnormalities to disease manifestations and to use this knowledge to design new therapeutic approaches. For these reasons, the study of pathogenesis has never been more exciting scientifically or more relevant to medicine.

Morphologic Changes.

The morphologic changes refer to the structural alterations in cells or tissues that are either characteristic of the disease or diagnostic of the etiologic process. The practice of diagnostic pathology is devoted to identifying the nature and progression of disease by studying morphologic changes in tissues and chemical alterations in patients. More recently, the limitations of morphology for diagnosing diseases have become increasingly evident, and the field of diagnostic pathology has expanded to encompass molecular biologic and immunologic approaches for analyzing disease states. Nowhere is this more striking than in the study of tumors — breast cancers and tumors of lymphocytes that look morphologically identical may have widely different courses, therapeutic responses, and prognosis. Molecular analysis by techniques such as DNA microarrays has begun to reveal genetic differences that bear on the behavior of the tumors. Increasingly, such techniques are being used to extend and even supplant traditional morphologic methods.

Functional Derangements and Clinical Manifestations.

The nature of the morphologic changes and their distribution in different organs or tissues influence normal function and determine the clinical features (symptoms and signs), course, and prognosis of the disease.

Virtually all forms of organ injury start with molecular or structural alterations in cells, a concept first put forth in the nineteenth century by Rudolf Virchow, known as the father of modern pathology. We therefore begin our consideration of pathology with the study of the origins, molecular mechanisms, and structural changes of cell injury. Yet different cells in tissues constantly interact with each other, and an elaborate system of *extracellular matrix* is necessary for the integrity of organs. Cell-cell and cell-matrix interactions contribute significantly to the response to injury, leading collectively to *tissue and organ injury*, which are as important as cell injury in defining the morphologic and clinical patterns of disease.

Overview: Cellular Responses to Stress and Noxious Stimuli

The normal cell is confined to a fairly narrow range of function and structure by its genetic programs of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates. It is nevertheless able to handle normal physiologic demands, maintaining a steady state called *homeostasis*. More severe physiologic stresses and some pathologic stimuli may bring about a number of physiologic and morphologic *cellular adaptations*, during which new but altered steady states are achieved, preserving the viability of the cell and modulating its function as it responds to such stimuli (Fig. 1-1 and Table 1-1). The adaptive response may consist of an increase in the number of cells, called *hyperplasia*, or an increase in the sizes of individual cells, called *hypertrophy*. Conversely, *atrophy* is an adaptive response in which there is a decrease in the size and function of cells.

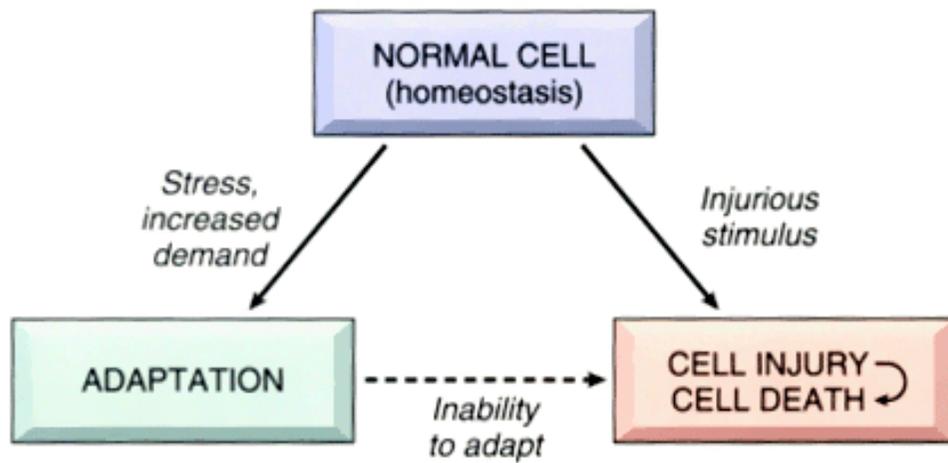


TABLE 1-1 -- Cellular Responses to Injury

Nature and Severity of Injurious Stimulus	Cellular Response
Altered physiologic stimuli:	Cellular adaptations:
• Increased demand, increased trophic stimulation (e.g. growth factors, hormones)	• Hyperplasia, hypertrophy
• Decreased nutrients, stimulation	• Atrophy
• Chronic irritation (chemical or physical)	• Metaplasia
Reduced oxygen supply; chemical injury; microbial infection	Cell injury:
• Acute and self-limited	• Acute reversible injury
• Progressive and severe (including DNA damage)	• Irreversible injury → cell death
	••••Necrosis
	••••Apoptosis
• Mild chronic injury	• Subcellular alterations in various organelles
Metabolic alterations, genetic or acquired	Intracellular accumulations; calcifications
Prolonged life span with cumulative sublethal injury	Cellular aging

hormone. It also occurs in certain pathologic conditions, when cells are damaged beyond repair, and especially if the damage affects the cell's nuclear DNA. We will return to a detailed discussion of these pathways of cell death later in the chapter.

Stresses of different types may induce changes in cells and tissues other than adaptations, cell injury, and death (see Table 1-1). Cells that are exposed to sublethal or chronic stimuli may not be damaged but may show a variety of *subcellular alterations*. Metabolic derangements in cells may be associated with *intracellular accumulations* of a number of substances, including proteins, lipids, and carbohydrates. Calcium is often deposited at sites of cell death, resulting in *pathologic calcification*. Finally, *cell aging* is also accompanied by characteristic morphologic and functional changes.

In this chapter, we discuss first how cells adapt to stresses, and then the causes, mechanisms, and consequences of the various forms of acute cell damage, including cell injury and cell death. We conclude with subcellular alterations induced by sublethal stimuli, intracellular accumulations, pathologic calcification, and cell aging.

Cellular Adaptations of Growth and Differentiation

Cells respond to increased demand and external stimulation by *hyperplasia* or *hypertrophy*, and they respond to reduced supply of nutrients and growth factors by *atrophy*. In some situations, cells change from one type to another, a process called *metaplasia*. There are numerous molecular mechanisms for cellular adaptations. Some adaptations are induced by direct stimulation of cells by factors produced by the responding cells themselves or by other cells in the environment. Others are due to activation of various cell surface receptors and downstream signaling pathways. Adaptations may be associated with the induction of new protein synthesis by the target cells, as in the response of muscle cells to increased physical demand, and the induction of cellular proliferation, as in responses of the endometrium to estrogens. Adaptations can also involve a switch by cells from producing one type of proteins to another or markedly overproducing one protein; such is the case in cells producing various types of collagens and extracellular matrix proteins in chronic inflammation and fibrosis (Chapter 2 and Chapter 3).

Figure 1-2 The relationships between normal, adapted, reversibly injured, and dead myocardial cells. The cellular adaptation depicted here is hypertrophy, and the type of cell death is ischemic necrosis. In reversibly injured myocardium, generally effects are only functional, without any readily apparent gross or even microscopic changes. In the example of myocardial hypertrophy, the left ventricular wall is more than 2 cm in thickness (normal is 1 to 1.5 cm). In the specimen showing necrosis, the transmural light area in the posterolateral left ventricle represents an acute myocardial infarction. All three transverse sections have been stained with triphenyltetrazolium chloride, an enzyme substrate that colors viable myocardium magenta. Failure to stain is due to enzyme leakage after cell death.

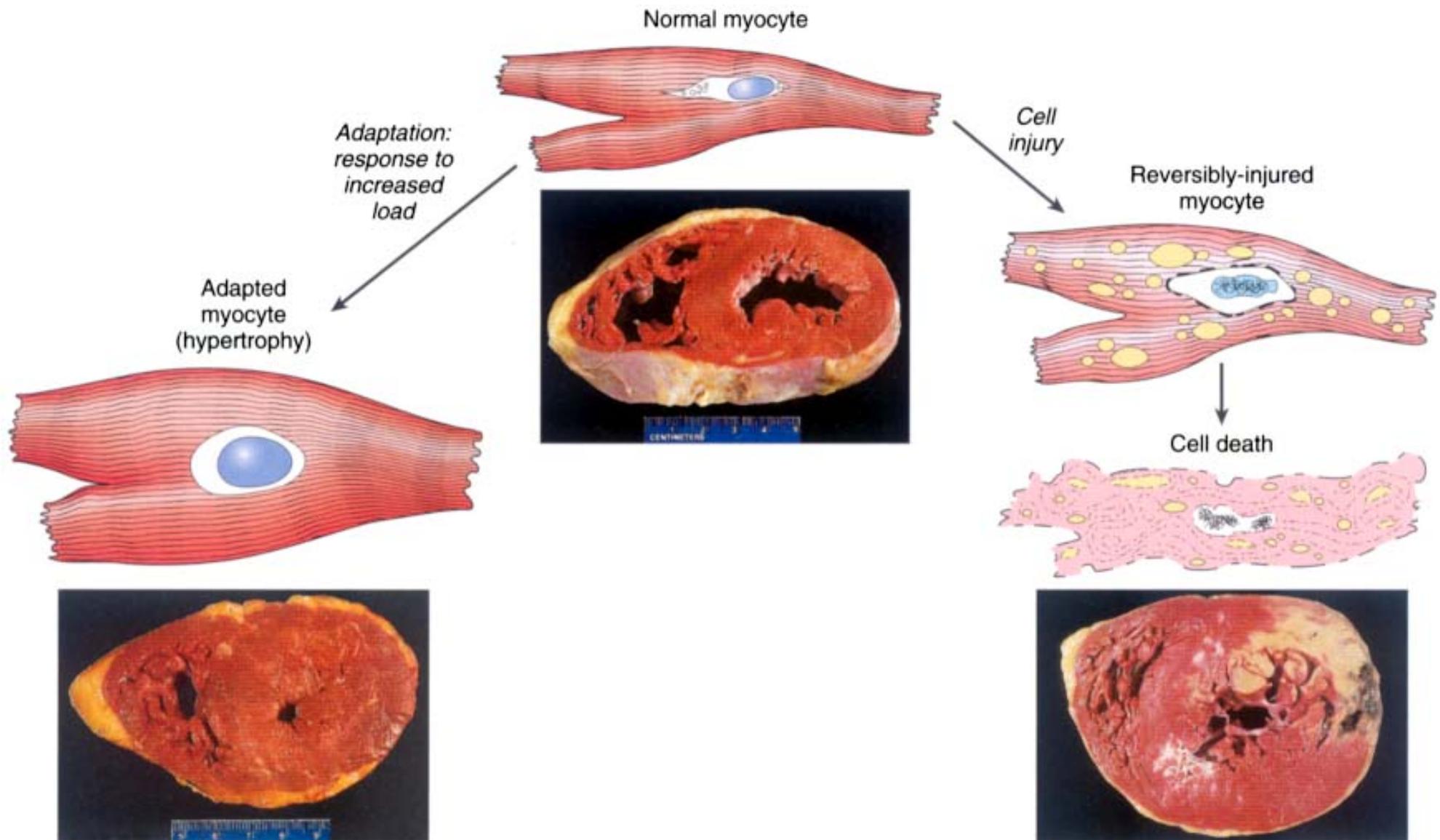


Figure 1-3 Physiologic hypertrophy of the uterus during pregnancy. *A*, Gross appearance of a normal uterus (*right*) and a gravid uterus (removed for postpartum bleeding) (*left*). *B*, Small spindle-shaped uterine smooth muscle cells from a normal uterus (*left*) compared with large plump cells in gravid uterus (*right*).

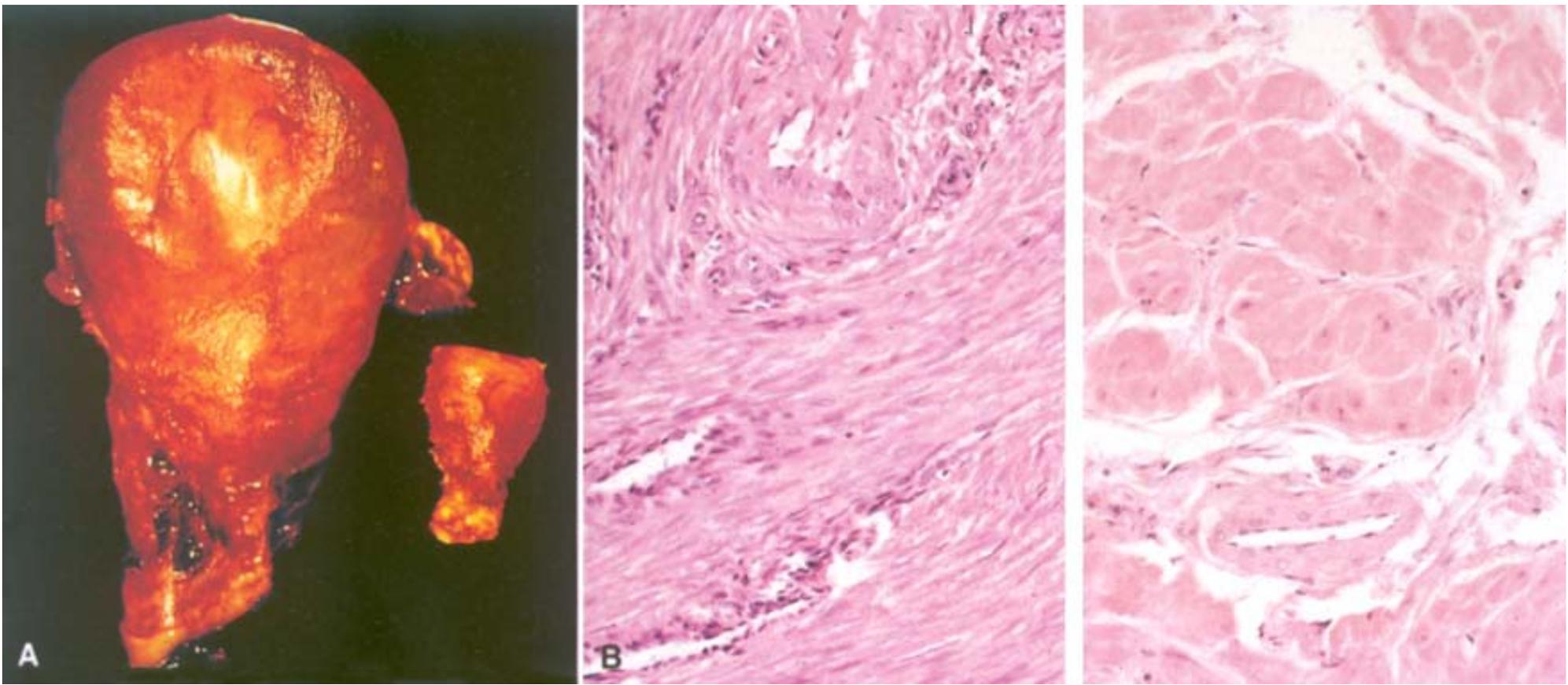


Figure 1-4 Changes in the expression of selected genes and proteins during myocardial hypertrophy.

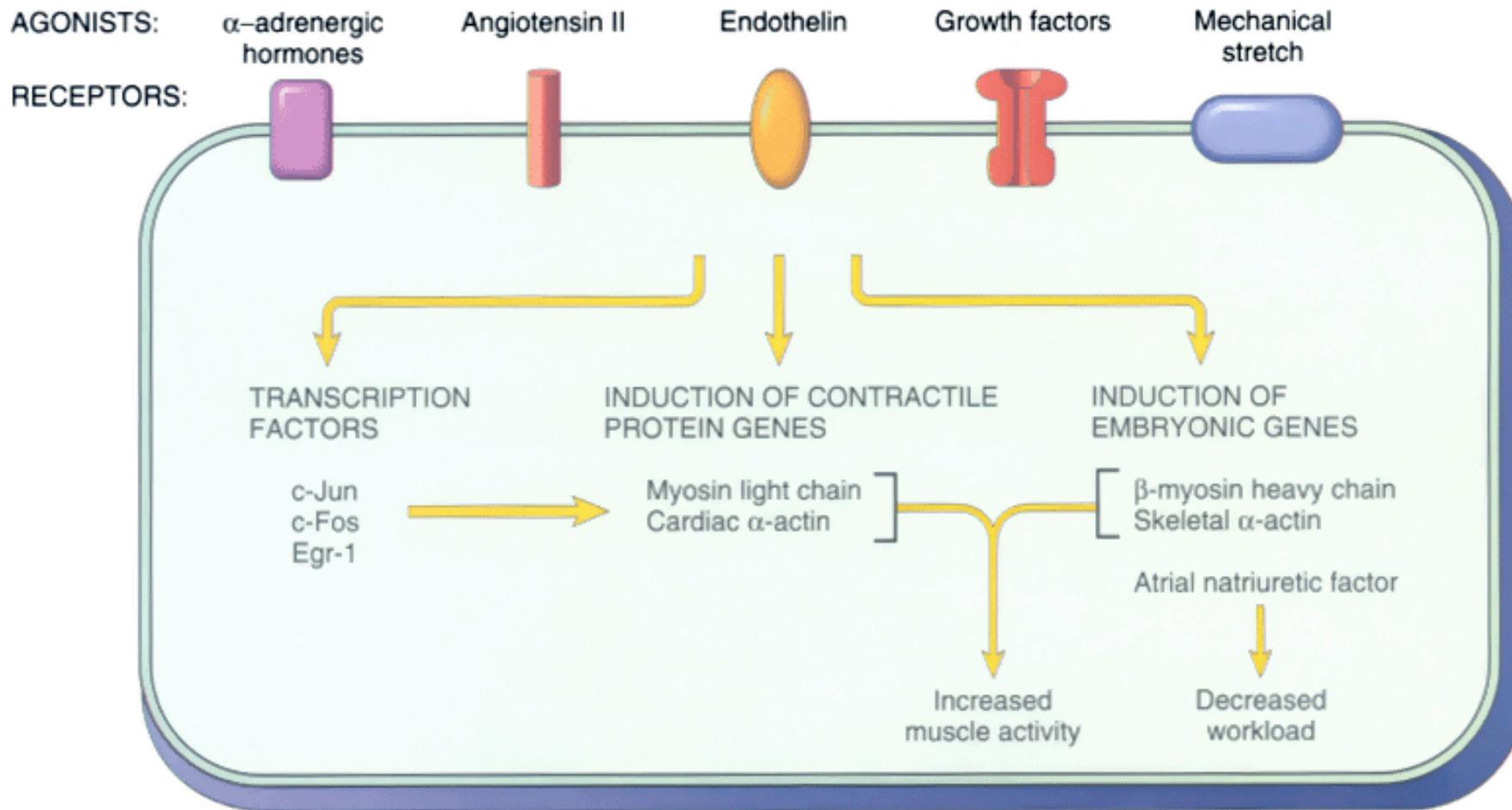


Figure 1-5 *A*, Atrophy of the brain in an 82-year-old male with atherosclerotic disease. Atrophy of the brain is due to aging and reduced blood supply. The meninges have been stripped. *B*, Normal brain of a 36-year-old male. Note that loss of brain substance narrows the gyri and widens the sulci.

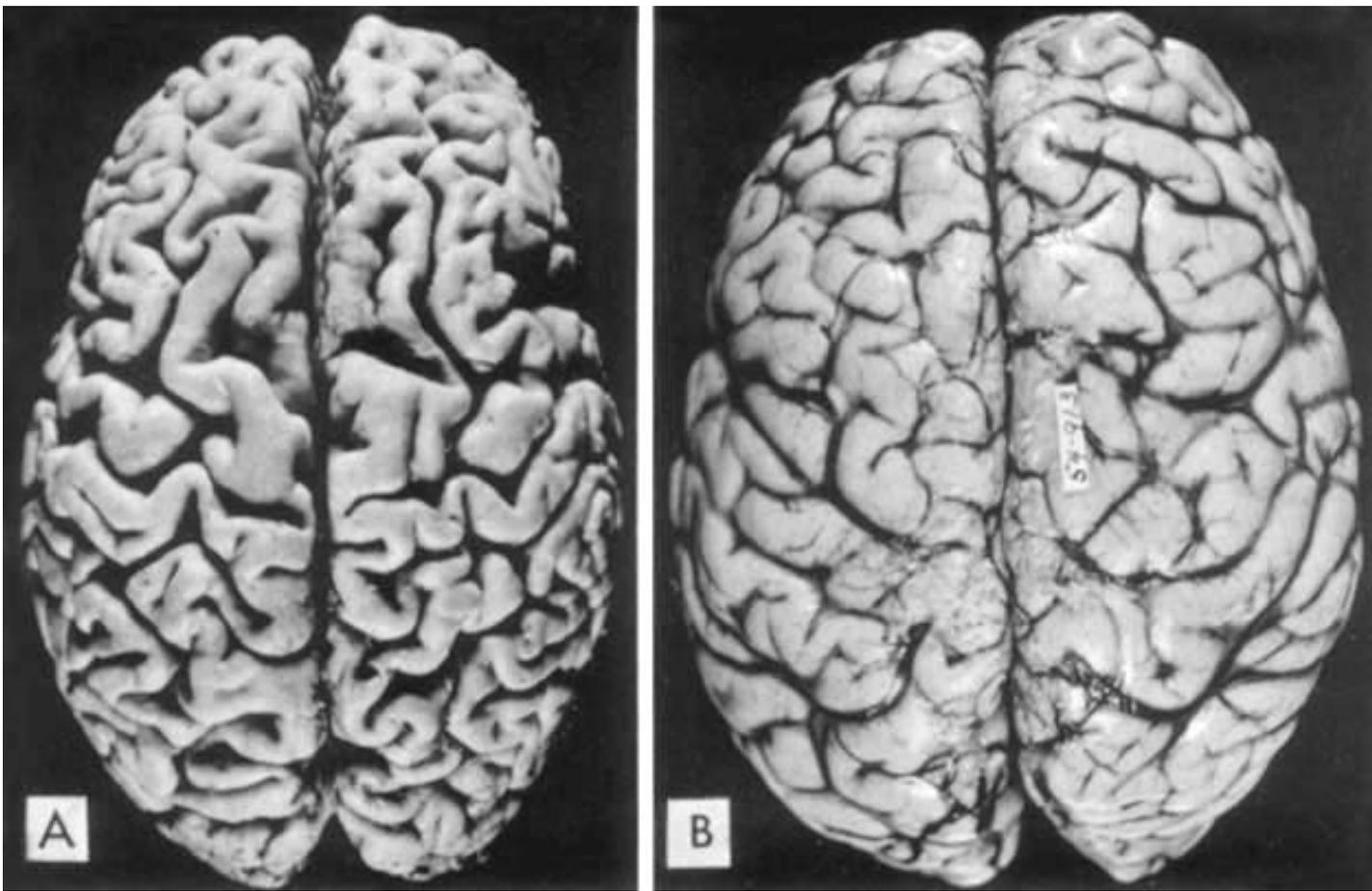
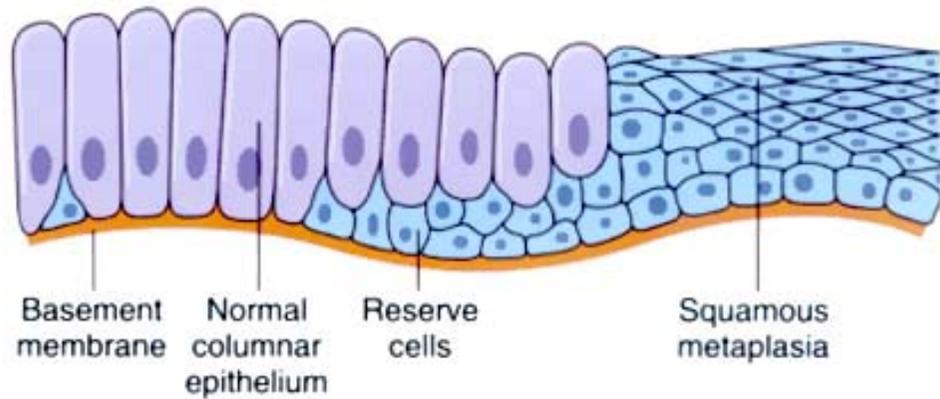
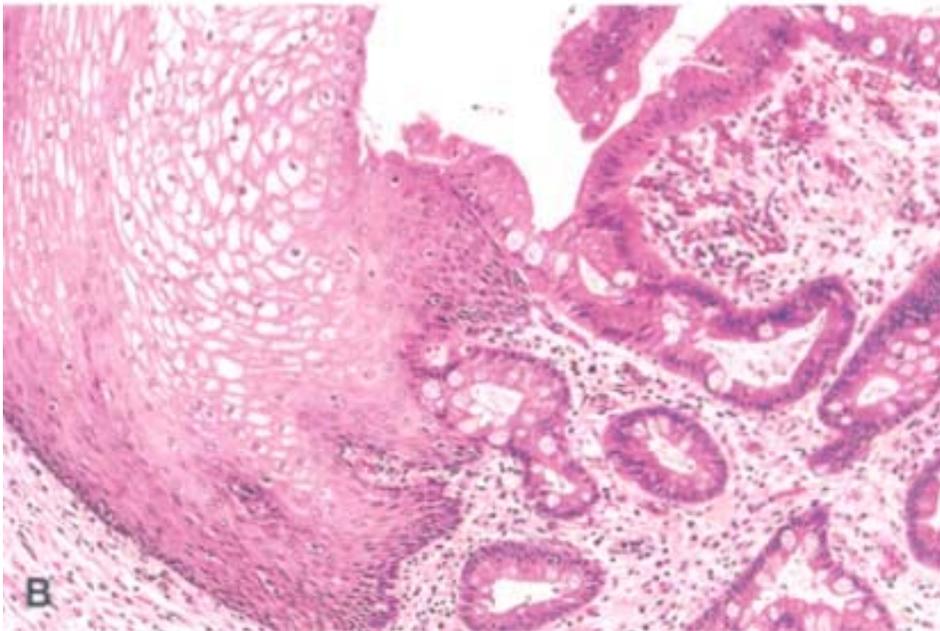


Figure 1-6 Metaplasia. *A*, Schematic diagram of columnar to squamous metaplasia. *B*, Metaplastic transformation of esophageal stratified squamous epithelium (*left*) to mature columnar epithelium (so-called Barrett metaplasia).



A



Irreversible injury and cell death. With continuing damage, the injury becomes irreversible, at which time the cell cannot recover. Is there a critical biochemical event (the "lethal hit") responsible for the point of no return? There are no clear answers to this question. However, as discussed later, in ischemic tissues such as the myocardium, certain structural changes (e.g., amorphous densities in mitochondria, indicative of severe mitochondrial damage) and functional changes (e.g., loss of membrane permeability) are indicative of cells that have suffered irreversible injury.

- *Irreversibly injured cells invariably undergo morphologic changes that are recognized as cell death.* There are two types of cell death, necrosis and apoptosis, which differ in their morphology, mechanisms, and roles in disease and physiology (Fig. 1-9 and Table 1-2). When damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest the cell, and cellular contents leak out, resulting in *necrosis*. Some noxious stimuli, especially those that damage DNA, induce another type of death, *apoptosis*, which is characterized by nuclear dissolution without complete loss of membrane integrity. *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with cell injury.* Although we emphasize the distinctions between necrosis and apoptosis, there may be some overlaps and common mechanisms between these two pathways. In addition, at least some types of stimuli may induce either apoptosis or necrosis, depending on the intensity and duration of the stimulus, the rapidity of the death process, and the biochemical derangements induced in the injured cell. The mechanisms and significance of these two death pathways are discussed later in the chapter.

Figure 1-7 Stages in the evolution of cell injury and death.

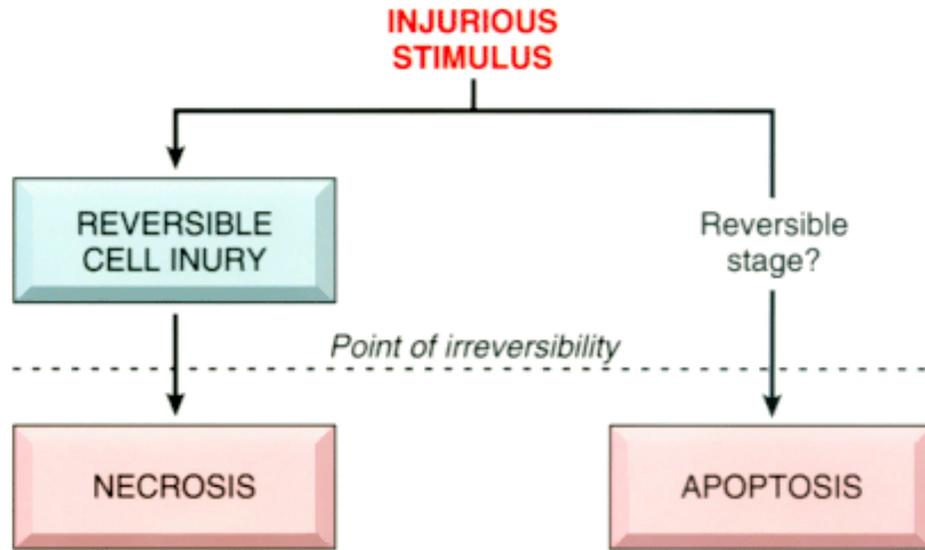
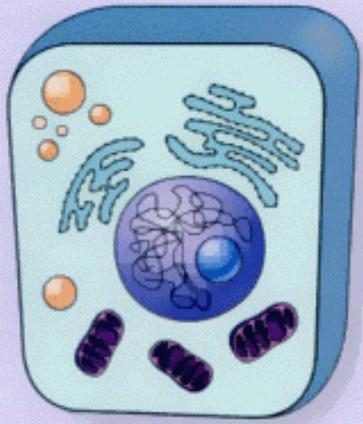


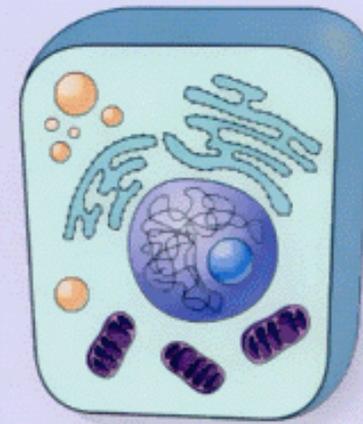
Figure 1-8 Schematic representation of a normal cell and the changes in reversible and irreversible cell injury. Depicted are morphologic changes, which are described in the following pages and shown in electron micrographs in Figure 1-17 . Reversible injury is characterized by generalized swelling of the cell and its organelles; blebbing of the plasma membrane; detachment of ribosomes from the endoplasmic reticulum; and clumping of nuclear chromatin. Transition to irreversible injury is characterized by increasing swelling of the cell; swelling and disruption of lysosomes; presence of large amorphous densities in swollen mitochondria; disruption of cellular membranes; and profound nuclear changes. The latter include nuclear condensation (pyknosis), followed by fragmentation (karyorrhexis) and dissolution of the nucleus (karyolysis). Laminated structures (myelin figures) derived from damaged membranes of organelles and the plasma membrane first appear during the reversible stage and become more pronounced in irreversibly damaged cells. The mechanisms underlying these changes are discussed in the text that follows.

NORMAL



Normal cell

Normal cell



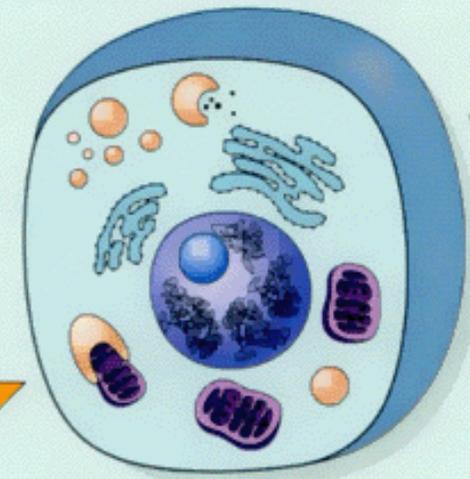
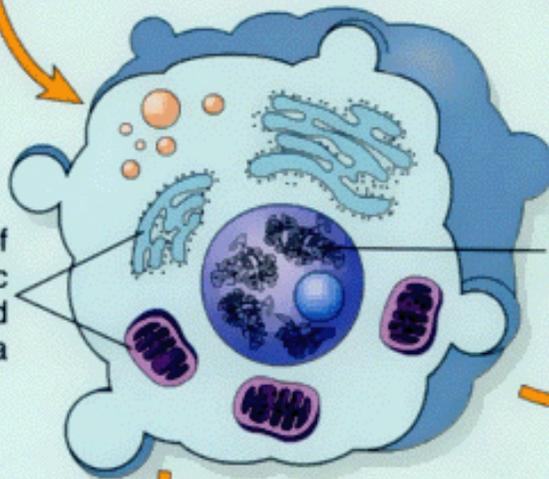
REVERSIBLE CELL INJURY

Injury

Swelling of endoplasmic reticulum and mitochondria

Clumping of chromatin

Recovery



IRREVERSIBLE CELL INJURY → NECROSIS

Death

Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture

Membrane blebs

Myelin figures

Nuclear condensation

Swollen mitochondria with amorphous densities

Necrosis

Fragmentation of cell membrane and nucleus

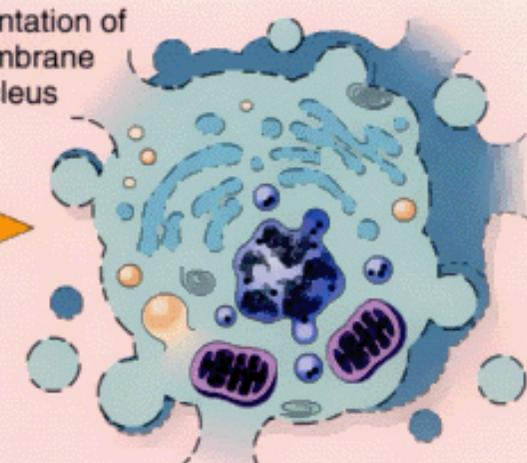
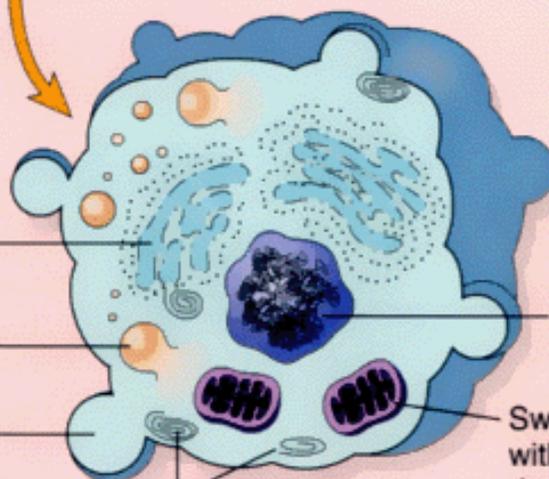


Figure 1-9 The sequential ultrastructural changes seen in necrosis (*left*) and apoptosis (*right*). In apoptosis, the initial changes consist of nuclear chromatin condensation and fragmentation, followed by cytoplasmic budding and phagocytosis of the extruded apoptotic bodies. Signs of cytoplasmic blebs, and digestion and leakage of cellular components. (*Adapted from Walker NI, et al: Patterns of cell death. Methods Archiv Exp Pathol 13:18-32, 1988. Reproduced with permission of S. Karger AG, Basel.*)

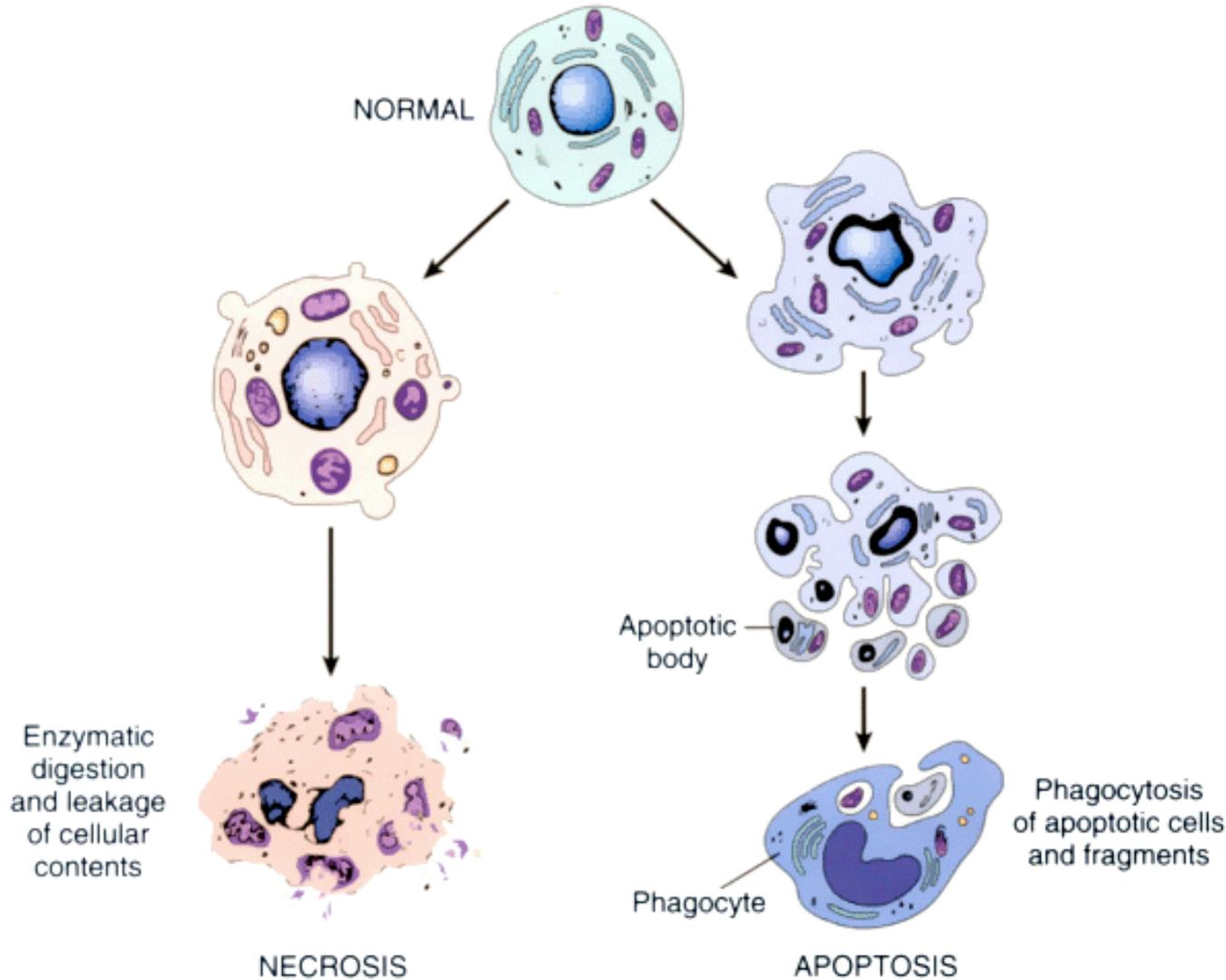


TABLE 1-2 -- Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments

Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

however, are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; social stimuli, such as alcohol and narcotic drugs; and the ever-increasing variety of therapeutic drugs.

Infectious Agents.

These agents range from the submicroscopic viruses to the large tapeworms. In between are the rickettsiae, bacteria, fungi, and higher forms of parasites. The ways by which this heterogeneous group of biologic agents cause injury are diverse and are discussed in Chapter 8 .

Immunologic Reactions.

Although the immune system serves an essential function in defense against infectious pathogens, immune reactions may, in fact, cause cell injury. The anaphylactic reaction to a foreign protein or a drug is a prime example, and reactions to endogenous self-antigens are responsible for a number of autoimmune diseases (Chapter 6).

Genetic Derangements.

Genetic defects as causes of cell injury are of major interest to scientists and physicians today (Chapter 5). The genetic injury may result in a defect as severe as the congenital malformations associated with Down syndrome, caused by a chromosomal abnormality, or as subtle as the decreased life of red blood cells caused by a single amino acid substitution in hemoglobin S in sickle cell anemia. The many inborn errors of metabolism arising from enzymatic abnormalities, usually an enzyme lack, are excellent examples of cell damage due to subtle alterations at the level of DNA. Variations in genetic makeup can also influence the susceptibility of cells to injury by chemicals and other environmental insults.

Nutritional Imbalances.

Nutritional imbalances continue to be major causes of cell injury. Protein-calorie deficiencies cause an appalling number of deaths, chiefly among underprivileged populations. Deficiencies of specific vitamins are found throughout the world (Chapter 9). Nutritional problems can be self-imposed, as in anorexia nervosa or self-induced starvation. Ironically, nutritional excesses have also become important causes of cell injury. Excesses of lipids predispose to atherosclerosis, and obesity is a manifestation of the overloading of some cells in the body with fats. Atherosclerosis is virtually endemic in the United States, and obesity is rampant. In addition to the problems of undernutrition and overnutrition, the composition of the diet makes a significant

Figure 1-10 Cellular and biochemical sites of damage in cell injury.

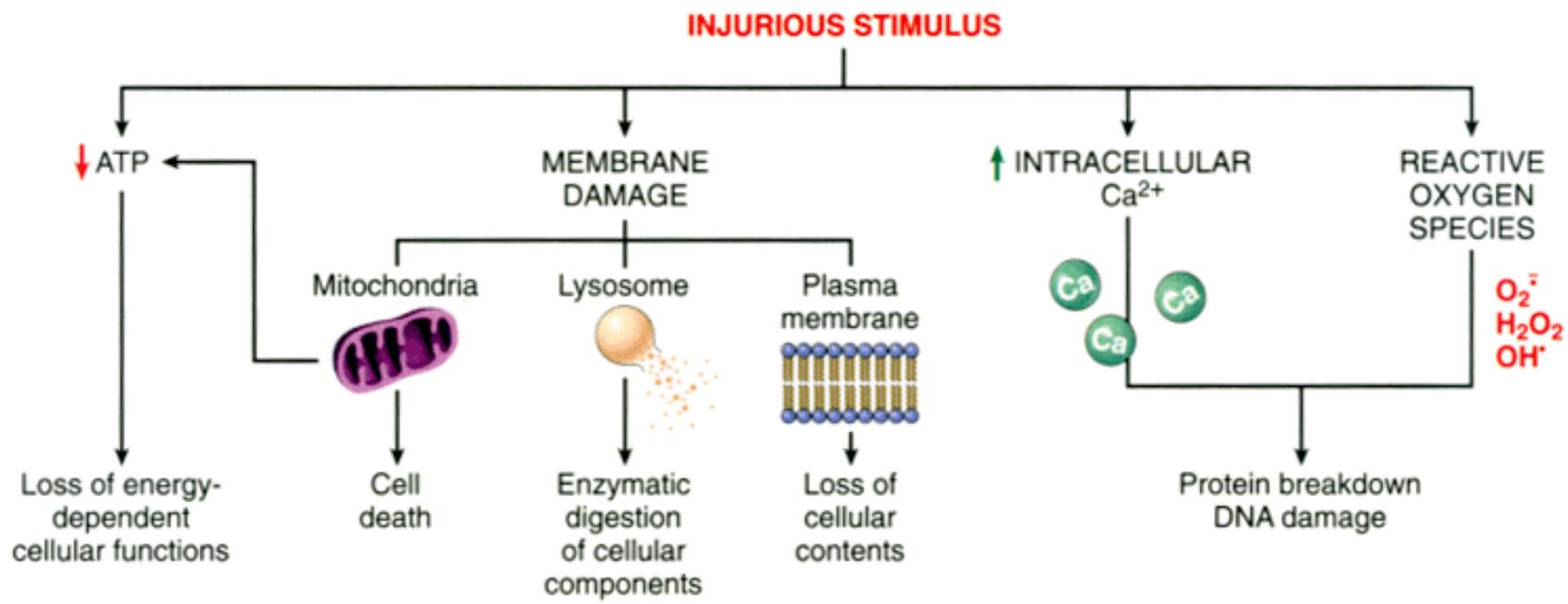


Figure 1-11 Functional and morphologic consequences of decreased intracellular ATP during cell injury.

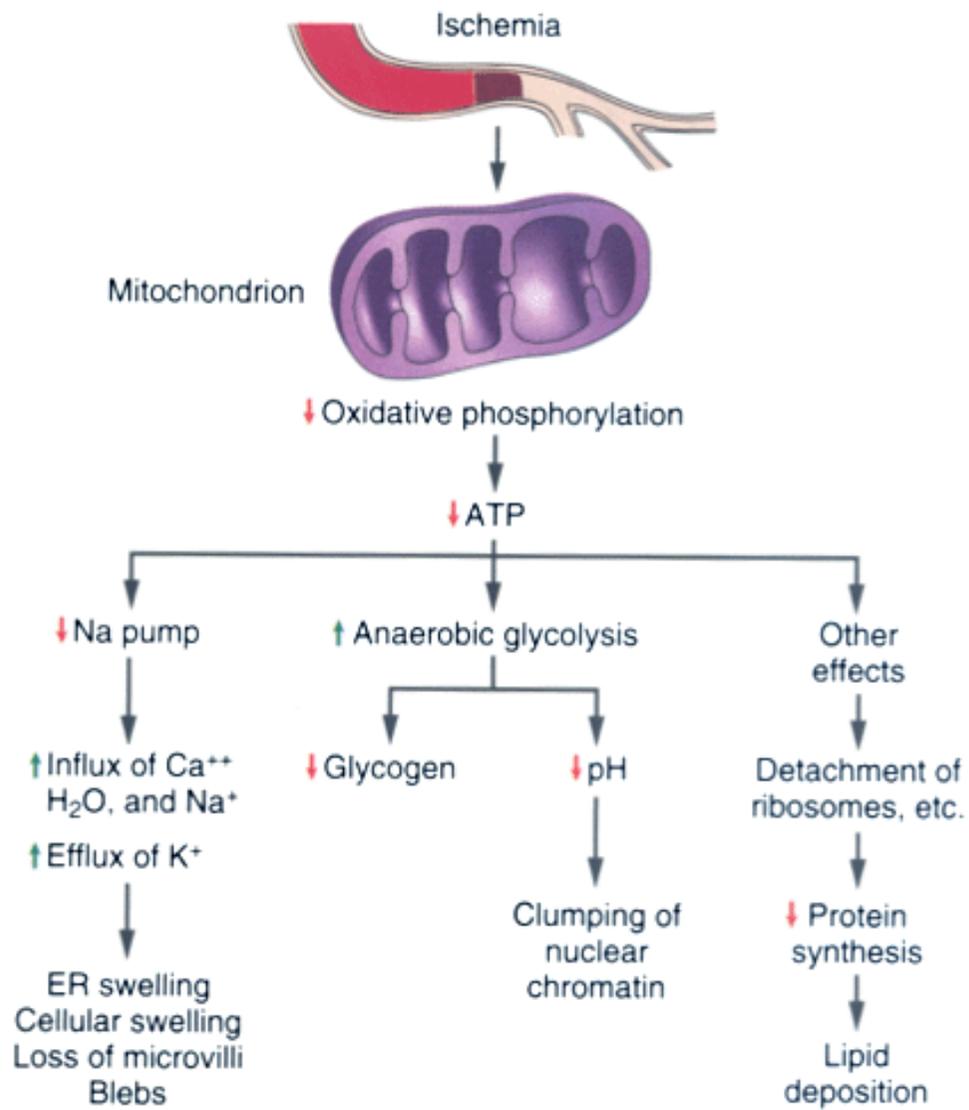


Figure 1-12 Mitochondrial dysfunction in cell injury.

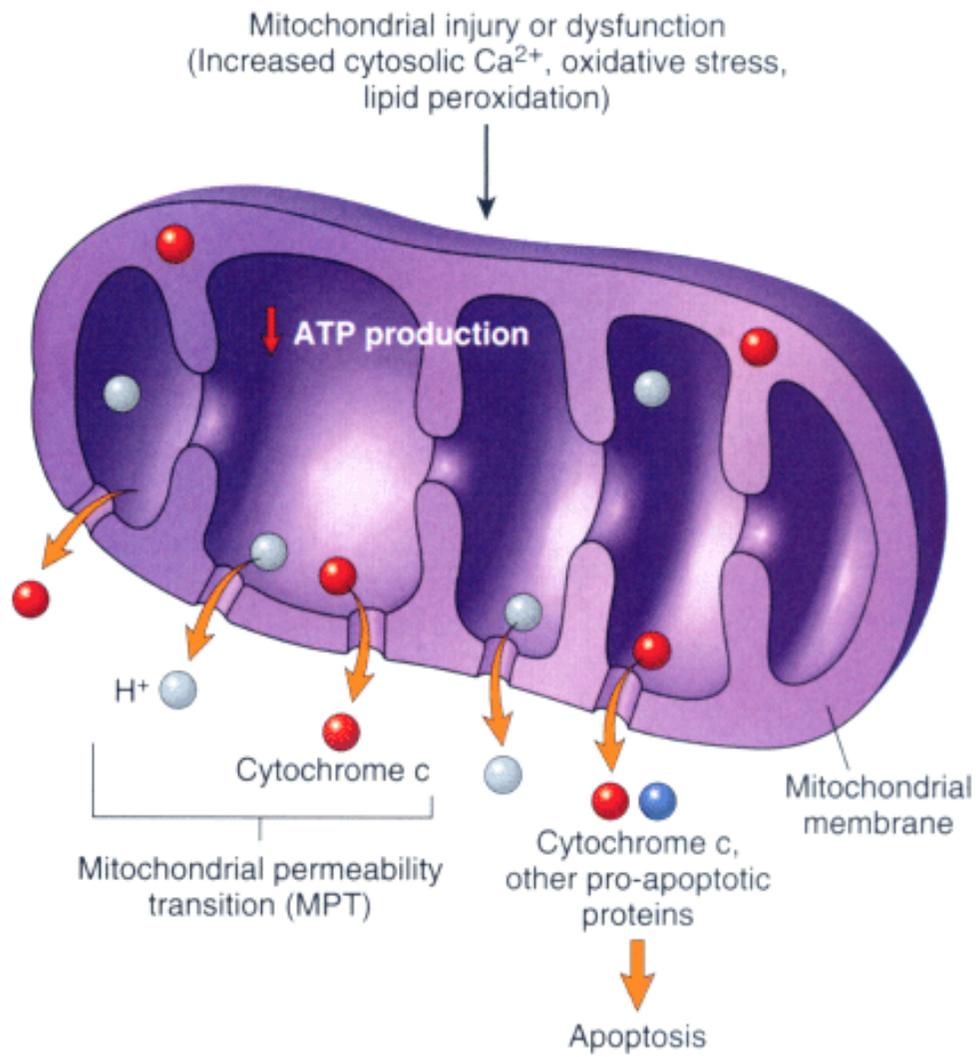


Figure 1-13 Sources and consequences of increased cytosolic calcium in cell injury. ATP, adenosine triphosphate.

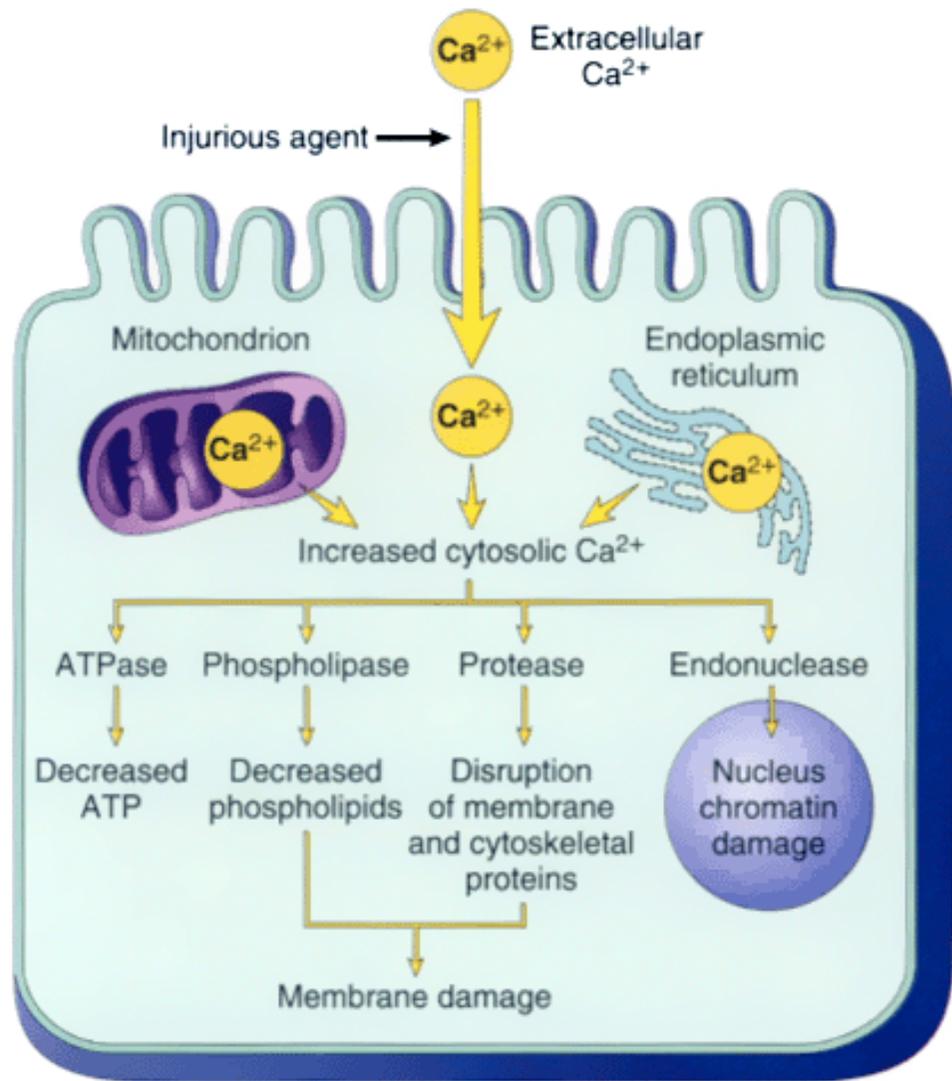
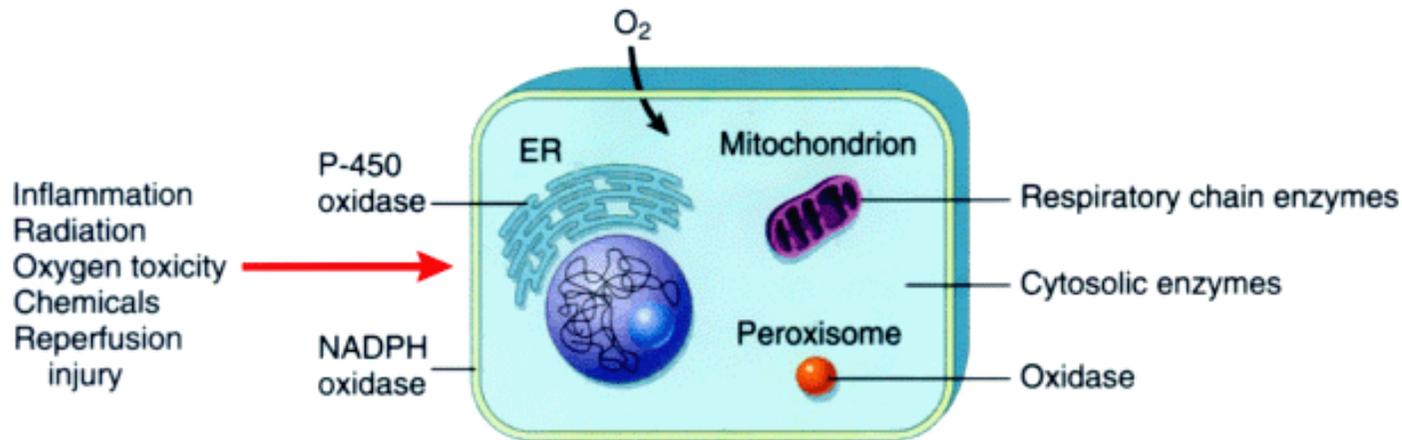


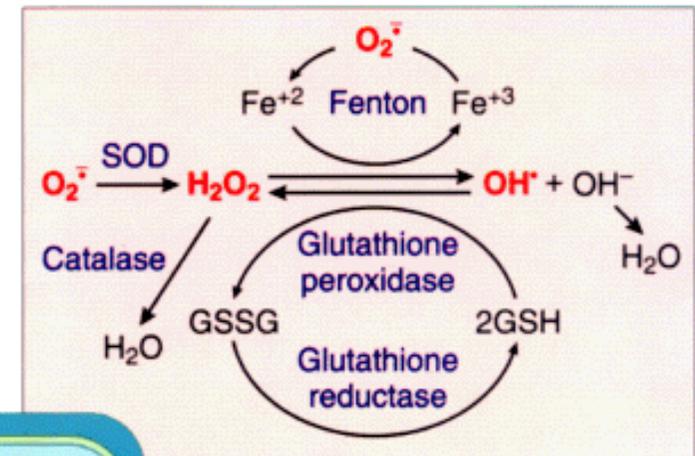
Figure 1-14 The role of reactive oxygen species in cell injury. O_2 is converted to superoxide (O_2^-) by oxidative enzymes in the endoplasmic reticulum (ER), mitochondria, plasma membrane, peroxisomes, and cytosol. O_2^- is converted to H_2O_2 by dismutation and thence to OH by the $\text{Cu}^{2+}/\text{Fe}^{2+}$ -catalyzed Fenton reaction. H_2O_2 is also derived directly from oxidases in peroxisomes. Not shown is another potentially injurious radical, singlet oxygen. Resultant free radical damage to lipid (peroxidation), proteins, and DNA leads to various forms of cell injury. Note that superoxide catalyzes the reduction of Fe^{3+} to Fe^{2+} , thus enhancing OH generation by the Fenton reaction. The major antioxidant enzymes are superoxide dismutase (SOD), catalase, and glutathione peroxidase. GSH, reduced glutathione; GSSG, oxidized glutathione; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate.

A. FREE RADICAL GENERATION



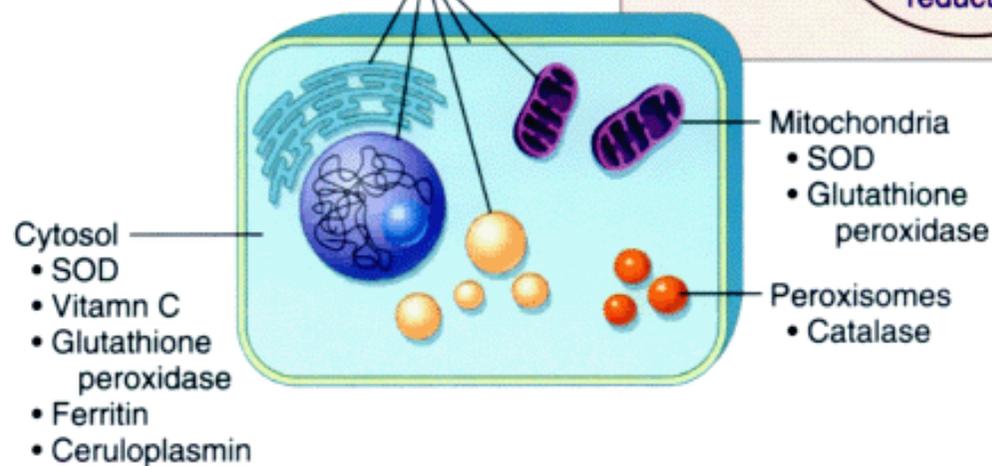
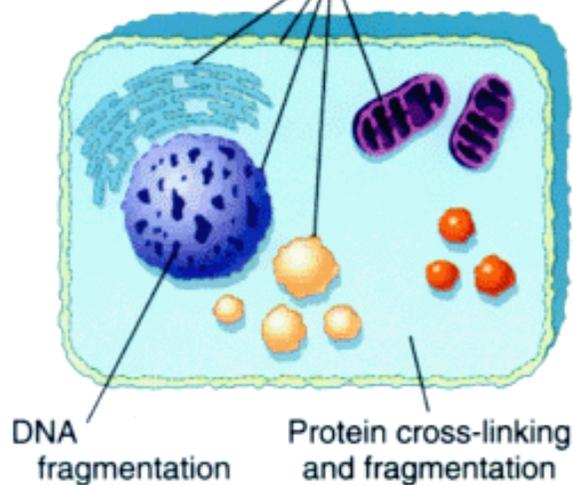
Reactive oxygen species:
O₂⁻, H₂O₂, OH[•]

Reactive oxygen species:
O₂⁻, H₂O₂, OH[•]



Membrane lipid peroxidation

All membranes
• Vitamins E and A
• β-carotene



B. CELL INJURY BY FREE RADICALS

C. NEUTRALIZATION OF FREE RADICALS – NO CELL INJURY

Figure 1-15 Mechanisms of membrane damage in cell injury. Decreased O_2 and increased cytosolic Ca^{2+} are typically seen in ischemia but may accompany other forms of cell injury. Reactive oxygen species, which are often produced on reperfusion of ischemic tissues, also cause membrane damage (not shown).

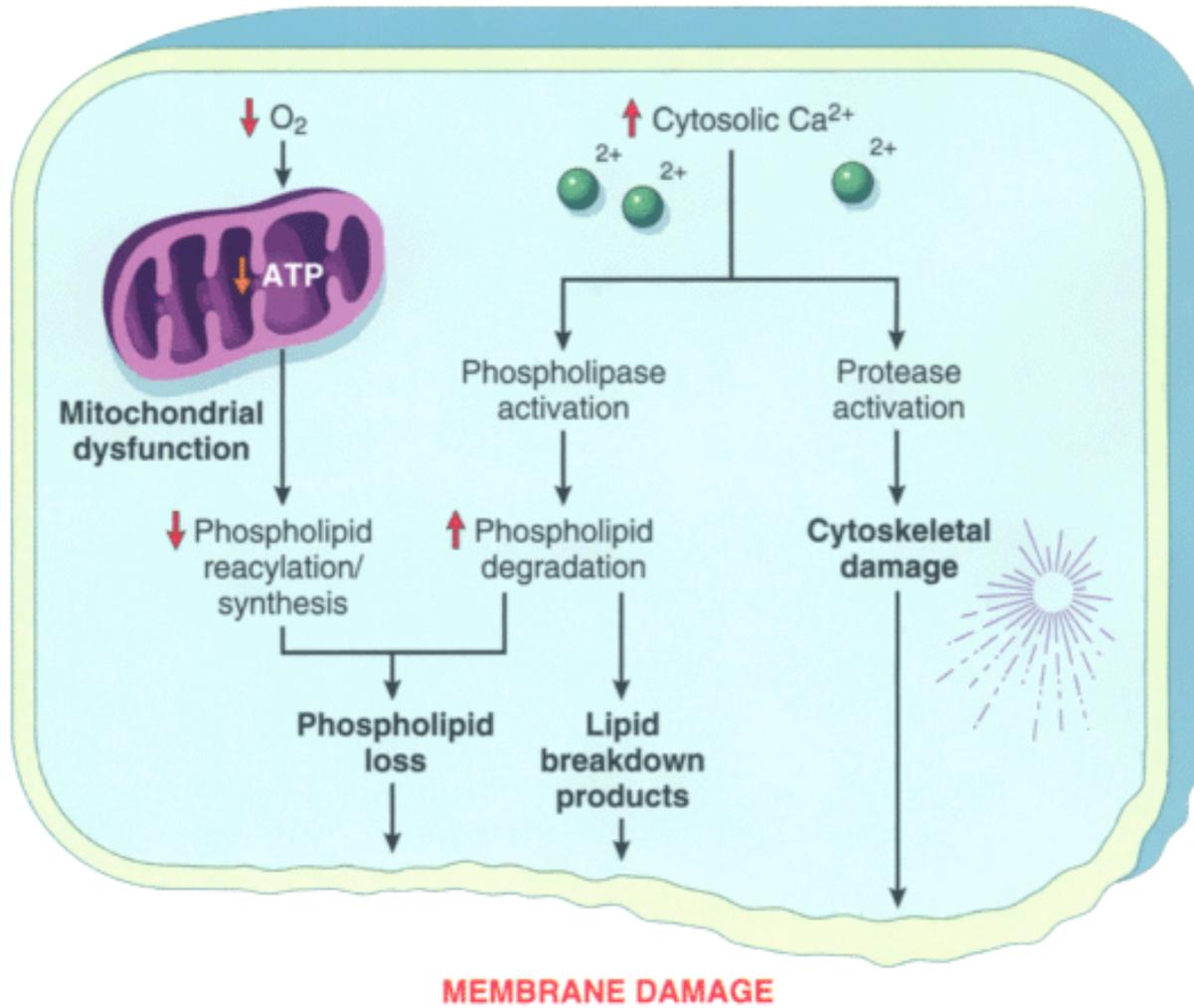


Figure 1-16 Timing of biochemical and morphologic changes in cell injury.

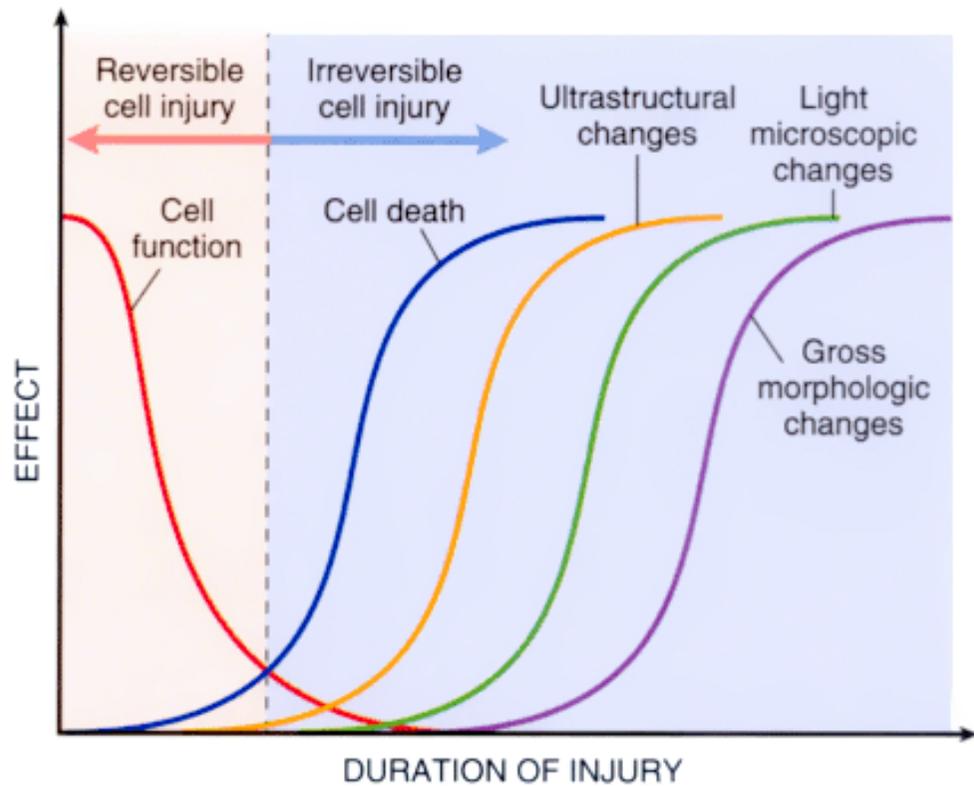


Figure 1-17 Morphologic changes in reversible and irreversible cell injury. *A*, Electron micrograph of a normal epithelial cell of the proximal kidney tubule. Note abundant microvilli (mv), lining the lumen (L). N, nucleus; V, apical vacuoles (which are normal structures in this cell type). *B*, Epithelial cell of the proximal tubule showing reversible ischemic changes. The microvilli (mv) are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen (L). Mitochondria are slightly dilated. (Compare with *A*.) *C*, Proximal tubular cell showing irreversible ischemic injury. Note the markedly swollen mitochondria containing amorphous densities, disrupted cell membranes, and dense pyknotic nucleus. (Courtesy of Dr. M. A. Venkatachalam, University of Texas, San Antonio, TX.)

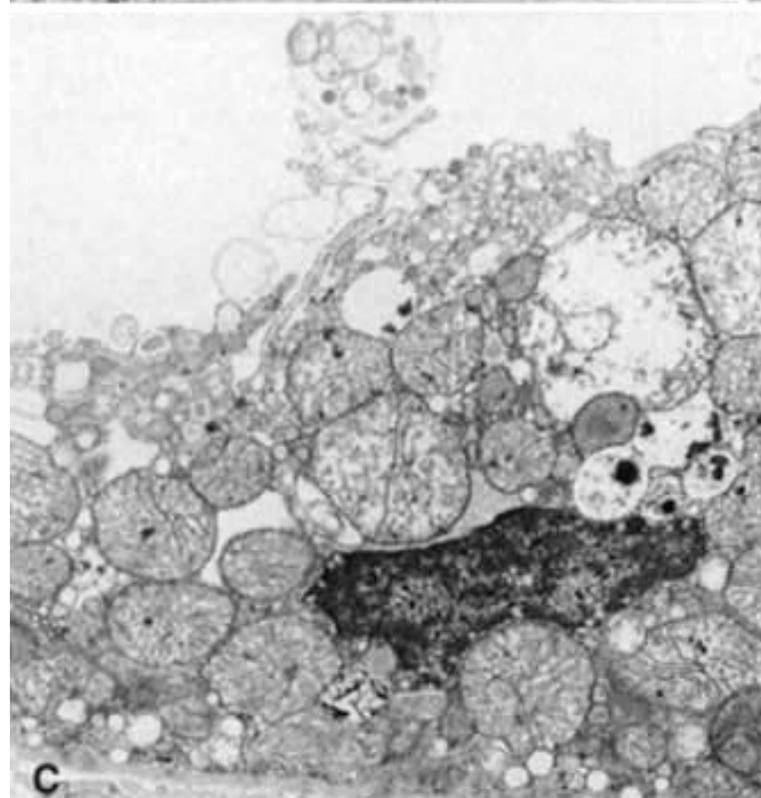
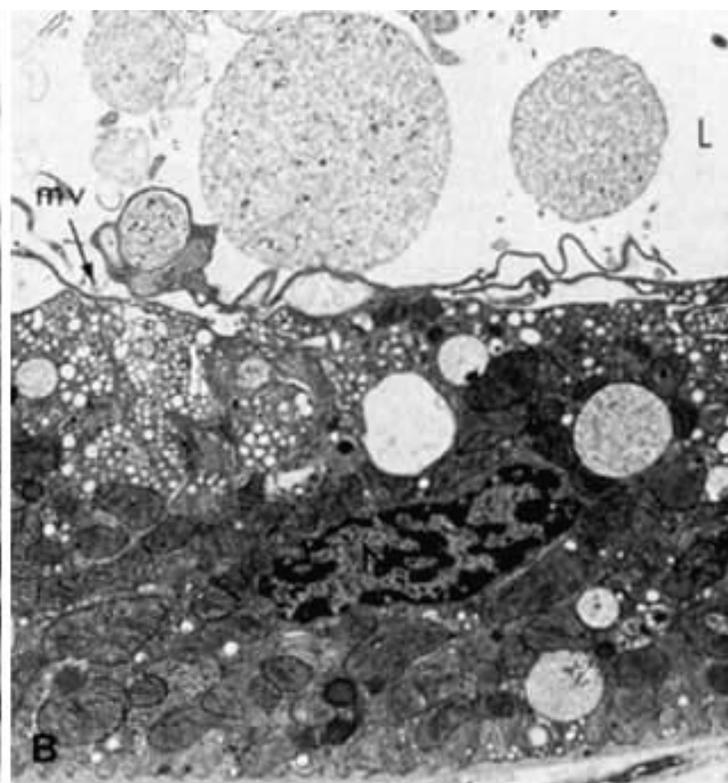




Figure 1-18 Ischemic necrosis of the myocardium. *A*, Normal myocardium. *B*, Myocardium with coagulation necrosis (upper two thirds of figure), showing strongly eosinophilic anucleate myocardial fibers. Leukocytes in the interstitium are an early reaction to necrotic muscle. Compare with *A* and with normal fibers in the lower part of the figure.

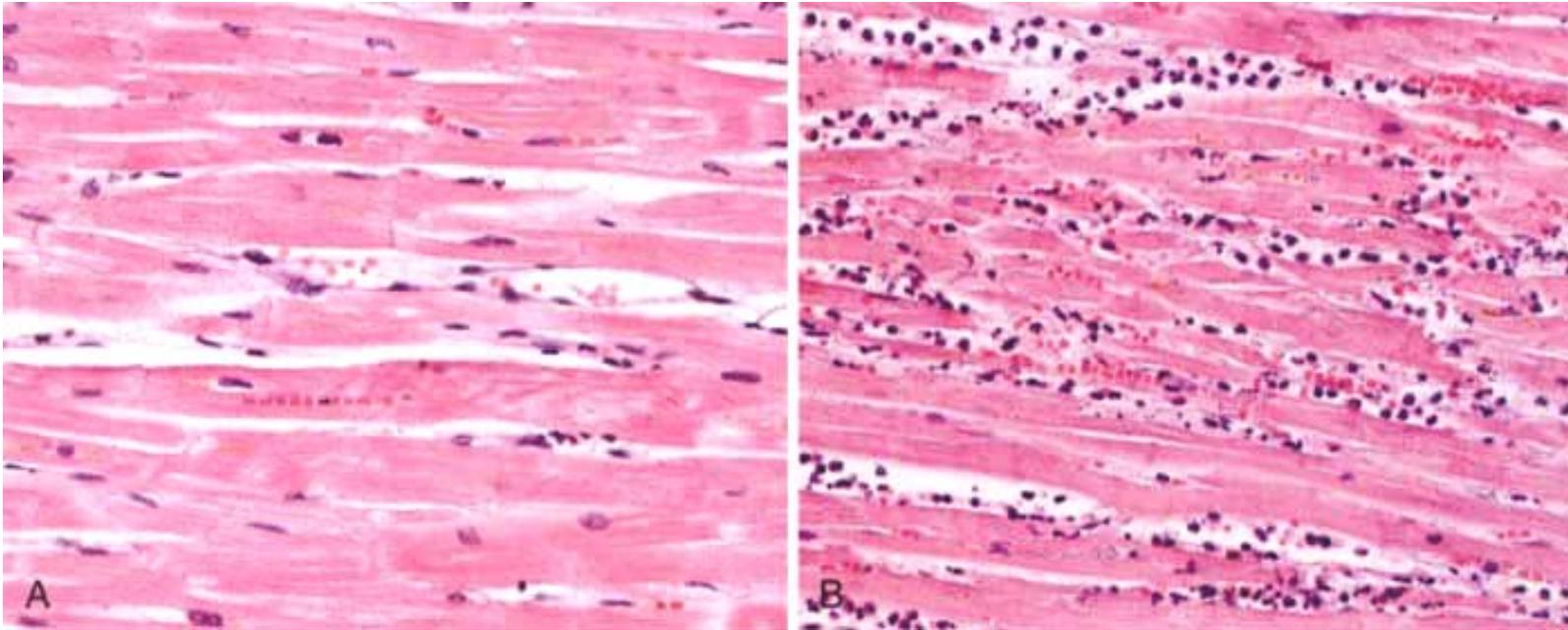


Figure 1-19 Coagulative and liquefactive necrosis. *A*, Kidney infarct exhibiting coagulative necrosis, with loss of nuclei and clumping of cytoplasm but with preservation of basic outlines of glomerular and tubular architecture. *B*, A focus of liquefactive necrosis in the kidney caused by fungal infection. The focus is filled with white cells and cellular debris, creating a renal abscess that obliterates the normal architecture.

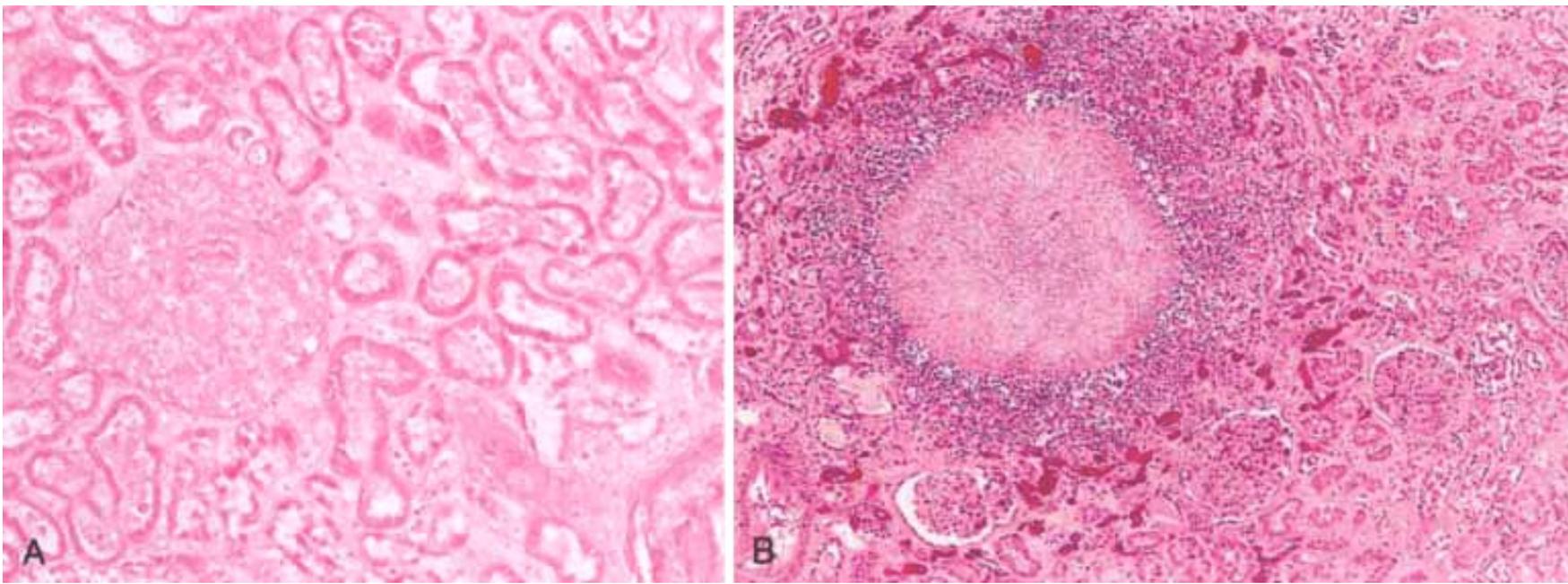


Figure 1-20 A tuberculous lung with a large area of caseous necrosis. The caseous debris is yellow-white and cheesy.



Figure 1-21 Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown.

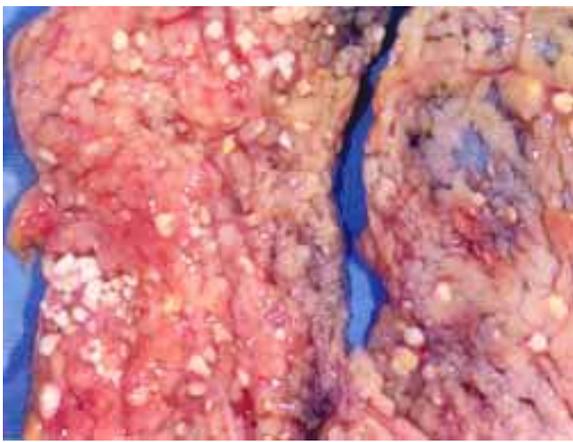


Figure 1-22 Postulated sequence of events in reversible and irreversible ischemic cell injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia can cause direct membrane damage. ER, endoplasmic reticulum; CK, creatine kinase; LDH, lactate dehydrogenase; RNP, ribonucleoprotein.

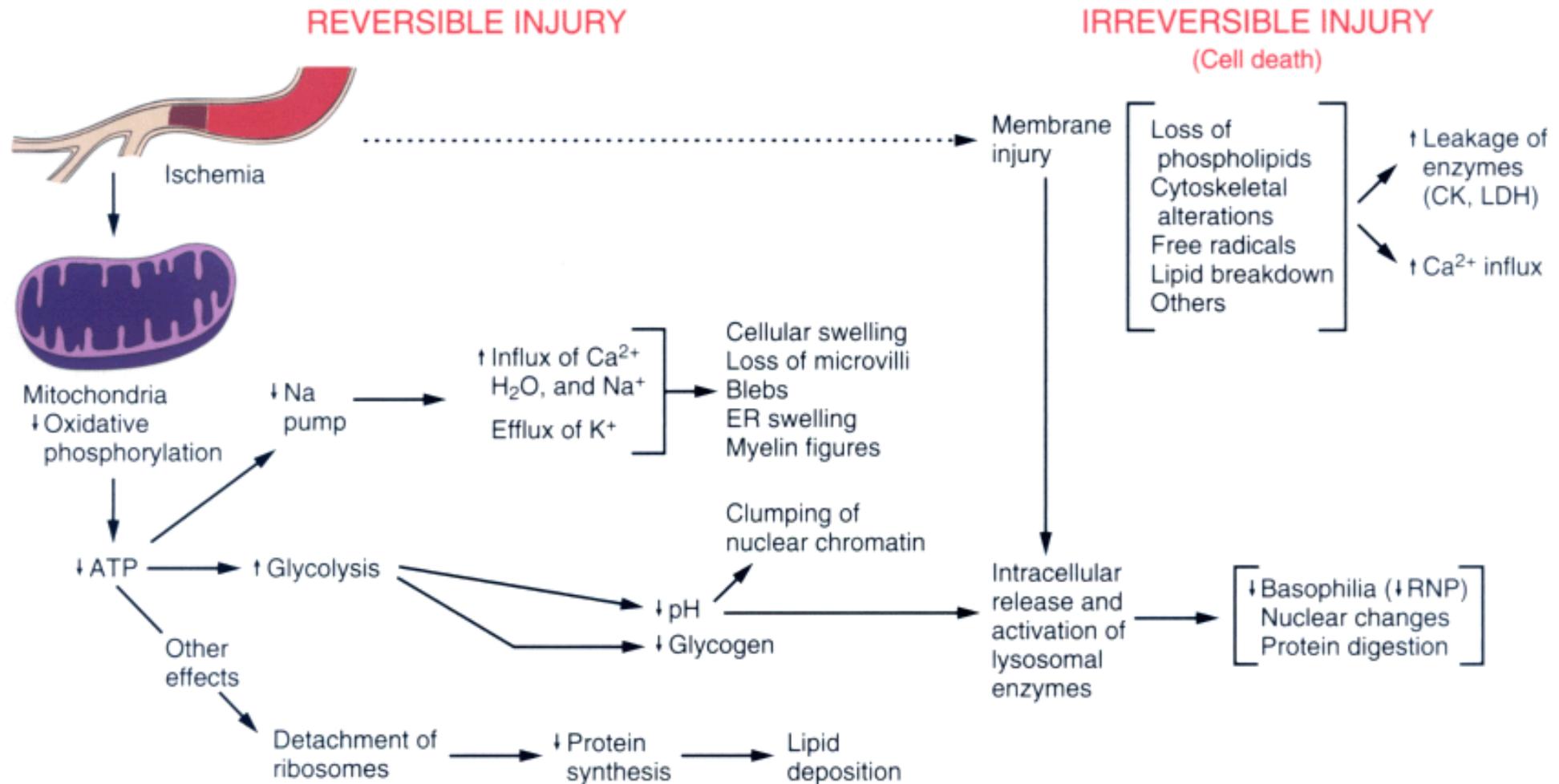
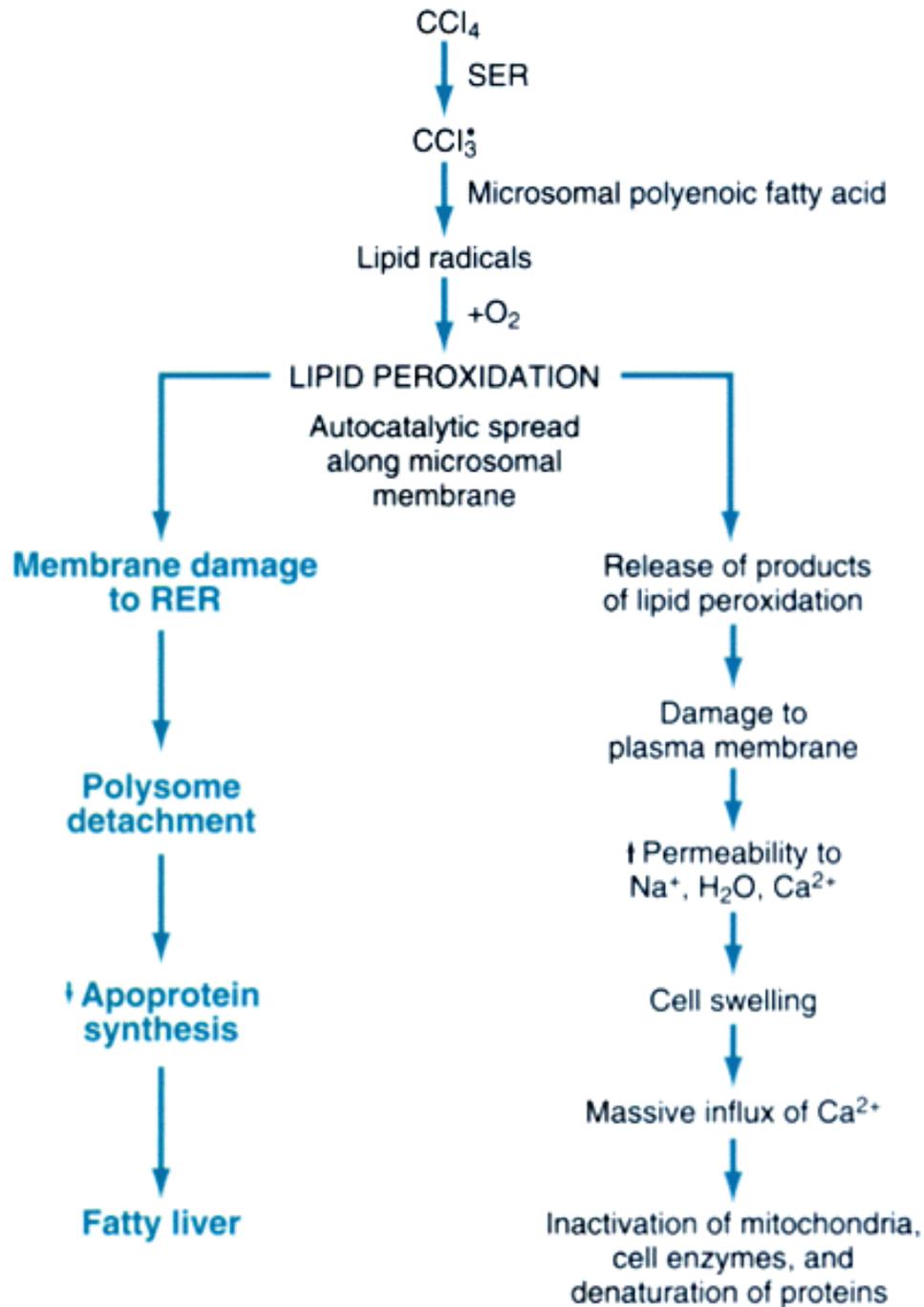


Figure 1-23 Sequence of events leading to fatty change and cell necrosis in carbon tetrachloride (CCl_4) toxicity. RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum.



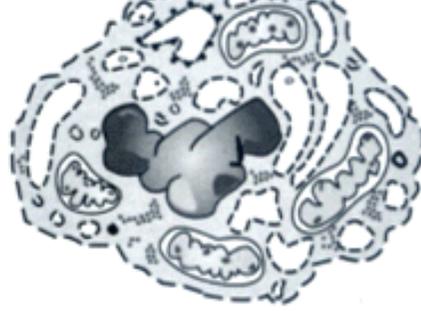
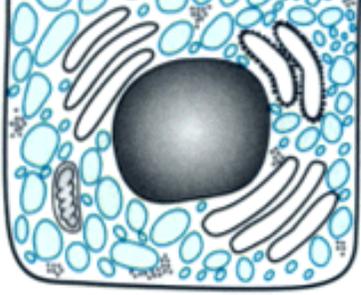


Figure 1-24 Rat liver cell 4 hours after carbon tetrachloride intoxication, with swelling of endoplasmic reticulum and shedding of ribosomes. At this stage, mitochondria are unaltered. (Courtesy of Dr. O. Iseri, University of Maryland, Baltimore, MD.)

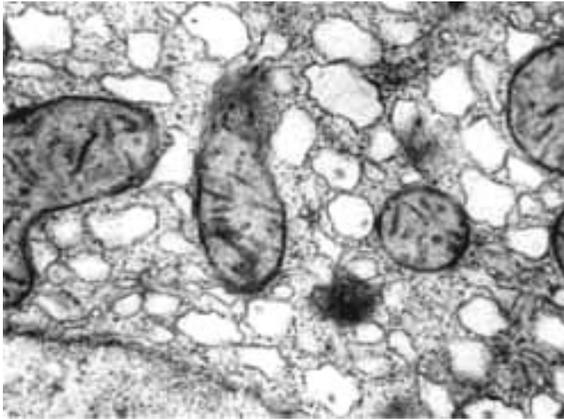


Figure 1-25 Ultrastructural features of apoptosis. Some nuclear fragments show peripheral crescents of compacted chromatin, whereas others are uniformly dense. (From Kerr JFR, Harmon BV: *Definition and incidence of apoptosis: a historical perspective*. In Tomei LD, Cope FO (eds): *Apoptosis: The Molecular Basis of Cell Death*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1991, pp 5–29.)

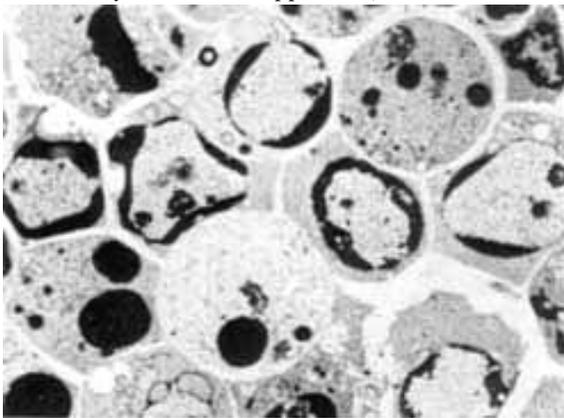


Figure 1-26 A, Apoptosis of epidermal cells in an immune-mediated reaction. The apoptotic cells are visible in the epidermis with intensely eosinophilic cytoplasm and small, dense nuclei. H&E stain. (Courtesy of Dr. Scott Granter, Brigham and Women's Hospital, Boston, AM.) B, High power of apoptotic cell in liver in immune-mediated hepatic cell injury. (Courtesy of Dr. Dhanpat Jain, Yale University, New Haven, CT.)

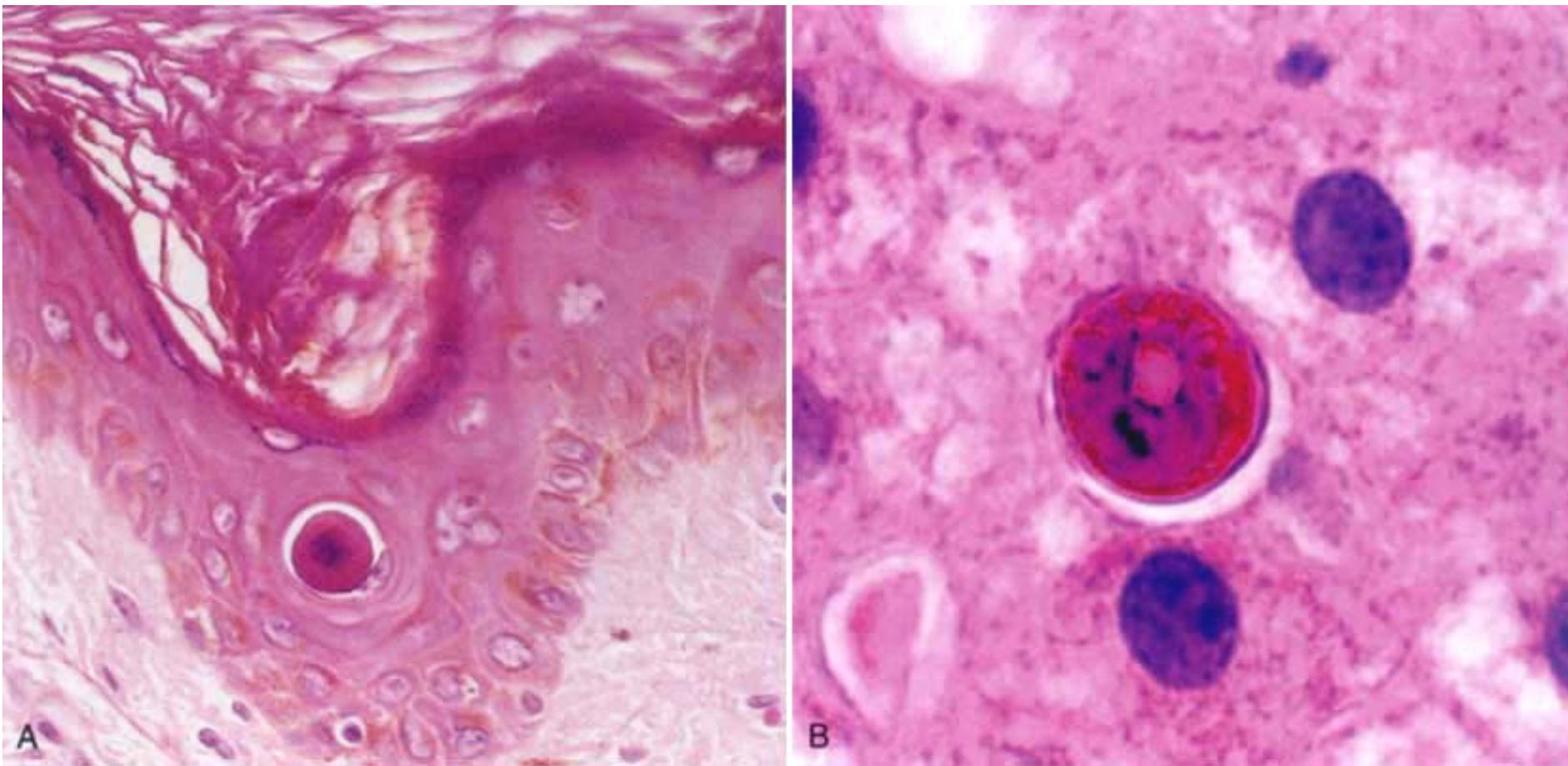


Figure 1-27 Agarose gel electrophoresis of DNA extracted from culture cells. Ethidium bromide stain; photographed under ultraviolet illumination. *Lane A*, Control culture. *Lane B*, Culture of cells exposed to heat showing extensive apoptosis; note ladder pattern of DNA fragments, which represent multiples of oligonucleosomes. *Lane C*, Culture showing massive necrosis; note diffuse smearing of DNA. The ladder pattern is produced by enzymatic cleavage of nuclear DNA into nucleosome-sized fragments, usually multiples of 180–200 base pairs. *These patterns are characteristic of but not specific for apoptosis and necrosis, respectively.* (From Kerr JFR, Harmon BV: *Definition and incidence of apoptosis: a historical perspective.* In Tomei LD, Cope FO [eds]: *Apoptosis: The Molecular Basis of Cell Death.* Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 1991, p 13.)

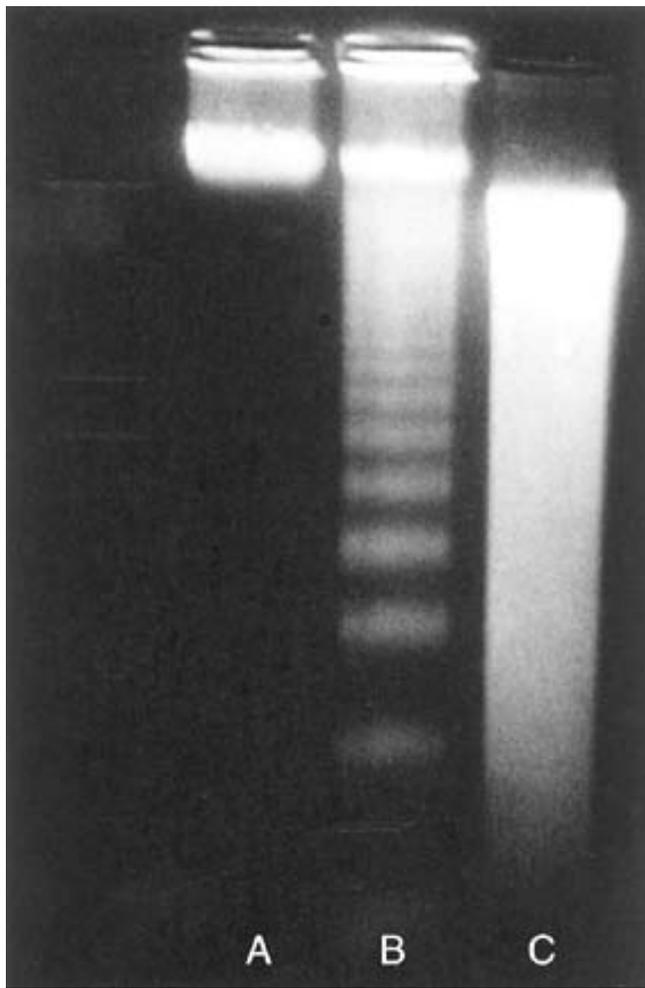


Figure 1-28 Mechanisms of apoptosis. Labeled (1) are some of the major inducers of apoptosis. These include specific death ligands (tumor necrosis factor [TNF] and Fas ligand), withdrawal of growth factors or hormones, and injurious agents (e.g., radiation). Some stimuli (such as cytotoxic cells) directly activate execution caspases (*right*). Others act by way of adapter proteins and initiator caspases, or by mitochondrial events involving cytochrome *c*. (2) Control and regulation are influenced by members of the Bcl-2 family of proteins, which can either inhibit or promote the cell's death. (3) Executioner caspases activate latent cytoplasmic endonucleases and proteases that degrade nuclear and cytoskeletal proteins. This results in a cascade of intracellular degradation, including fragmentation of nuclear chromatin and breakdown of the cytoskeleton. (4) The end result is formation of apoptotic bodies containing intracellular organelles and other cytosolic components; these bodies also express new ligands for binding and uptake by phagocytic cells.

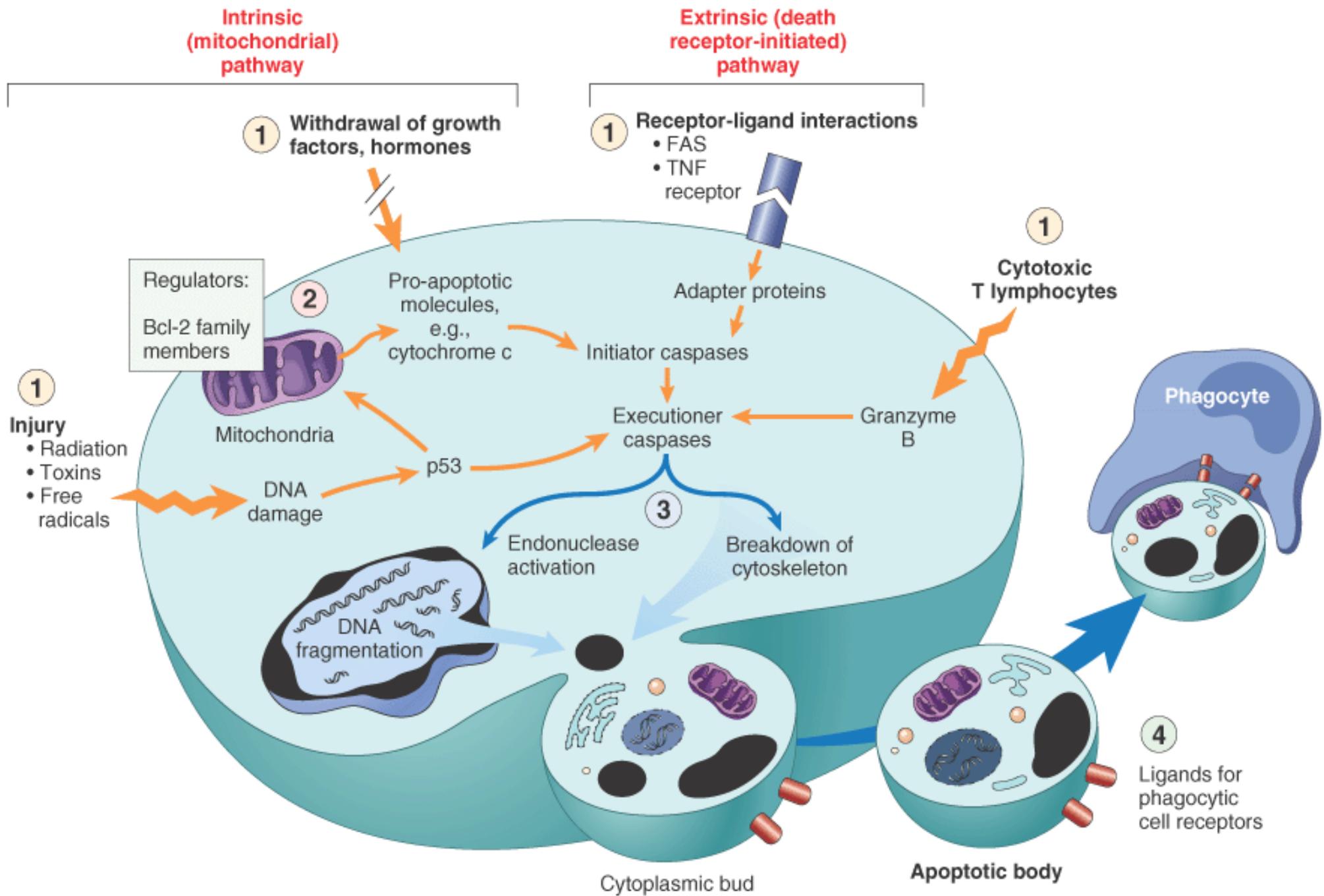


Figure 1-29 The extrinsic (death receptor-initiated) pathway of apoptosis, illustrated by the events following Fas engagement (see text).

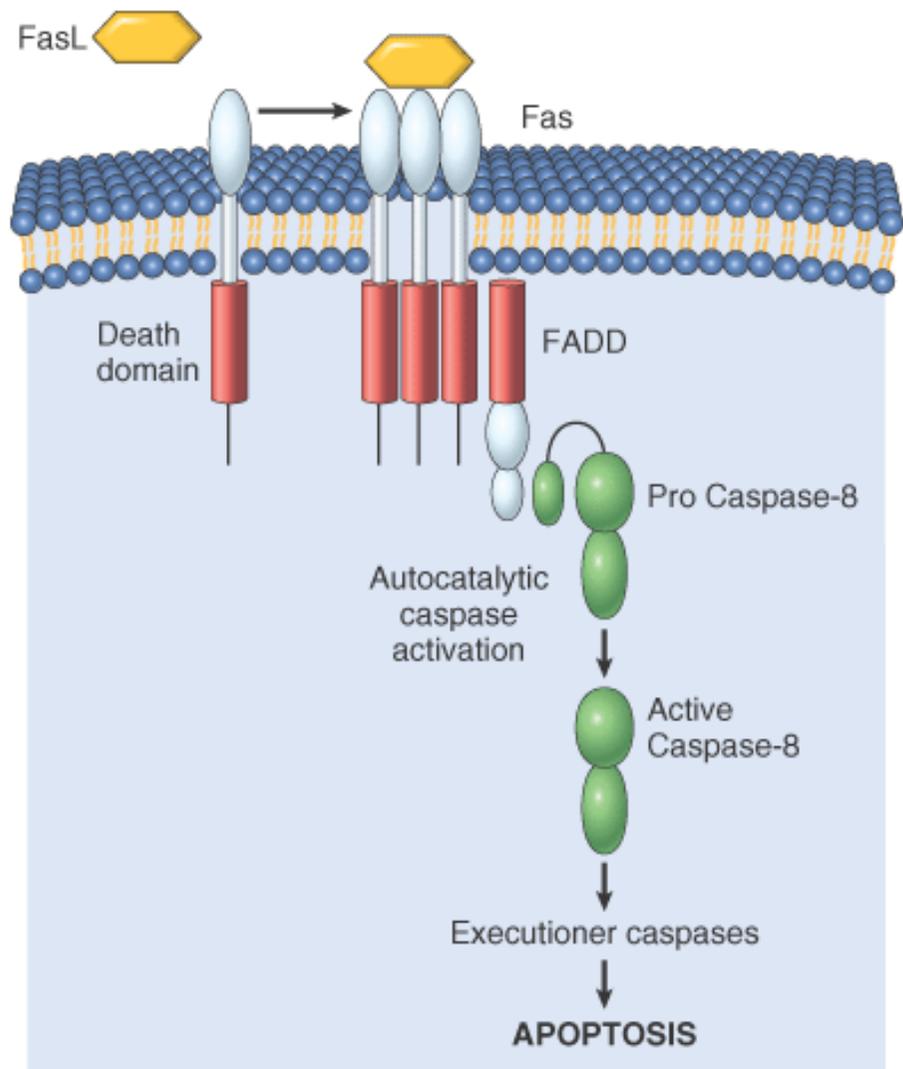


Figure 1-30 The intrinsic (mitochondrial) pathway of apoptosis. Death agonists cause changes in the inner mitochondrial membrane, resulting in the mitochondrial permeability transition (MPT) and release of cytochrome *c* and other pro-apoptotic proteins into the cytosol, which activate caspases (see text).

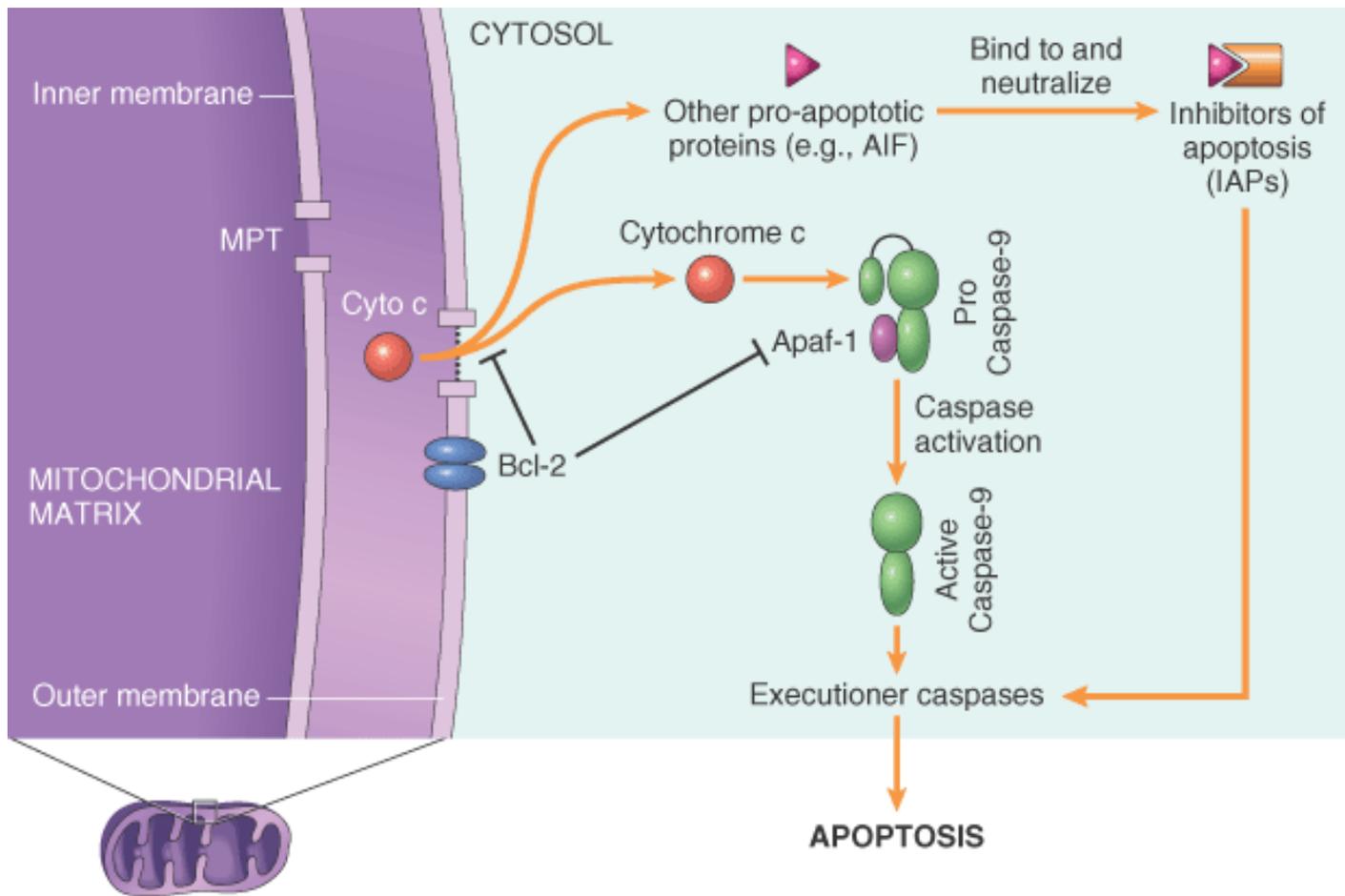
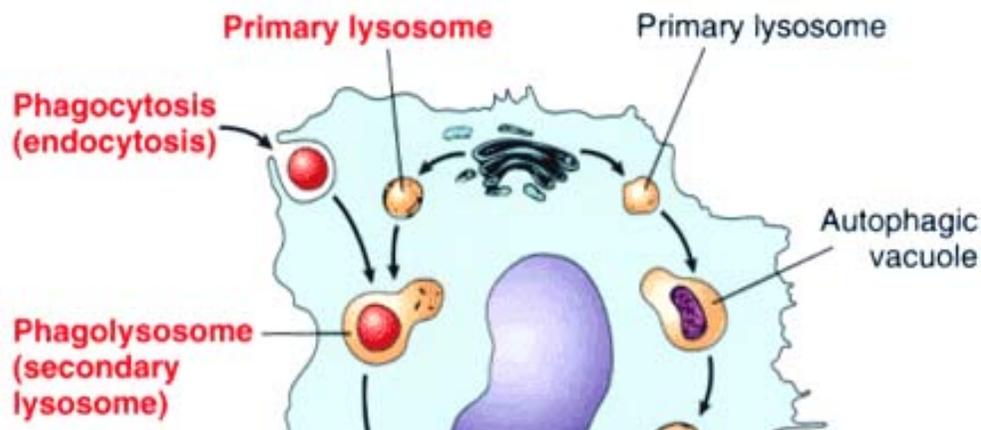


Figure 1-31 A, schematic representation of heterophagy (*left*) and autophagy (*right*). (Redrawn from Fawcett DW: *A Textbook of Histology*, 11th ed. Philadelphia, WB Saunders, 1986, p 17.) B, Electron micrograph of an autophagolysosome containing a degenerating mitochondrion and amorphous material.

HETEROPHAGY

AUTOPHAGY



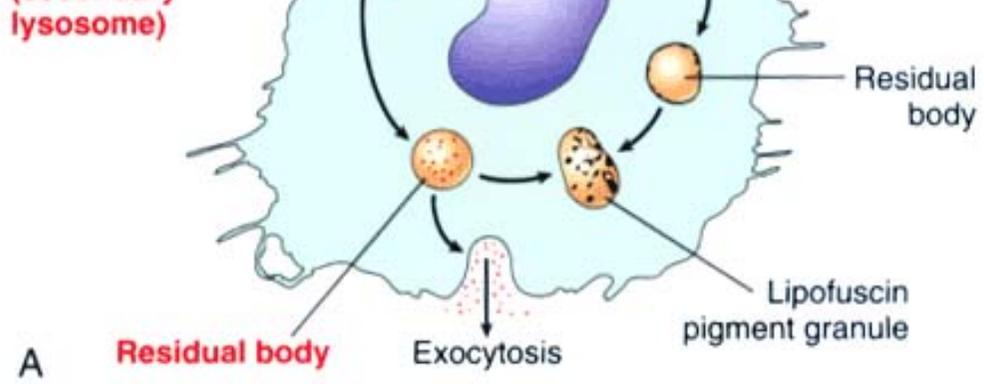


Figure 1-32 Electron micrograph of liver from phenobarbital-treated rat showing marked increase in smooth endoplasmic reticulum. (From Jones AL, Fawcett DW: *Hypertrophy of the agranular endoplasmic reticulum in hamster liver induced by Phenobarbital*. *J Histochem Cytochem* 14:215, 1966. Courtesy of Dr. Fawcett.)

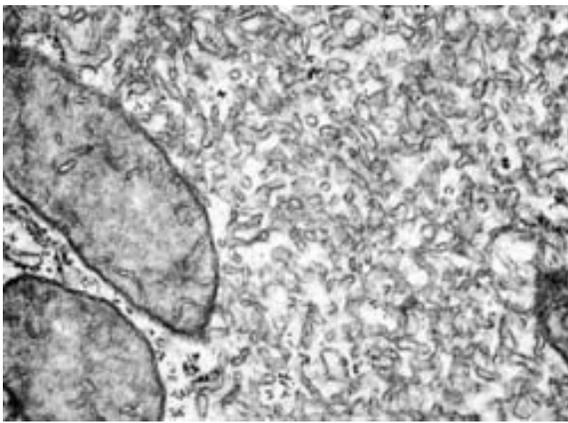


Figure 1-33 Enlarged, abnormally shaped mitochondria from the liver of a patient with alcoholic cirrhosis. Note also crystalline formations in the mitochondria.

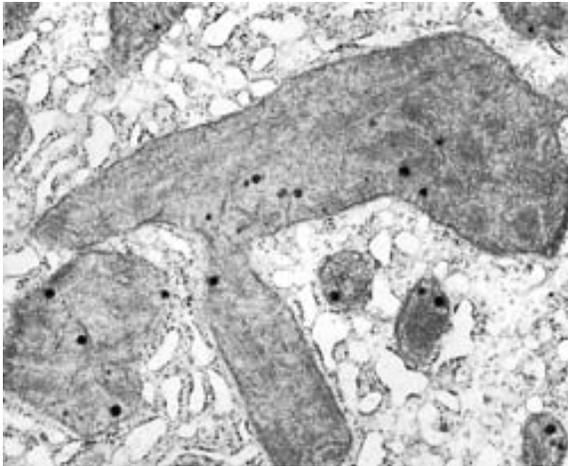


Figure 1-34 *A*, The liver of alcohol abuse (chronic alcoholism). Hyaline inclusions in the hepatic parenchymal cell in the center appear as eosinophilic networks disposed about the nuclei (*arrow*). *B*, Electron micrograph of alcoholic hyalin. The material is composed of intermediate (prekeratin) filaments and an amorphous matrix.

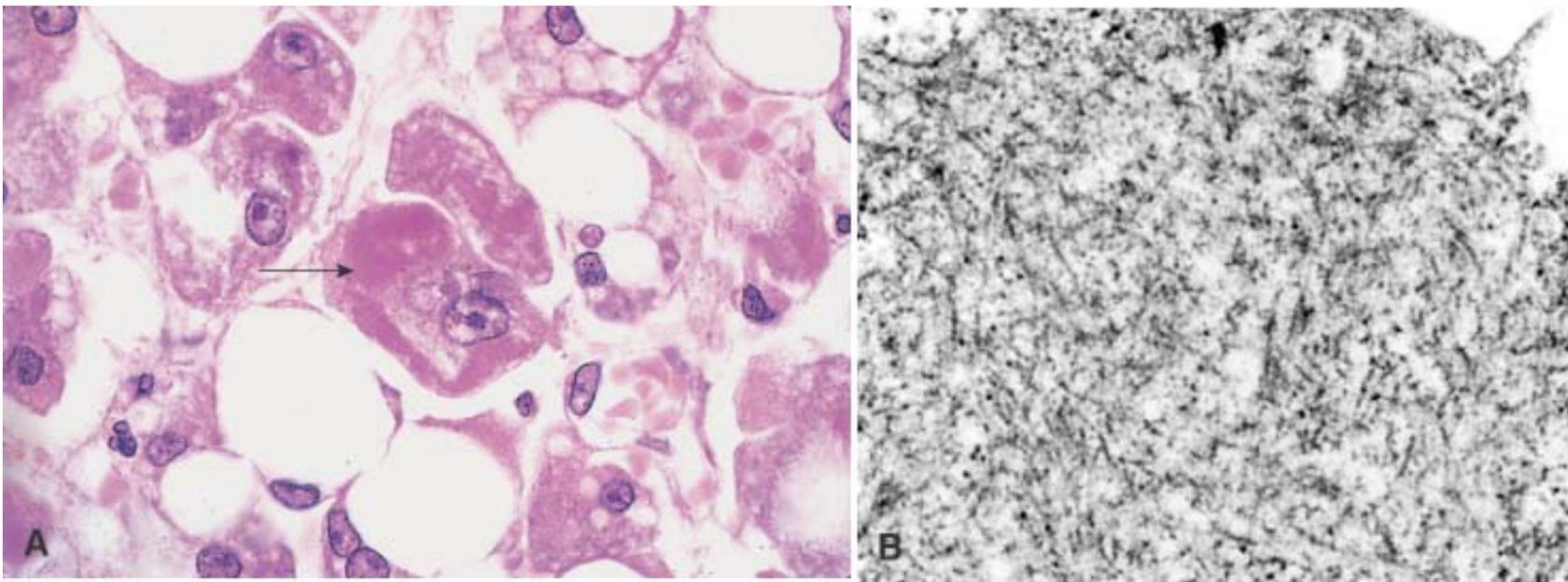
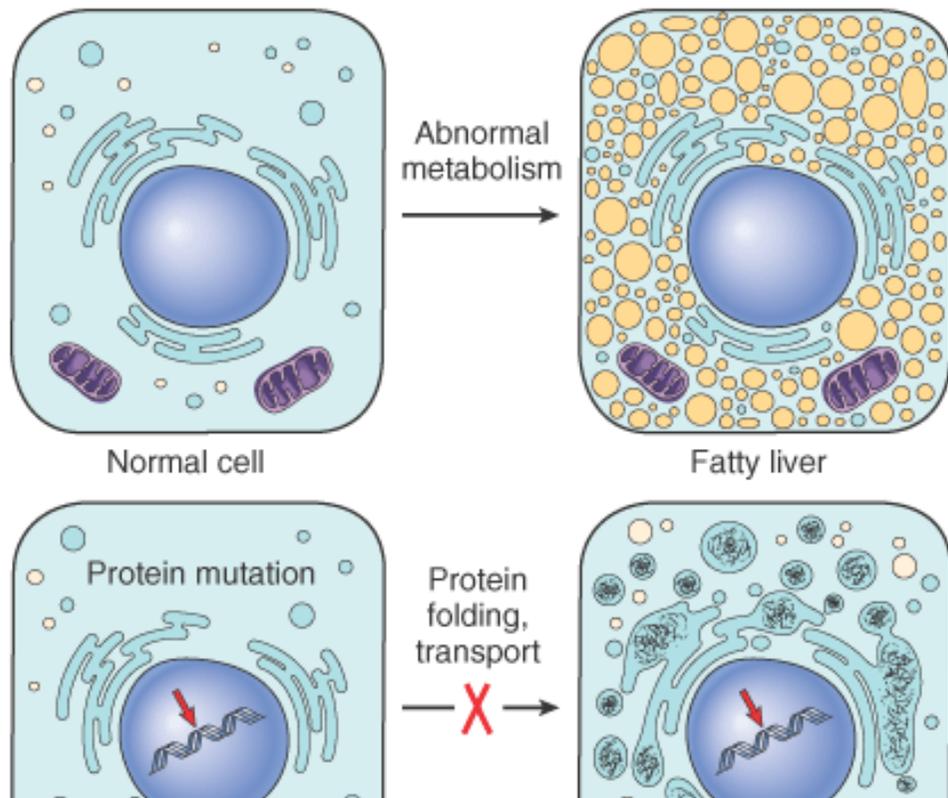


Figure 1-35 Mechanisms of intracellular accumulations: (1) abnormal metabolism, as in fatty change in the liver; (2) mutations causing alterations in protein folding and transport, as in α_1 -antitrypsin deficiency; (3) deficiency of critical enzymes that prevent breakdown of substrates that accumulate in lysosomes, as in lysosomal storage diseases; and (4) inability to degrade phagocytosed particles, as in hemosiderosis and carbon pigment accumulation.



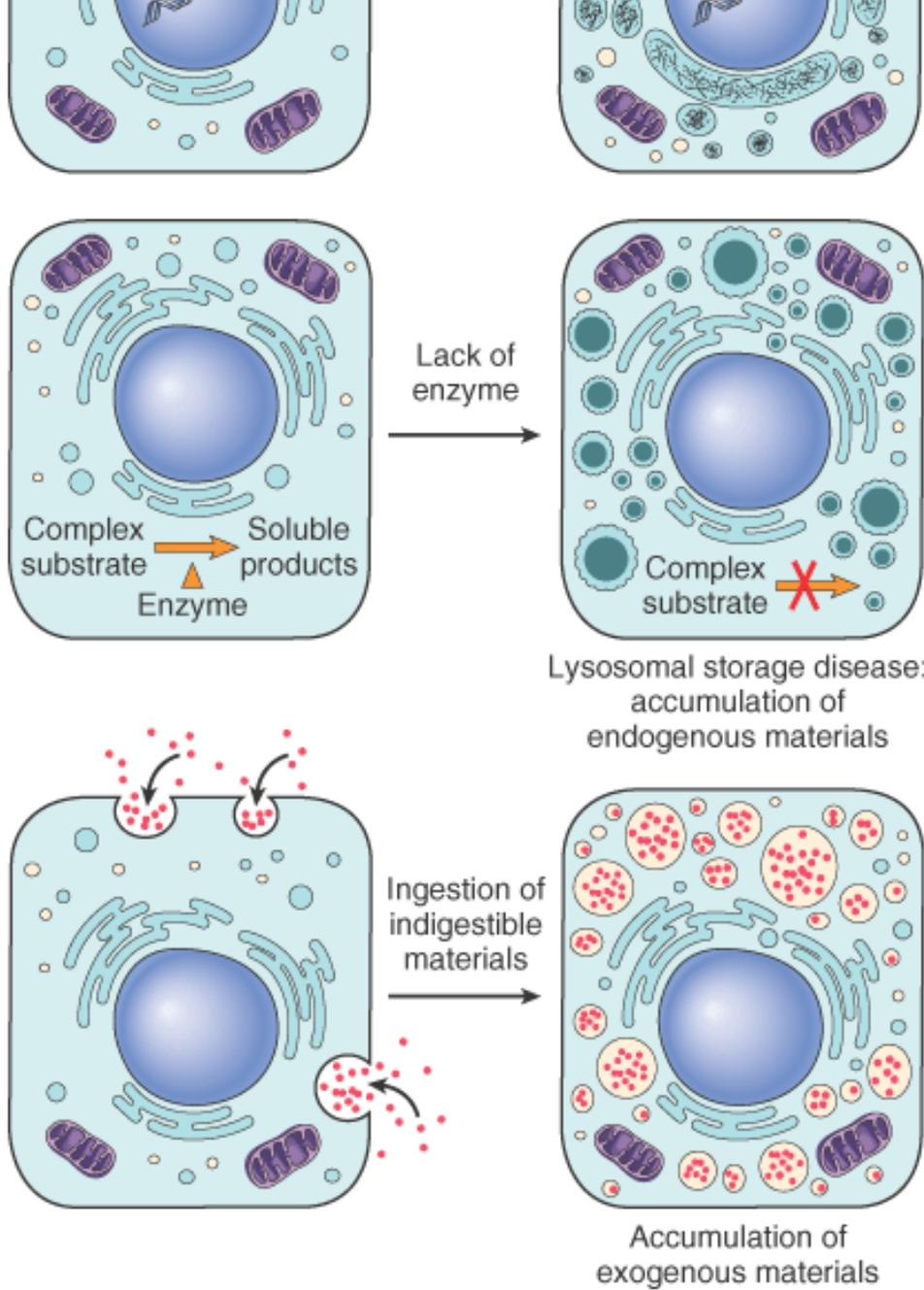


Figure 1-36 Fatty liver. *A*, Schematic diagram of the possible mechanisms leading to accumulation of triglycerides in fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can result in lipid accumulation. *B*, High-power detail of fatty change of the liver. In most cells, the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole. (*B*, Courtesy of Dr. James Crawford, Department of Pathology, Yale University School of Medicine, New Haven, CT.)

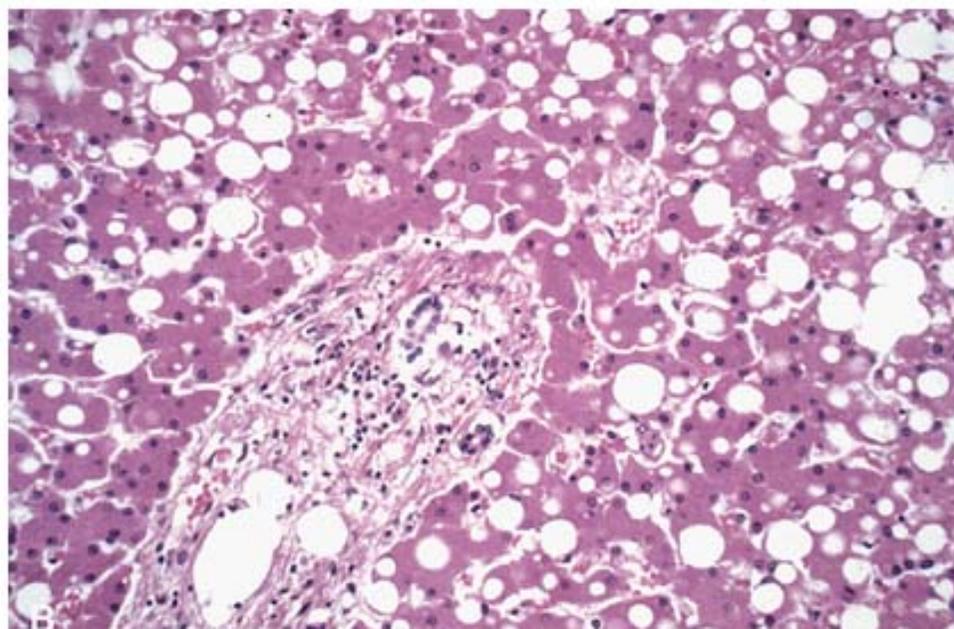
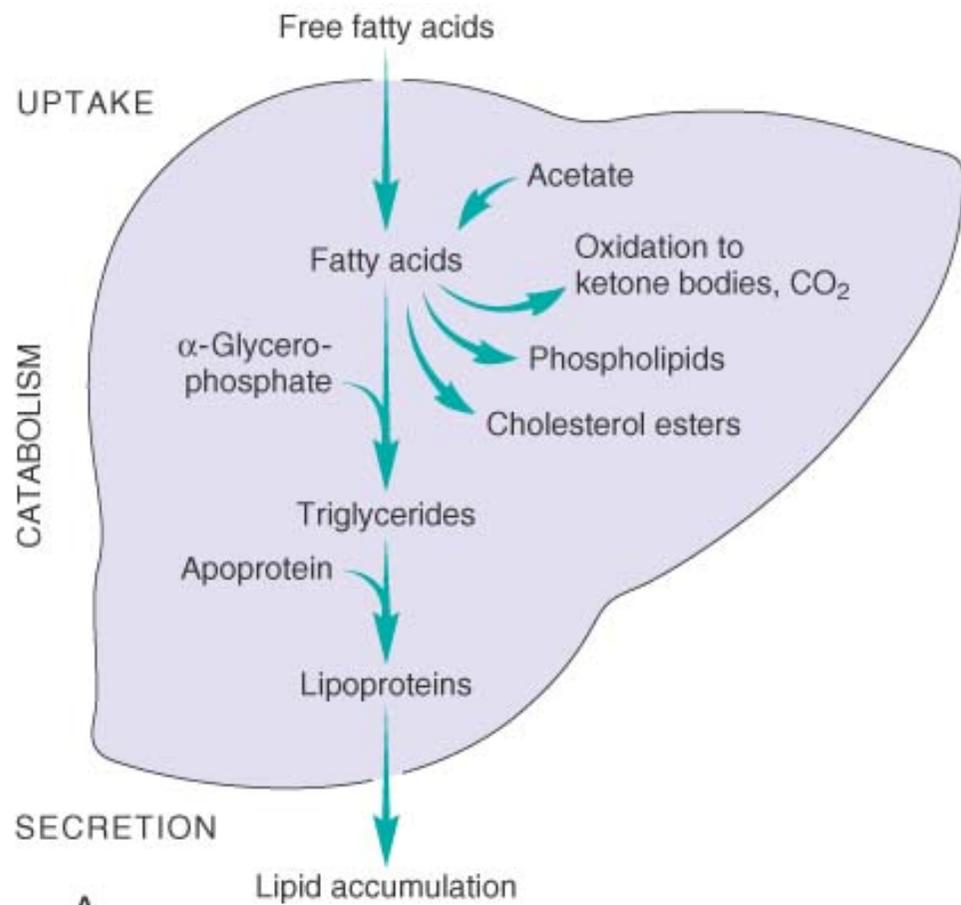




Figure 1-37 Cholesterolosis. Cholesterol-laden macrophages (foam cells) from a focus of gallbladder cholesterolosis (*arrow*). (Courtesy of Dr. Matthew Yeh, University of Washington, Seattle, WA.)

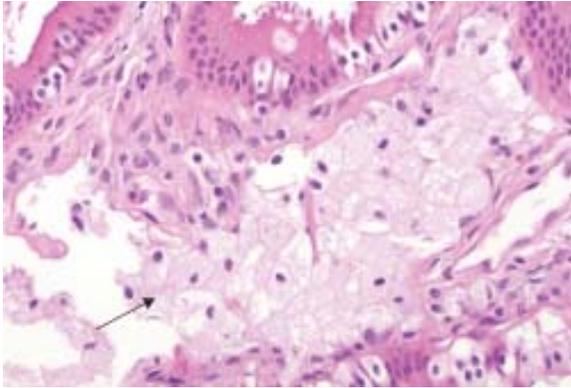


Figure 1-38 Protein reabsorption droplets in the renal tubular epithelium. (Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)

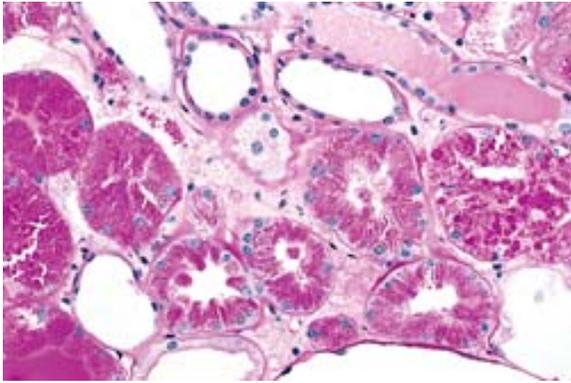
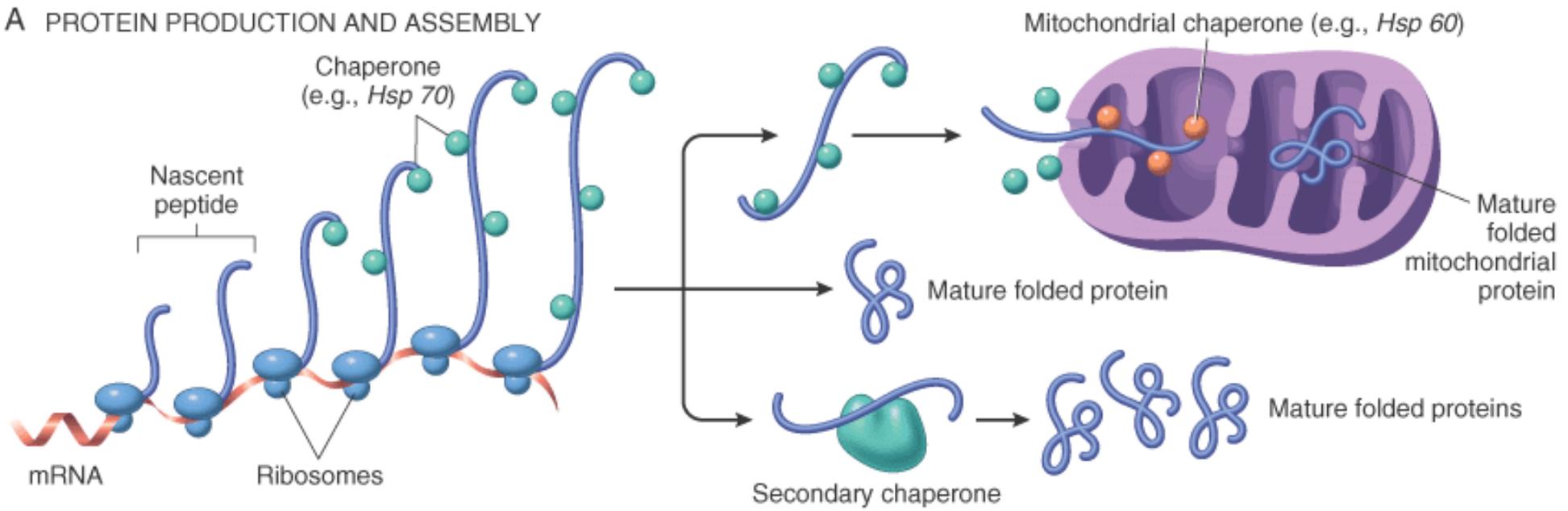


Figure 1-39 Mechanisms of protein folding and the role of chaperones. *A*, Chaperones, such as heat shock proteins (Hsp), protect unfolded or partially folded protein from degradation and guide proteins into organelles. *B*, Chaperones repair misfolded proteins; when this process is ineffective, proteins are targeted for degradation in the proteasome, and if misfolded proteins accumulate they trigger apoptosis.

A PROTEIN PRODUCTION AND ASSEMBLY



B REPAIR OF PROTEIN DAMAGE

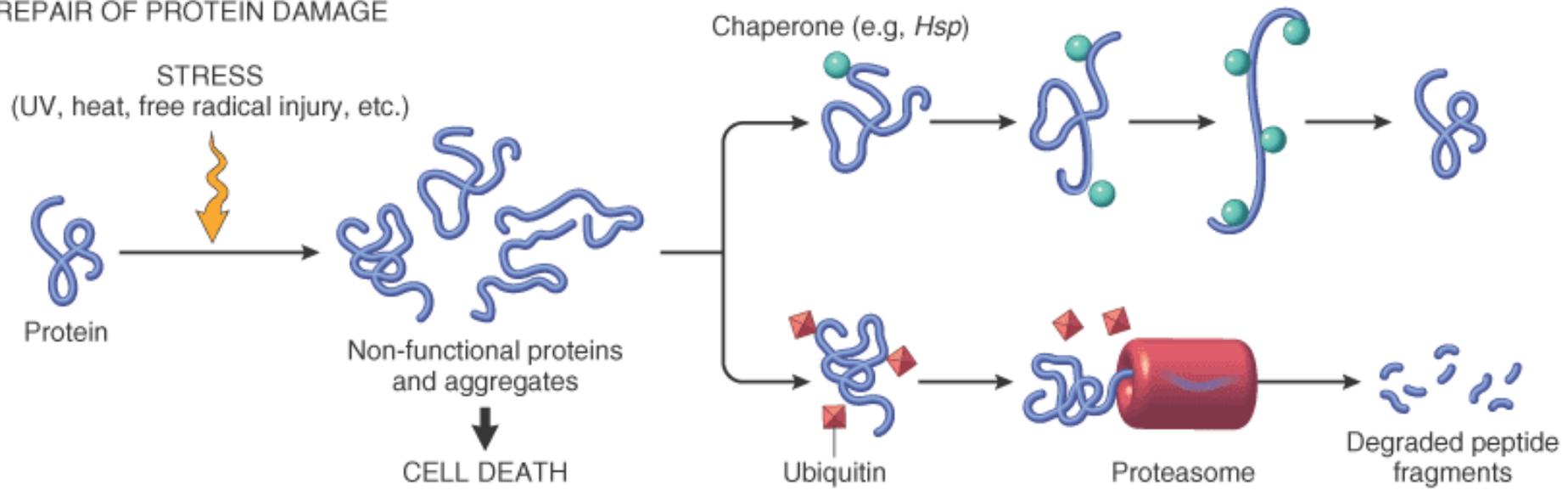


Figure 1-40 Lipofuscin granules in a cardiac myocyte as shown by A, light microscopy (deposits indicated by *arrows*), and B, electron microscopy (note the perinuclear, intralysosomal location).

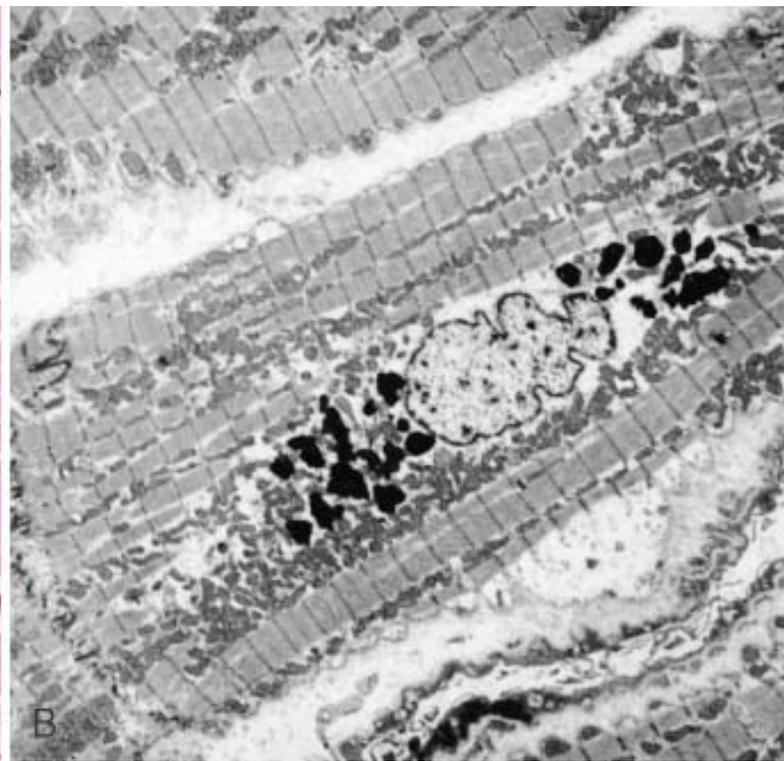
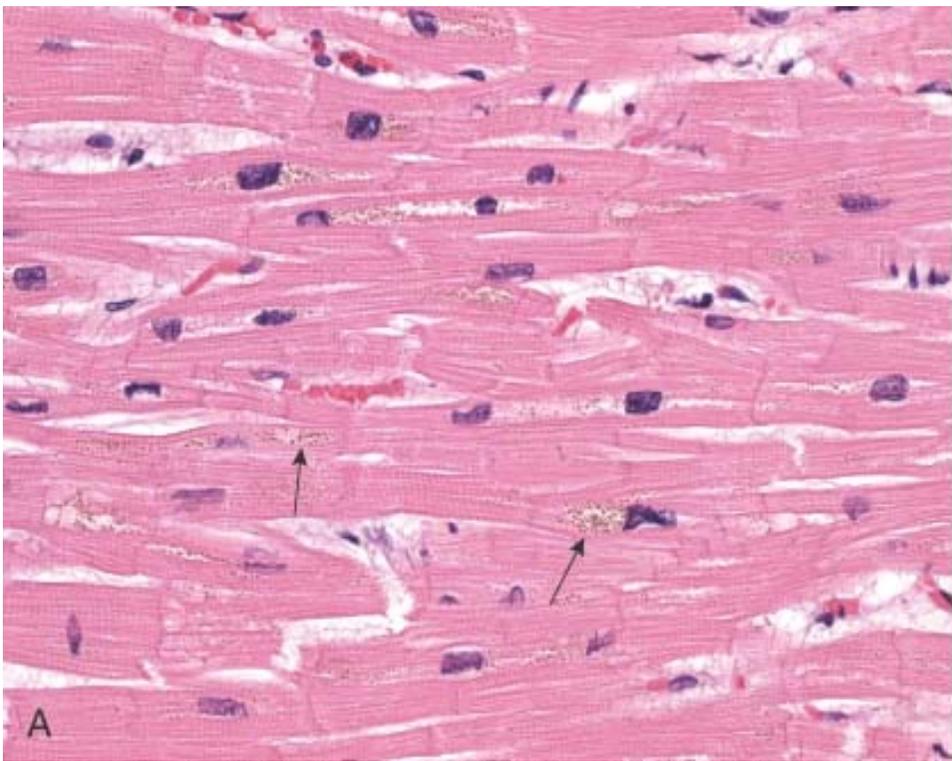


Figure 1-41 Hemosiderin granules in liver cells. *A*, H&E section showing golden-brown, finely granular pigment. *B*, Prussian blue reaction, specific for iron.

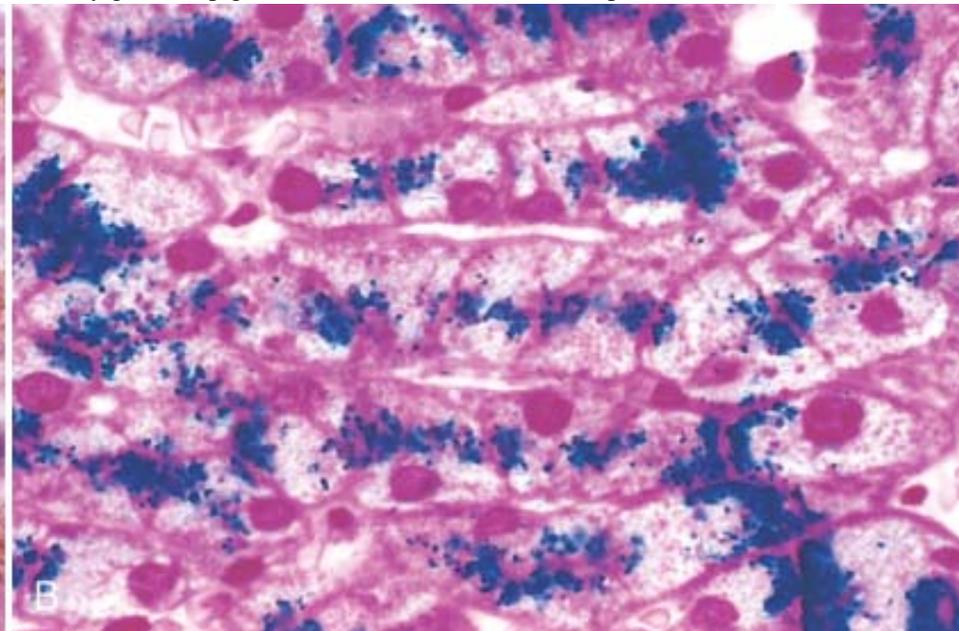
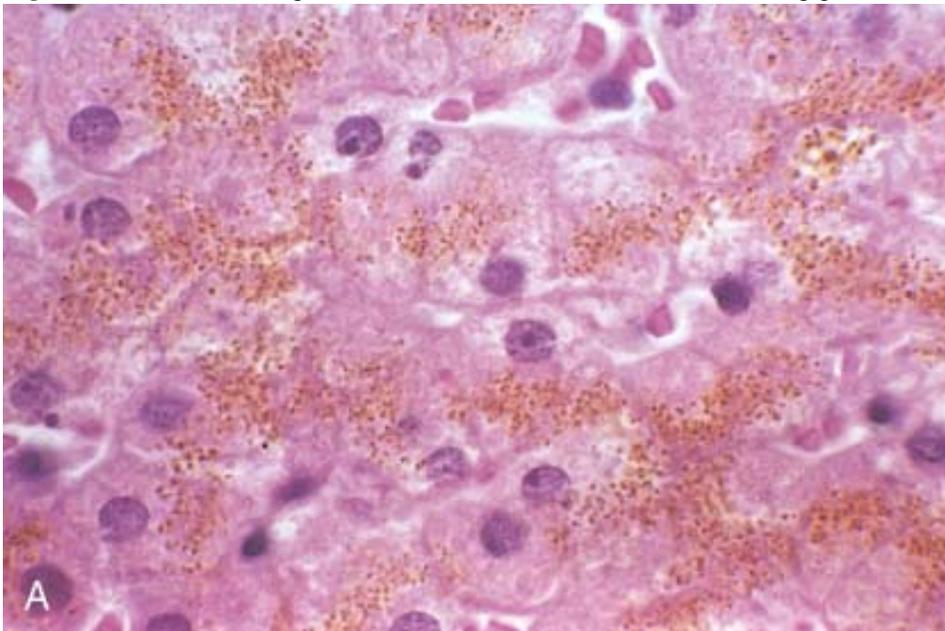


Figure 1-42 View looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. The semilunar cusps are thickened and fibrotic. Behind each cusp are seen irregular

masses of piled-up dystrophic calcification.



Figure 1-43 Mechanisms of cellular aging. Genetic factors and environmental insults combine to produce the cellular abnormalities characteristic of aging.

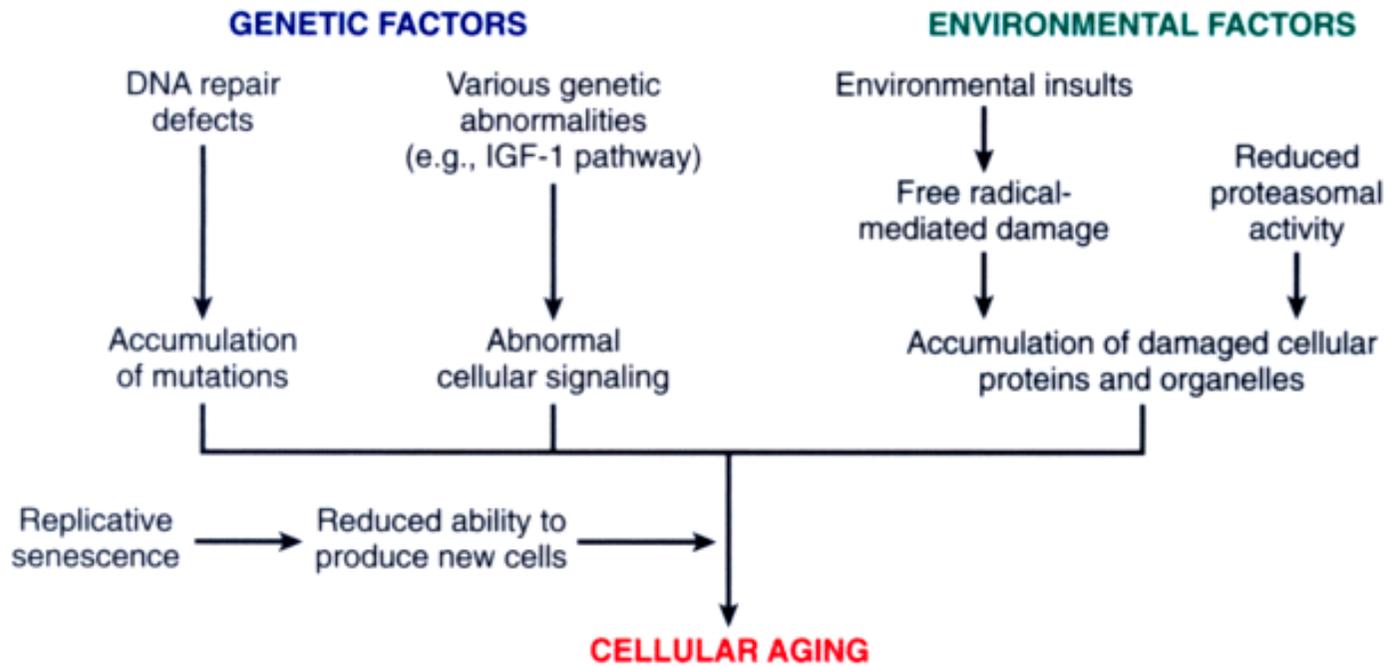


Figure 1-44 Finite population doublings of primary human fibroblasts derived from a newborn, a 100-year-old person, and a 20-year-old patient with Werner's syndrome. The ability of cells to grow to a confluent monolayer decreases with increasing population-doubling levels. (From Dice JF: *Cellular and molecular mechanisms of aging*. *Physiol Rev* 73:150, 1993.)

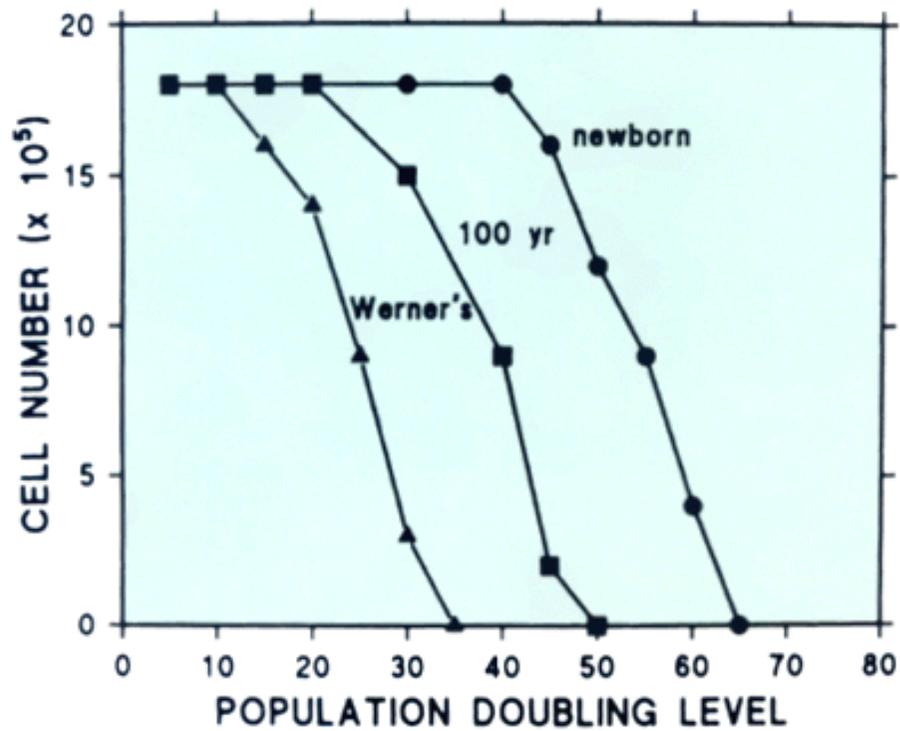
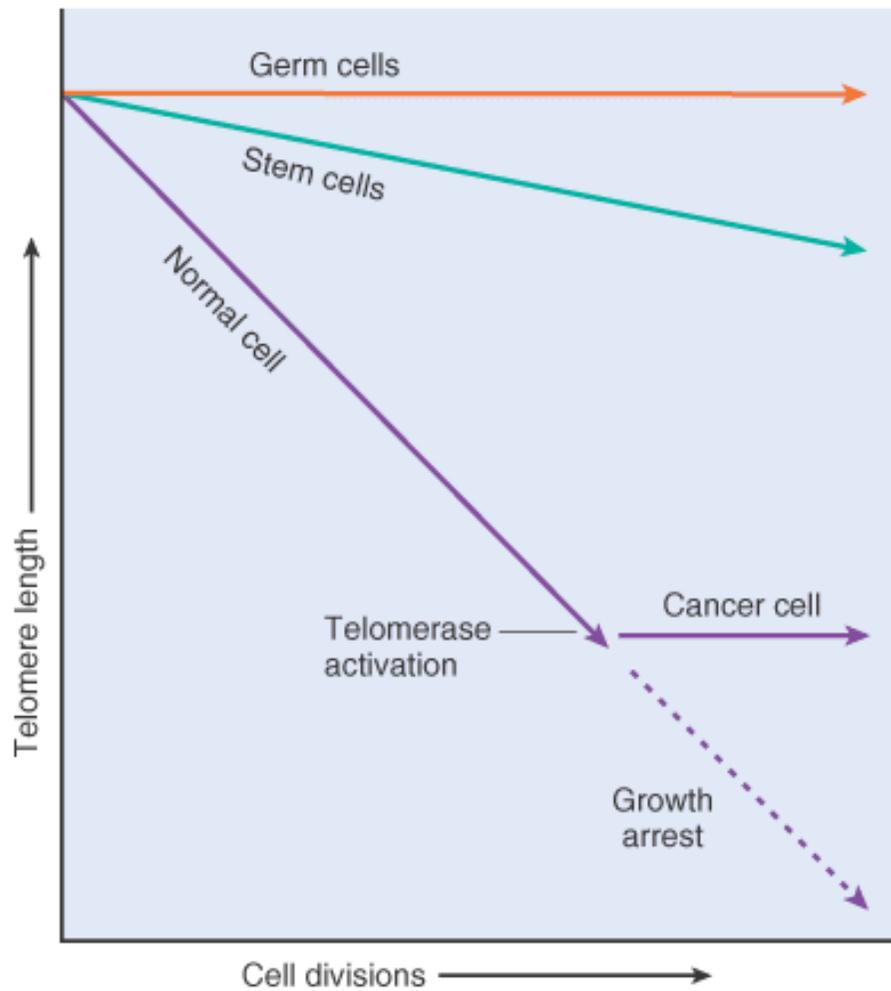


Figure 1-45 The role of telomeres and telomerase in replicative senescence of cells. *A*, Telomerase directs RNA template-dependent DNA synthesis, in which nucleotides are added to one strand at the end of a chromosome. The lagging strand is presumably filled in by DNA polymerase α . The RNA sequence in the telomerase is different in different species. (*Modified from Alberts BR, et al: Molecular Biology of the Cell, 2002, Garland Science, New York.*) *B*, Telomere-telomerase hypothesis and proliferative capacity. Telomere length is plotted against the number of cell divisions. In normal somatic cells, there is no telomerase activity, and telomeres progressively shorten with increasing cell divisions until growth arrest, or senescence, occurs. Germ cells and stem cells both contain active telomerase, but only the germ cells have sufficient levels of the enzyme to stabilize telomere length completely. Telomerase activation in cancer cells inactivates the teleomeric clock that limits the proliferative capacity of normal somatic cells. (*Modified and redrawn with permission from Holt SE, et al.: Refining the telomer-telomerase hypothesis of aging and cancer. Nature Biotech 14:836, 1996. Copyright 1996, Macmillan Magazines Limited.*)



References

1. Majno G: The Healing Hand: Man and Wound in the Ancient World. Cambridge: Harvard University Press, 1975, p 43.
2. Taub R: Transcriptional control of liver regeneration. *FASEB J* 10:413, 1997.
3. Thorgeirsson SS: Hepatic stem cells in liver regeneration. *FASEB J* 10:1249, 1996.
4. Forbes S, et al: Hepatic stem cells. *J Pathol* 197:510, 2002.
5. Korbling M, Estrovz Z: Adult stem cells for tissue repair: a new therapeutic concept? *New Eng J Med* 349:570, 2003.
6. Anversa P, Nadal-Ginard B: Myocyte renewal and ventricular remodeling. *Nature* 415:240, 2002.
7. Molkenkin JD, Dorn GW: Cytoplasmic signaling pathways that regulate cardiac hypertrophy. *Annu Rev Physiol* 63:391, 2001.

8. MacLellan WR, Schneider MD: Genetic dissection of cardiac growth control pathways. *Annu Rev Physiol* 62:289, 2000.
 9. Saito Y, et al: Augmented expression of atrial natriuretic polypeptide gene in ventricle of human failing heart. *J Clin Invest* 83:298, 1989.
 10. Kozma SC, Thomas G: Regulation of cell size in growth, development and human disease: PI3K, PKB and S6K. *Bioessays* 24:65, 2002.
-

11. Anversa P, et al: Myocyte death in heart failure. *Curr Opin Cardiol* 11:245, 1996.
12. Glickman MH, Ciechanover A: The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. *Physiol Rev* 82:373, 2002.
13. Lugo M, Putong PB: Metaplasia: an overview. *Arch Pathol Lab Med* 108:185, 1984.
14. Tosh D, Slack JM: How cells change their phenotype. *Nat Rev Mol Cell Biol* 3:187, 2002.
15. Reddi HA: BMPs: actions in flesh and bone. *Nat Med* 3:837, 1997.
16. Ross SA, McCaffrey PJ, Drager UC, DeLuca LM: Retinoids in embryonal development. *Physiol Rev* 80:1021, 2000.
17. Newmeyer DD, Ferguson-Miller S: Mitochondria: releasing power for life and unleashing the machineries of death. *Cell* 112:481, 2003.
18. Trump BF, Berezsky I: The reactions of cells to lethal injury: oncosis and necrosis—the role of calcium. In Lockshin RA (ed): *When Cells Die—A Comprehensive Evaluation of Apoptosis and Programmed Cell Death*. New York: Wiley-Liss, 1998, p 57.
19. Orrenius S, Zhivotovsky B, Nicotera P: Regulation of cell death: the calcium-apoptosis link. *Nat Rev Mol Cell Biol* 4:552, 2003.
20. Paschen W: Role of calcium in neuronal cell injury: which subcellular compartment is involved? *Brain Res Bull* 53:409, 2000.
21. Droge W: Free radicals in the physiological control of cell function. *Physiol Rev* 82:47, 2002.
22. Hensley K, Robinson KA, Gabbita SP, Salsman S, Floyd RA: Reactive oxygen species, cell signaling, and cell injury. *Free Radic Biol Med* 28:1456, 2000.
23. Salvemini D, Cuzzocrea S: Superoxide, superoxide dismutase and ischemic injury. *Curr Opin Investig Drugs* 3:886, 2002.
24. Li C, Jackson RM: Reactive species mechanisms of cellular hypoxia-reoxygenation injury. *Am J Physiol Cell Physiol* 282:C227, 2002.
25. Mitch WE, Goldberg AE: Mechanisms of muscle wasting: the role of the ubiquitin-proteasome pathway. *N Engl J Med* 335:1897, 1996.
26. Kim JS, He L, Lemaster JJ: Mitochondrial permeability transition: a common pathway to necrosis and apoptosis. *Biochem Biophys Res Commun* 304:463, 2003.
27. Trump BF, et al: Cell injury and cell death: apoptosis, oncosis, and necrosis. In Acosta D (ed): *Cardiovascular Toxicology*, 3rd ed. London and New York: Taylor & Francis, 2001, p 105.
28. Sheridan AM, Bonventre JV: Cell biology and molecular mechanisms of injury in ischemic acute renal failure. *Curr Opin Nephrol Hypertens* 9:427, 2000.

29. Hou ST, McManus JP: Molecular mechanisms of cerebral ischemia-induced neuronal death. *Int Rev Cytol* 221:93, 2002.
30. Daemen MARC, De Vries B, Buurman WA: Apoptosis and inflammation in renal reperfusion injury. *Transplantation* 73:1693, 2002.
31. Anaya-Prado R, et al: Ischemia/reperfusion injury. *J Surg Res* 105:248, 2002.
32. Kaminski KA, et al: Oxidative stress and neutrophil activation — the two keystones of ischemia/reperfusion injury. *Int J Cardiol* 86:41, 2002.
33. Thiagarajan RR, et al: The role of leukocyte and endothelial adhesion molecules in ischemia-reperfusion injury. *Thromb Haemost* 78:310, 1997.
34. Riedemann NC, Ward PA: Complement in ischemia reperfusion injury. *Am J Pathol* 162:363, 2003.
35. Weiser MR, et al: Reperfusion injury of ischemic skeletal muscle is mediated by natural antibody and complement. *J Exp Med* 183:2343, 1996.
36. Snyder JW: Mechanisms of toxic cell injury. *Clin Lab Med* 10:311, 1990.
37. Coon MJ, et al: Cytochrome P450: peroxidative reactions of diversozymes. *FASEB J* 10:428, 1996.
38. Gonzalez FJ: The use of gene knockout mice to unravel the mechanisms of toxicity and chemical carcinogenesis. *Toxicol Lett* 120:199, 2001.
39. Plaa GL: Chlorinated methanes and liver injury: highlights of the past 50 years. *Annu Rev Pharmacol Toxicol* 40:42, 2000.
40. Jaeschke H, et al: Mechanisms of hepatotoxicity. *Toxicol Sci* 65:166, 2002.
41. Cohen SD, Khairallah EA: Selective protein arylation and acetaminophen-induced hepatotoxicity. *Drug Metab Rev* 29:59, 1997.
42. Kerr JF, et al: Apoptosis: a basic biological phenomenon with wideranging implications in tissue kinetics. *Br J Cancer* 26:239, 1972.
43. Metzstein MM, Stanfield GM, Horvitz HR: Genetics of programmed cell death in *C. elegans*: past, present and future. *Trends Genet* 14:410, 1998.
44. Wyllie AH: Apoptosis: an overview. *Br Med Bull* 53:451, 1997.
45. Strasser A, O'Connor L, Dixit VM: Apoptosis signaling. *Annu Rev Biochem* 69:217, 2000.
46. Vaux D, Silke J: Mammalian mitochondrial IAP-binding proteins. *Biochem Biophys Res Commun* 203:449, 2003.
47. McCarthy NJ, Evan GI: Methods for detecting and quantifying apoptosis. *Curr Top Dev Biol* 36:259, 1998.
48. Hanayama R, et al: Identification of a factor that links apoptotic cells to phagocytes. *Nature* 417:182, 2002.
49. Savill J, Fadok V: Copse clearing defines the meaning of cell death. *Nature* 407:784, 2000.
50. Vaux DL, Strasser A: The molecular biology of apoptosis. *Proc Natl Acad Sci U S A* 93:2239, 1996.
51. Wallach D, et al: Tumor necrosis factor receptor and Fas signaling mechanisms. *Annu Rev Immunol* 17:331, 1999.
52. Thome M, Tschopp J: Regulation of lymphocyte proliferation and death by FLIP. *Nat Rev Immunol* 1:50, 2001.
53. Van Blitterswijk WJ, et al: Ceramide: second messenger or modulator of membrane structure and dynamics? *Biochem J* 369:199, 2003.
54. Scorrano L, Korsmeyer SJ: Mechanisms of cytochrome release by proapoptotic BCL-2 family members. *Biochem Biophys Res Commun* 304:347, 2003.

55. Ravagnan L, Roumier T, Kroemer G: Mitochondria, the killer organelles and their weapons. *J Cell Physiol* 192:131, 2002.
56. Cory S, Adams JM: The Bcl2 family: regulators of the cellular life-or-death switch. *Nature Rev Cancer* 2:647, 2002.
57. Reed JC: Cytochrome *c*: can't live with it — can't live without it. *Cell* 91:559, 1997.
58. Salvesen GS, Duckett CS: IAP proteins: blocking the road to death's door. *Nature Rev Mol Cell Biol* 3:401, 2002.
59. Joza N, Kroemer G, Penninger JM: Genetic analysis of the mammalian cell death machinery. *Trends Genet* 18:142, 2002.
60. Salvesen GS, Dixit VM: Caspases: intracellular signaling by proteolysis. *Cell* 91:443, 1997.
61. Ravichandran KS: "Recruitment signals" from apoptotic cells: invitation to a quiet meal. *Cell* 113:817, 2003.
62. Rathmell JC, Thompson CB: Pathways of apoptosis in lymphocyte development, homeostasis, and disease. *Cell* 109:S97, 2002.
63. Vousden KH, Lu X: Live or let die: the cell's response to p53. *Nature Rev Cancer* 2:594, 2002.
64. Siegel RM, et al: The multifaceted role of Fas signaling in immune cell homeostasis and autoimmunity. *Nat Immunol* 1:469, 2000.
65. Locksley RM, Killeen N, Lenardo MJ: The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell* 104:487, 2001.
66. Russell JH, Ley TJ: Lymphocyte-mediated cytotoxicity. *Annu Rev Immunol* 20:323, 2002.
67. Webb SJ, et al: Apoptosis. An overview of the process and its relevance in disease. *Adv Pharmacol* 41:1, 1997.
68. Dunn WA: Studies on the mechanisms of autophagy. *J Cell Biol* 110:1923, 1990.
69. Klionsky DJ, Emr SD: Autophagy as a regulated pathway of cellular degradation. *Science* 290:1717, 2000.
70. Di Mauro S, Schon EA: Mitochondrial respiratory-chain diseases. *New Engl J Med* 348:2656, 2003.
71. Mermall V, et al: Unconventional myosins in cell movement, membrane traffic and signal transduction. *Science* 279:527, 1998.
72. Fuchs E, Cleveland DW: A structural scaffolding of intermediate filaments in health and disease. *Science* 279:514, 1998.
73. Denk H, Stumptner C, Zatloukal K: Mallory bodies revisited. *J Hepatol* 32:689, 2000.
74. Snapper SB, Rosen FS: The Wiskott-Aldrich syndrome protein (WASP): roles in signaling and cytoskeletal organization. *Annu Rev Immunol* 17:905, 1999.
75. Lee RJ: Fatty change and steatohepatitis. In Lee RJ (ed): *Diagnostic Liver Pathology*. St. Louis: Mosby-Year Book, 1994, p 167.
76. Soto C: Protein misfolding and disease; protein refolding and therapy. *FEBS Lett* 498:204, 2001.
77. Horwich A: Protein aggregation in disease: a role for folding intermediates forming specific multimeric interactions. *J Clin Invest* 110:1221, 2002.
78. Hartl FU, Hayer-Hartl M: Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* 295:1852, 2002.
79. Kaufman RJ: Orchestrating the unfolded protein response in health and disease. *J Clin Invest* 110:1389, 2002.

81. Ma Y, Hendershot LM: The unfolding tale of the unfolded protein response. *Cell* 107:827, 2001.
 82. Hayflick L, Moorhead PS: The serial cultivation of human diploid cell strains. *Exp Cell Res* 25:585, 1961.
 83. Smith JR, Pereira-Smith OM: Replicative senescence: implications for in vivo aging and tumor suppression. *Science* 273:63, 1996.
 84. Blackburn EH: Switching and signaling at the telomere. *Cell* 106:661, 2001.
 85. Wong JMY, Collins K: Telomere maintenance and disease. *Lancet* 362:983, 2003.
 86. Stewart SA, Weinberg RA: Senescence: does it all happen at the ends? *Oncogene* 21:627, 2002.
 87. Guarente L, Kenyon C: Genetic pathways that regulate ageing in model organisms. *Nature* 408:255, 2000.
 88. Martin GM, Oshima J: Lessons from human progeroid syndromes. *Nature* 408:263, 2000.
 89. Finkel T, Holbrook NJ: Oxidants, oxidative stress, and the biology of ageing. *Nature* 408:239, 2000.
 90. Gilchrest BA, Bohr VA: Aging processes, DNA damage, and repair. *FASEB J* 11:322, 1997.
 91. Bohr VA: Human premature aging syndromes and genomic instability. *Mech Ageing Dev* 123:987, 2002.
 92. Carrard G, et al: Impairment of proteasome structure and function in aging. *Int J Biochem Cell Biol* 34:1461, 2002.
-

Chapter 2 - Acute and Chronic Inflammation

General Features of Inflammation

In Chapter 1, we saw how various exogenous and endogenous stimuli can cause cell injury. In vascularized tissues, these same stimuli also provoke a host response called *inflammation*. *Inflammation agents such as microbes and damaged, usually necrotic, cells that consists of vascular responses, migration and activation of leukocytes, and systemic reactions.* Invertebrates with no vascular system, and even single-celled organisms, are able to get rid of injurious agents such as microbes by a variety of mechanisms. These mechanisms include entrapment and

phagocytosis of the offending agent, sometimes by specialized cells (hemocytes), and neutralization of noxious stimuli by hypertrophy of the host cell or one of its organelles. These cellular reactions have been retained through evolution, and the more potent defensive reaction of inflammation has been added in higher species. The unique feature of the inflammatory process is the *reaction of blood vessels, leading to the accumulation of fluid and leukocytes in extravascular tissues.*

The inflammatory response is closely intertwined with the process of repair. Inflammation serves to destroy, dilute, or wall off the injurious agent, and it sets into motion a series of events that try to heal and reconstitute the damaged tissue. Repair begins during the early phases of inflammation but reaches completion usually after the injurious influence has been neutralized. During repair, the injured tissue is replaced through *regeneration* of native parenchymal cells, by filling of the defect with fibrous tissue (*scarring*) or, most commonly, by a combination of these two processes.

Figure 2-1 The components of acute and chronic inflammatory responses: circulating cells and proteins, cells of blood vessels, and cells and proteins of the extracellular matrix.

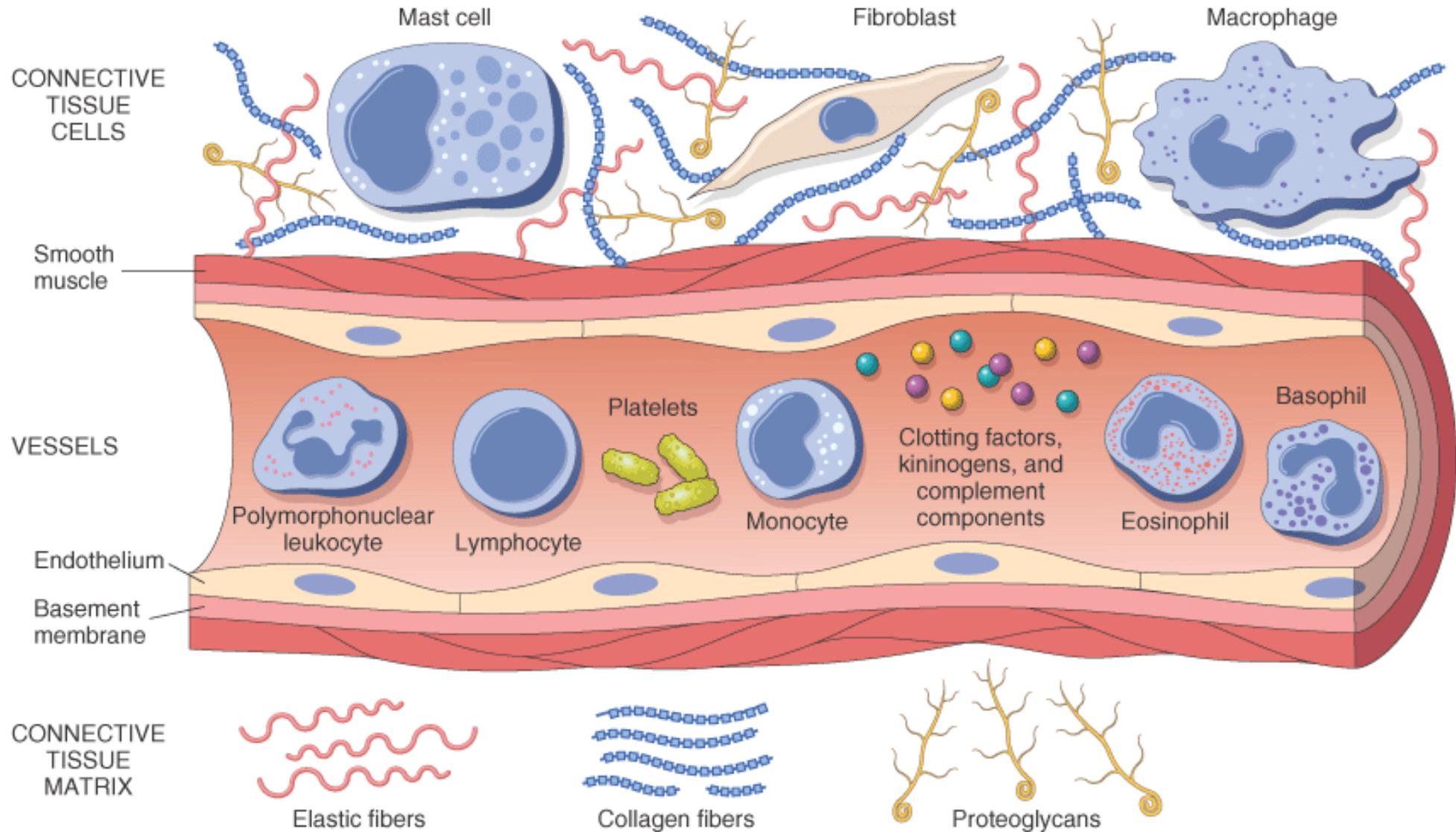
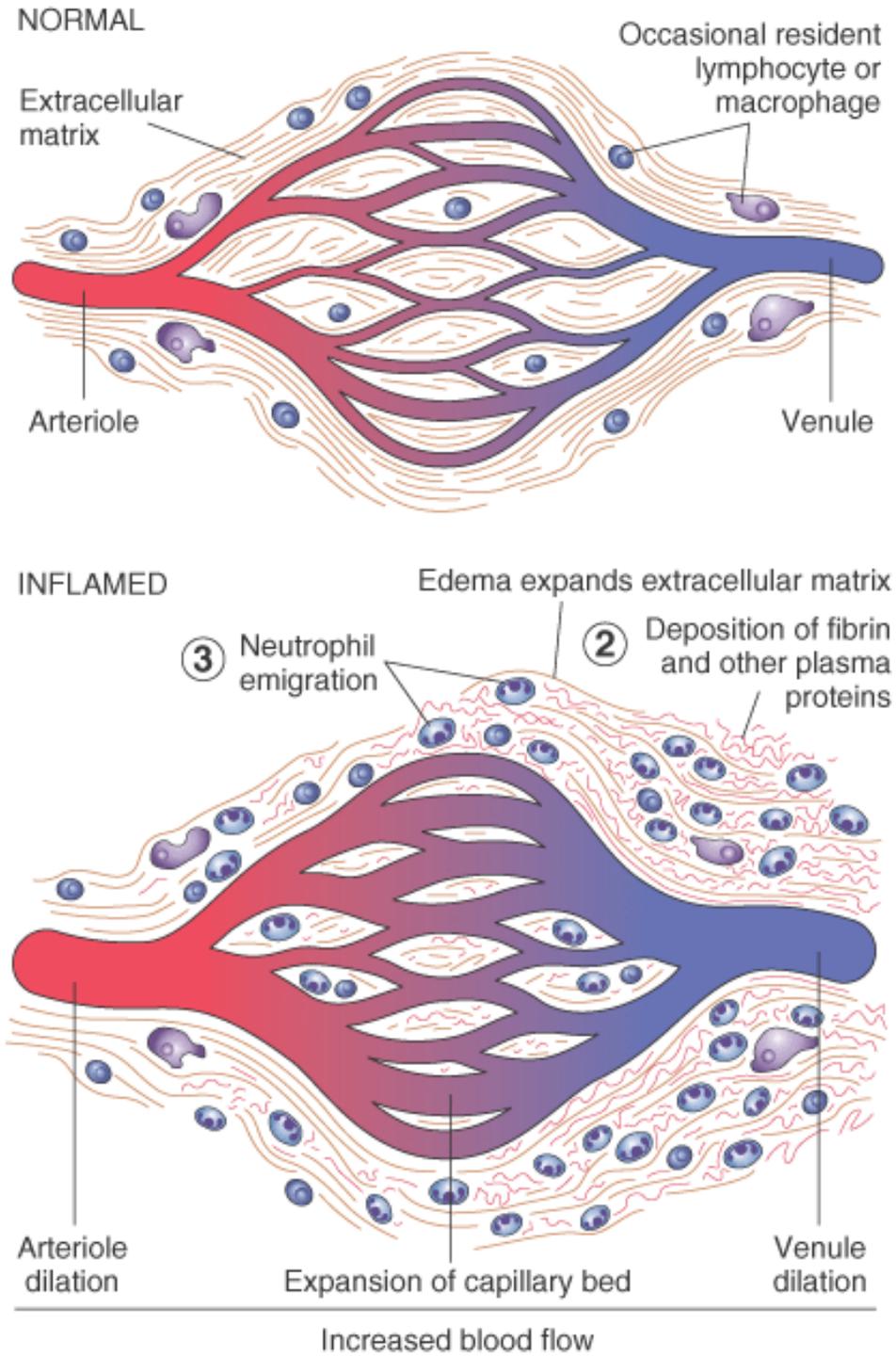
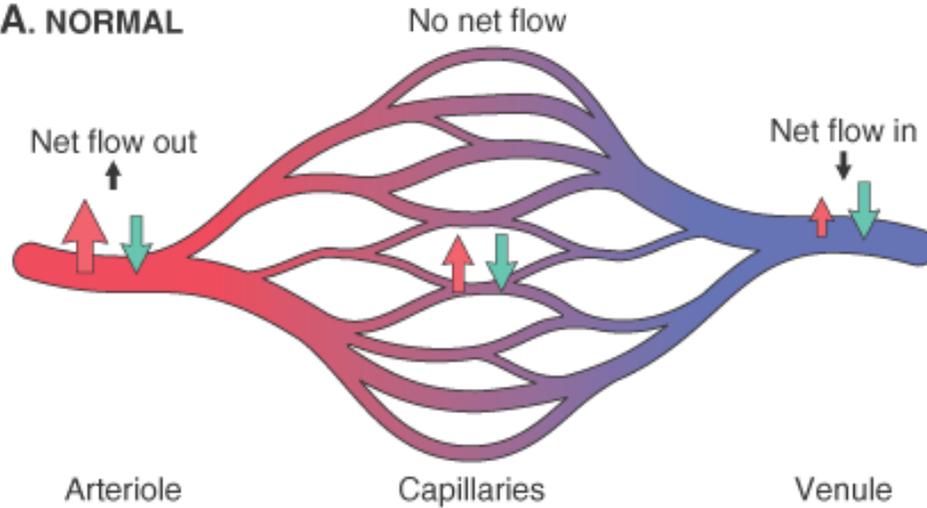
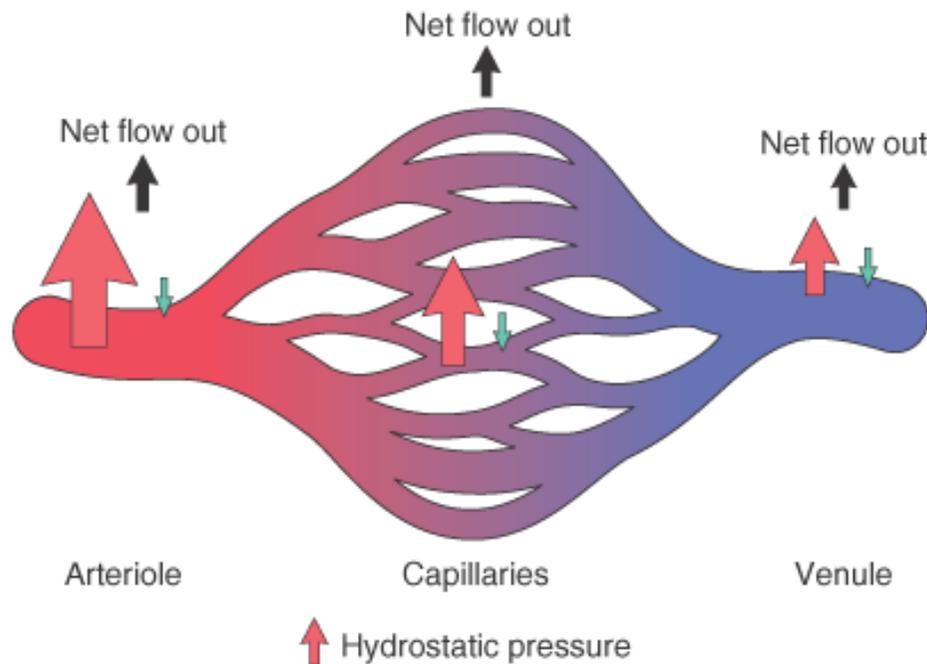


Figure 2-2 The major local manifestations of acute inflammation, compared to normal. (1) Vascular dilation and increased blood flow (causing erythema and warmth), (2) extravasation and deposition of plasma fluid and proteins (edema), and (3) leukocyte emigration and accumulation in the site of injury.



①

Figure 2-3 Blood pressure and plasma colloid osmotic forces in normal and inflamed microcirculation. *A*, Normal hydrostatic pressure (*red arrows*) is about 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (*green arrows*), which is equal to the mean capillary pressure. Although fluid tends to leave the precapillary arteriole, it is returned in equal amounts via the postcapillary venule, so that the net flow (*black arrows*) in or out is zero. *B*, Acute inflammation. Arteriolar pressure is increased to 50 mm Hg, the mean capillary pressure is increased because of arteriolar dilation, and the venous pressure increases to approximately 30 mm Hg. At the same time, osmotic pressure is reduced (averaging 20 mm Hg) because of protein leakage across the venule. The net result is an excess of extravasated fluid.

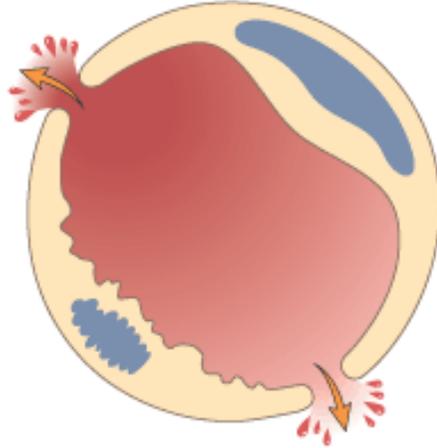
A. NORMAL**B. ACUTE INFLAMMATION**

↑ Hydrostatic pressure
↓ Colloid osmotic pressure

Figure 2-4 Diagrammatic representation of five mechanisms of increased vascular permeability in inflammation (see text).

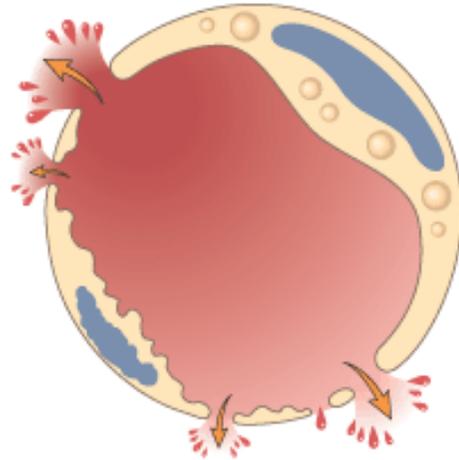
Gaps due to endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)



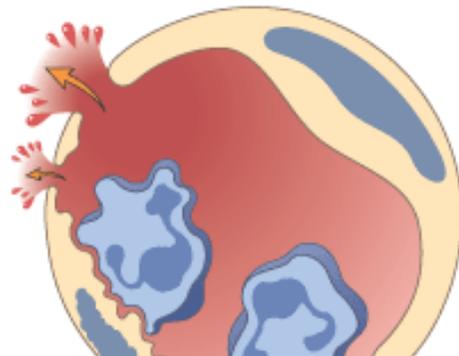
Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)

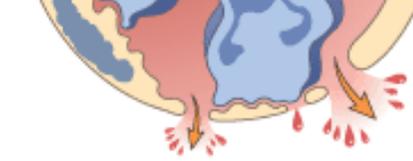


Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)

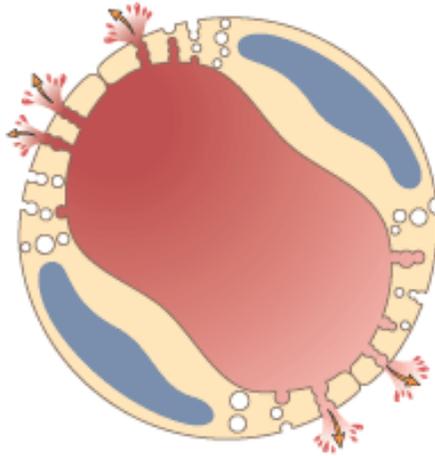


- Long-lived (hours)



Increased transcytosis

- Venules
- Vascular endothelium–derived growth factor



New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form

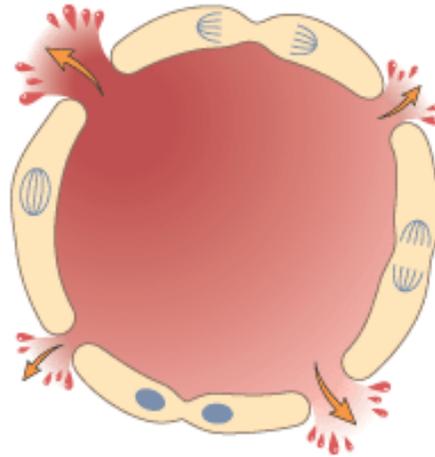


Figure 2-5 Vascular leakage induced by chemical mediators. *A*, This is a fixed and cleared preparation of a rat cremaster muscle examined unstained by transillumination. One hour before sacrifice, bradykinin was injected over this muscle, and colloidal carbon was given intravenously. Plasma, loaded with carbon, escaped, but most of the carbon particles were retained by the basement membrane of the leaking vessels, with the result that these became "labeled" black. Note that not all the vessels leak—only the venules. In *B*, a higher power, the capillary network is faintly visible in the background. (Courtesy of Dr. Guido Majno, University of Massachusetts Medical School, Worcester, MA.)

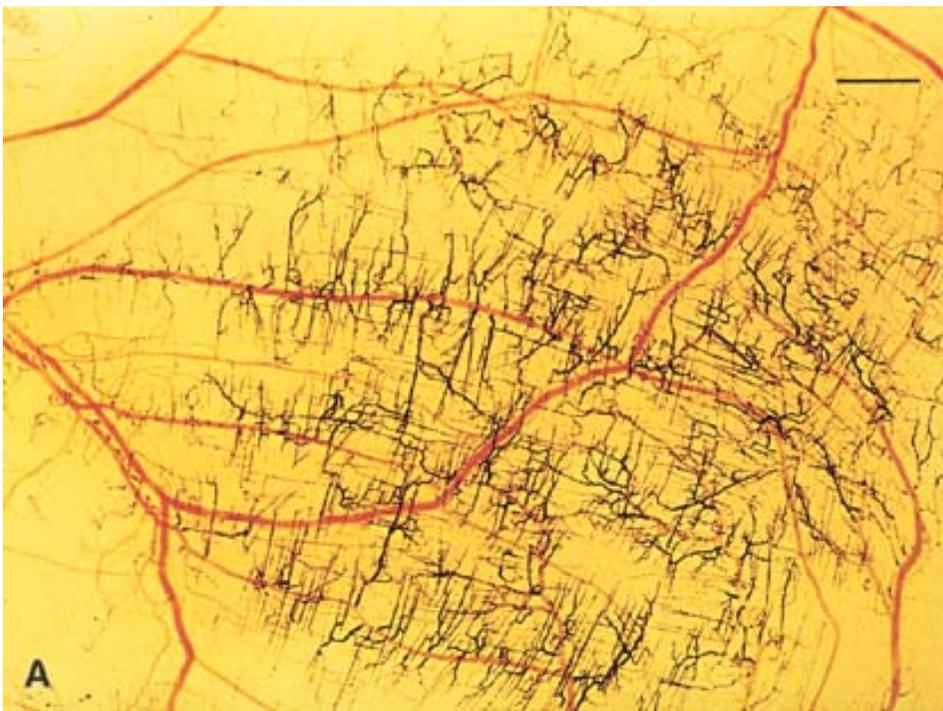


Figure 2-6 The multistep process of leukocyte migration through blood vessels, shown here for neutrophils. The leukocytes first roll, then become activated and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and migrate toward chemoattractants emanating from the source of injury. Different molecules play predominant roles in different steps of this process—selectins in rolling; chemokines in activating the neutrophils to increase avidity of integrins (in green); integrins in firm adhesion; and CD31 (PECAM-1) in transmigration.

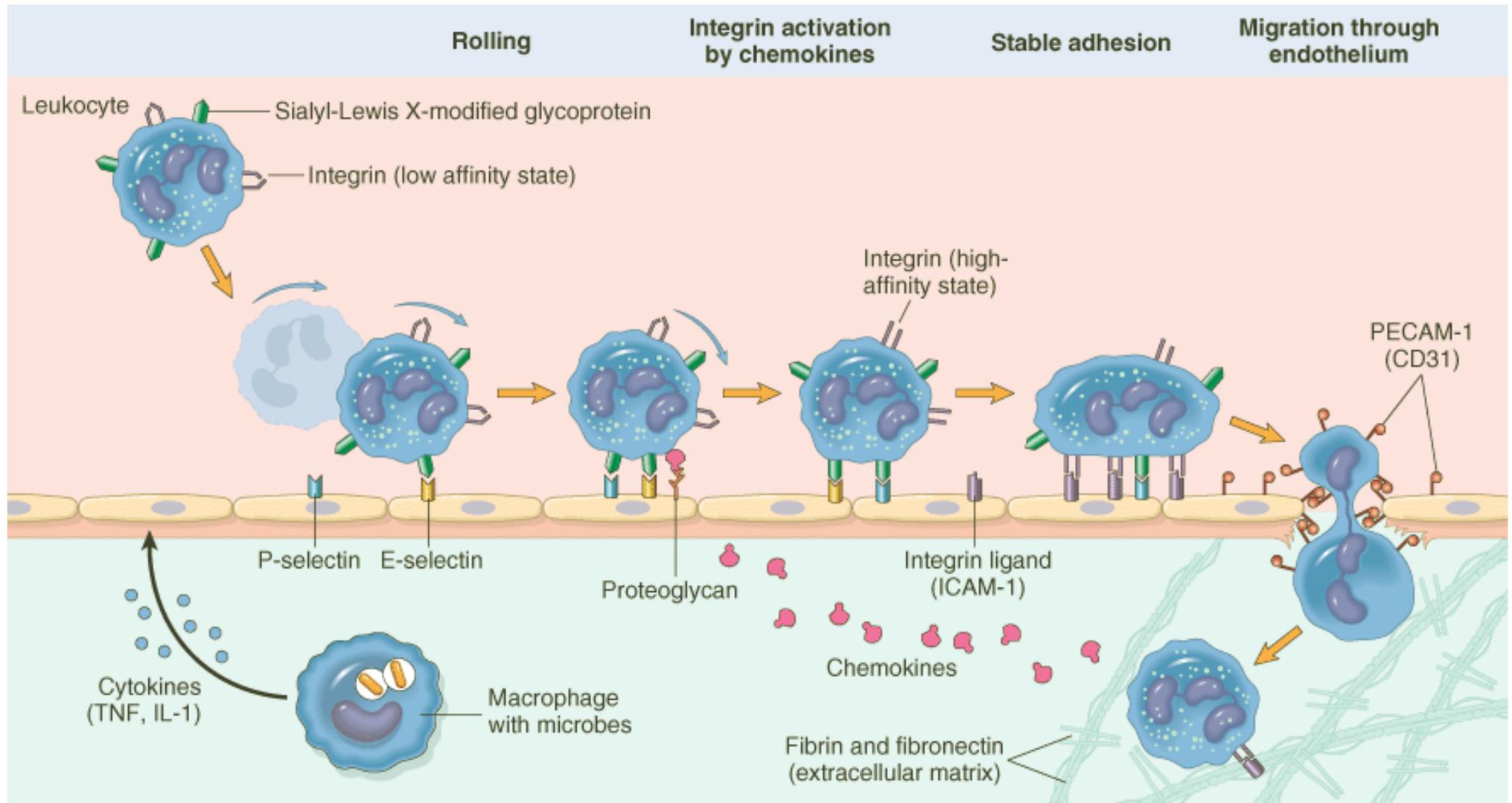


TABLE 2-1 -- Endothelial/Leukocyte Adhesion Molecules

Endothelial Molecule	Leukocyte Receptor	Major Role
P-selectin	Sialyl-Lewis X PSGL-1	Rolling (neutrophils, monocytes, lymphocytes)
E-selectin	Sialyl-Lewis X	Rolling, adhesion to activated endothelium (neutrophils, monocytes, T cells)
ICAM-1	CD11/CD18 (integrins) (LFA-1, Mac-1)	Adhesion, arrest, transmigration (all leukocytes)
VCAM-1	$\alpha 4\beta 1$ (VLA4) (integrins)	Adhesion (eosinophils, monocytes, lymphocytes)

	$\alpha 4\beta 7$ (LPAM-1)	
GlyCAM-1	L-selection	Lymphocyte homing to high endothelial venules
CD31 (PECAM)	CD31	Leukocyte migration through endothelium
*ICAM-1, VCAM-1, and CD31 belong to the immunoglobulin family of proteins; PSGL-1, P-selectin glycoprotein ligand 1.		

Leukocyte Adhesion and Transmigration

Leukocyte adhesion and transmigration are regulated largely by the binding of complementary adhesion molecules on the leukocyte and endothelial surfaces, and chemical mediators—chemoattractants and certain cytokines—affect these processes by modulating the surface expression or avidity of such adhesion molecules.^{[16] [17]} The adhesion receptors involved belong to four molecular families—the *selectins*, the *immunoglobulin superfamily*, the *integrins*, and *mucin-like glycoproteins*. The most important of these are listed in Table 2-1 .

- *Selectins*, so called because they are characterized by an extracellular N-terminal domain related to sugar-binding mammalian lectins, consist of E-selectin (CD62E, previously known as ELAM-1), which is confined to endothelium; P-selectin (CD62P, previously called GMP140 or PADGEM), which is present in endothelium and platelets; and L-selectin (CD62L, previously known by many names, including LAM-1), which is expressed on most leukocyte types (Box 2-1).^{[18] [19]} Selectins bind, through their lectin domain, to sialylated forms of oligosaccharides (e.g., sialylated Lewis X), which themselves are covalently bound to various *mucin-like glycoproteins* (GlyCAM-1, PSGL-1, ESL-1, and CD34).
- The *immunoglobulin family* molecules include two endothelial adhesion molecules: ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1). Both these molecules serve as ligands for integrins found on leukocytes.
- *Integrins* are transmembrane heterodimeric glycoproteins, made up of α and β chains, that are expressed on many cell types and bind to ligands on endothelial cells, other leukocytes, and the extracellular matrix (Box 2-1).^[20] The β_2 integrins LFA-1 and Mac-1 (CD11a/CD18 and CD11b/CD18) bind to ICAM-1, and the β_1 integrins (such as VLA-4) bind VCAM-1.
- *Mucin-like glycoproteins*, such as heparan sulfate, serve as ligands for the leukocyte adhesion molecule called CD44. These glycoproteins are found in the extracellular matrix and on cell surfaces.

The recruitment of leukocytes to sites of injury and infection is a multistep process involving attachment of circulating leukocytes to endothelial cells and their migration through the endothelium (see Fig. 2-6). The first events are the induction of adhesion molecules on endothelial cells, by a number of mechanisms (Fig. 2-7). Mediators such as histamine, thrombin, and platelet activating factor (PAF) stimulate the redistribution of P-selectin from its normal intracellular stores in granules (Weibel-Palade bodies) to the cell surface. Resident tissue macrophages, mast cells, and endothelial cells respond to injurious agents by secreting the cytokines TNF, IL-1, and chemokines (chemoattractant cytokines). (Cytokines are described in more detail below and in Chapter 6 .) TNF and IL-1 act on the endothelial cells of postcapillary venules adjacent to the infection and induce the expression of several adhesion molecules. Within 1 to 2 hours, the endothelial cells begin to express E-selectin. Leukocytes express at the tips of their microvilli carbohydrate ligands for the selectins, which bind to the endothelial selectins. These are low-affinity interactions with a fast off-rate, and they are easily disrupted by the flowing blood. As a result, the bound leukocytes detach and bind again, and thus begin to roll along the endothelial surface.

TNF and IL-1 also induce endothelial expression of ligands for integrins, mainly VCAM-1 (the ligand for the VLA-4 integrin) and ICAM-1 (the ligand for the LFA-1 and Mac-1 integrins). Leukocytes normally express these integrins in a low-affinity state. Meanwhile, chemokines that were produced at the site of injury enter the blood vessel, bind to endothelial cell heparan sulfate glycosaminoglycans (labeled "proteoglycan" in Figure 2-6), and are displayed at high concentrations on the endothelial surface.^[21] These chemokines act on the rolling leukocytes and activate the leukocytes. One of the consequences of activation is the conversion of VLA-4 and LFA-1 integrins on the leukocytes to a high-affinity state. The combination of induced expression of integrin ligands on the endothelium and activation of integrins on the leukocytes results in firm integrin-mediated binding of the leukocytes to the endothelium at the site of infection. The leukocytes stop rolling, their cytoskeleton is reorganized, and they spread out on the endothelial surface.

The next step in the process is migration of the leukocytes through the endothelium, called transmigration or *diapedesis*. Chemokines act on the adherent leukocytes and stimulate the cells to migrate through interendothelial spaces toward the chemical concentration gradient, that is, toward the site of injury or infection. Certain homophilic adhesion molecules (i.e., adhesion

Box 2-1. Selectins and Integrins: Adhesion Molecules Involved in the Inflammatory Response

The specific (nonrandom) adhesion of cells to other cells or to extracellular matrices is a basic component of cell migration and recognition and underlies many biologic processes, including embryogenesis, tissue repair, and immune and inflammatory responses. It is, therefore, not surprising that many different genes have evolved that encode proteins with specific adhesive functions. Two families of adhesive proteins that are especially important in inflammation are the *selectins* and the *integrins*.

Selectins

The selectins are a family of three closely related proteins that differ in their cellular distribution but all function in adhesion of leukocytes to endothelial cells. All selectins are single-chain transmembrane glycoproteins with an amino terminus that is related to carbohydrate-binding proteins known as C-type lectins. Like other C-type lectins, ligand binding by selectins is calcium-dependent (hence the name C-type). The binding of selectins to their ligands has a fast on rate but also has a fast off rate and is of low affinity; this property allows selectins to mediate initial attachment and subsequent rolling of leukocytes on endothelium in the face of flowing blood.

L-selectin, or *CD62L*, is expressed on lymphocytes and other leukocytes. It serves as a homing receptor for lymphocytes to enter lymph nodes by binding to high endothelial venules (HEVs). It also serves to bind neutrophils to cytokine-activated endothelial cells at sites of inflammation. L-selectin is located on the tips of microvillus projections of leukocytes, facilitating its interaction with ligands on endothelium. At least three endothelial cell ligands can bind L-selectin—glycan-bearing cell adhesion molecule-1 (GlyCAM-1), a secreted proteoglycan found on HEVs of lymph node; mucosal addressin cell adhesion molecule-1 (MadCAM-1), expressed on endothelial cells in gut-associated lymphoid tissues; and CD34, a proteoglycan on endothelial cells (and bone marrow cells). The protein backbones of all these ligands are modified by specific carbohydrates, which are the molecules actually recognized by the selectin.

E-selectin, or *CD62E*, previously known as endothelial leukocyte adhesion molecule-1 (ELAM-1), is expressed only on cytokine-activated endothelial cells, hence the designation E. E-selectin recognizes complex sialylated carbohydrate groups related to the Lewis X or Lewis A family found on various surface proteins of granulocytes, monocytes, and previously activated effector and memory T cells. E-selectin is important in the homing of effector and memory T cells to some peripheral sites of inflammation, particularly in the skin. Endothelial cell expression of E-selectin is a hallmark of acute cytokine-mediated inflammation, and antibodies to E-selectin can block leukocyte accumulation in vivo.

P-selectin (*CD62P*) was first identified in the secretory granules of platelets, hence the designation P. It has since been found in secretory granules of endothelial cells, called Weibel-Palade bodies. When endothelial cells or platelets are stimulated, P-selectin is translocated within minutes to the cell surface. On reaching the cell surface, P-selectin mediates binding of neutrophils, T lymphocytes, and monocytes. The complex carbohydrate ligands recognized by P-selectin appear similar to those recognized by E-selectin.

The essential physiologic roles of selectins have been reinforced by studies of gene knockout mice. L-selectin-deficient mice have small, poorly formed lymph nodes with few T cells. Mice lacking either E-selectin or P-selectin have only mild defects in leukocyte recruitment, suggesting that these two molecules are functionally redundant. Double knockout mice lacking both E-selectin and P-selectin have significantly impaired leukocyte recruitment and increased susceptibility to infections. Humans who lack one of the enzymes needed to express the carbohydrate ligands for E-selectin and P-selectin on neutrophils have similar problems, resulting in a syndrome called leukocyte adhesion deficiency-2 (LAD-2) (see text).

Integrins

The integrin superfamily consists of about 30 structurally homologous proteins that promote cell-cell or cell-matrix interactions. The name of this family of proteins derives from the hypothesis that they coordinate (i.e., "integrate") signals from extracellular ligands with cytoskeleton-dependent motility, shape change, and phagocytic responses.

All integrins are heterodimeric cell surface proteins composed of two noncovalently linked polypeptide chains, α and β . The extracellular domains of the two chains bind to various ligands, including extracellular matrix glycoproteins, activated complement components, and proteins on the surfaces of other cells. Several integrins bind to Arg-Gly-Asp (RGD) sequences in the fibronectin and vitronectin molecules. The cytoplasmic domains of the integrins interact with cytoskeletal components (including vinculin, talin, actin, α -actinin, and tropomyosin).

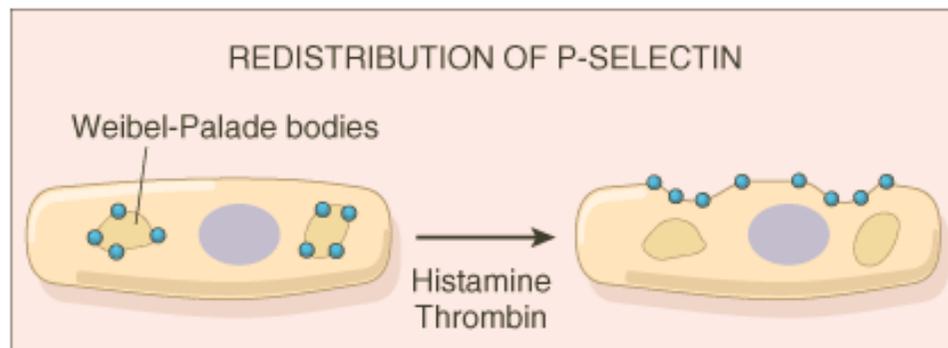
Three integrin subfamilies were originally defined on the basis of which of three β subunits were used to form the heterodimers. More recently, five additional β chains have been identified.

The β_1 -containing integrins are also called VLA molecules, referring to "very late activation" molecules, because $\alpha_1\beta_1$ and $\alpha_2\beta_1$ were first shown to be expressed on T cells 2 to 4 weeks after repetitive stimulation in vitro. In fact, other VLA integrins are constitutively expressed on some leukocytes and rapidly induced on others. The β_1 integrins are also called CD49a-hCD29, CD49a-h referring to different α chains (α_1 - α_8) and CD29 referring to the common β_1 subunit. Most of the β_1 integrins are widely expressed on leukocytes and other cells and mediate attachment of cells to extracellular matrices. VLA-4 ($\alpha_4\beta_1$) is expressed only on leukocytes and can mediate attachment of these cells to endothelium by interacting with vascular cell adhesion molecule-1 (VCAM-1). VLA-4 is one of the principal surface proteins that mediate homing of lymphocytes to endothelium at peripheral sites of inflammation.

The β_2 integrins are also called CD11a-cCD18, or the leukocyte function-associated antigen-1 (LFA-1) family, CD11a-c referring to different α chains and CD18 to the common β_2 subunit. LFA-1 (CD11aCD18) plays an important role in the adhesion of lymphocytes and other leukocytes with other cells, such as antigen-presenting cells and vascular endothelium. Other members of the family include CD11bCD18 (Mac-1 or CR3) and CD11cCD18 (p150,95 or CR4), which mediate leukocyte attachment to endothelial cells and subsequent extravasation. CD11bCD18 also functions as a fibrinogen receptor and as a complement receptor on phagocytic cells, binding particles opsonized with a by-product of complement activation called the inactivated C3b (iC3b) fragment.

The other integrins are expressed on platelets and other cell types, and bind to extracellular matrix proteins as well as proteins involved in coagulation.

Figure 2-7 Regulation of endothelial and leukocyte adhesion molecules. *A*, Redistribution of P-selectin. *B*, Cytokine activation of endothelium. *C*, Increased binding avidity of integrins (see text).

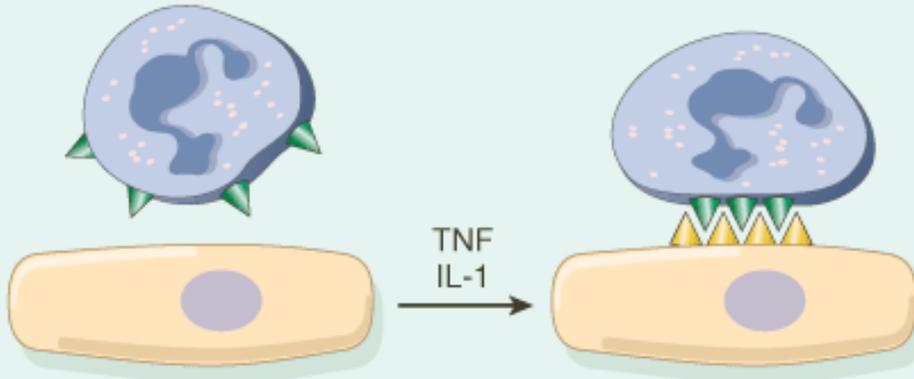


Thrombin

A

CYTOKINE INDUCTION OF ENDOTHELIAL ADHESION MOLECULES

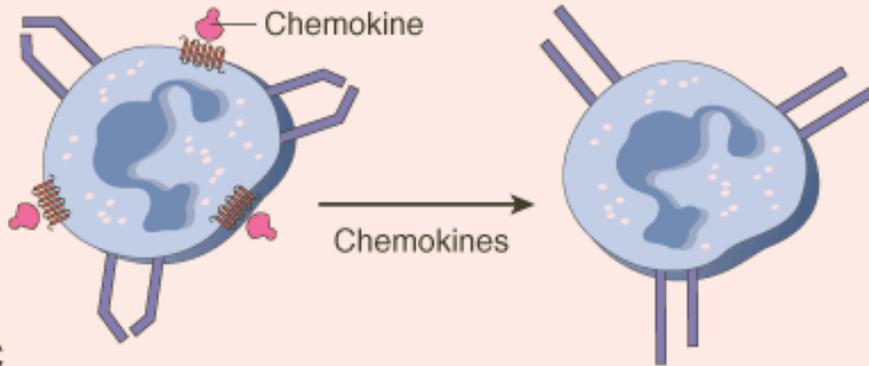
Neutrophil



B

INCREASED AVIDITY OF INTEGRINS

Chemokine



C

Figure 2-8 Schematic and histologic sequence of events following acute injury. The photomicrographs are representative of the early (neutrophilic) (*left*) and later (mononuclear) cellular infiltrates (*right*) of infarcted myocardium. The kinetics of edema and cellular infiltration are approximations. For sake of simplicity, edema is shown as an acute transient response, although secondary waves of delayed edema and neutrophil infiltration can also occur.

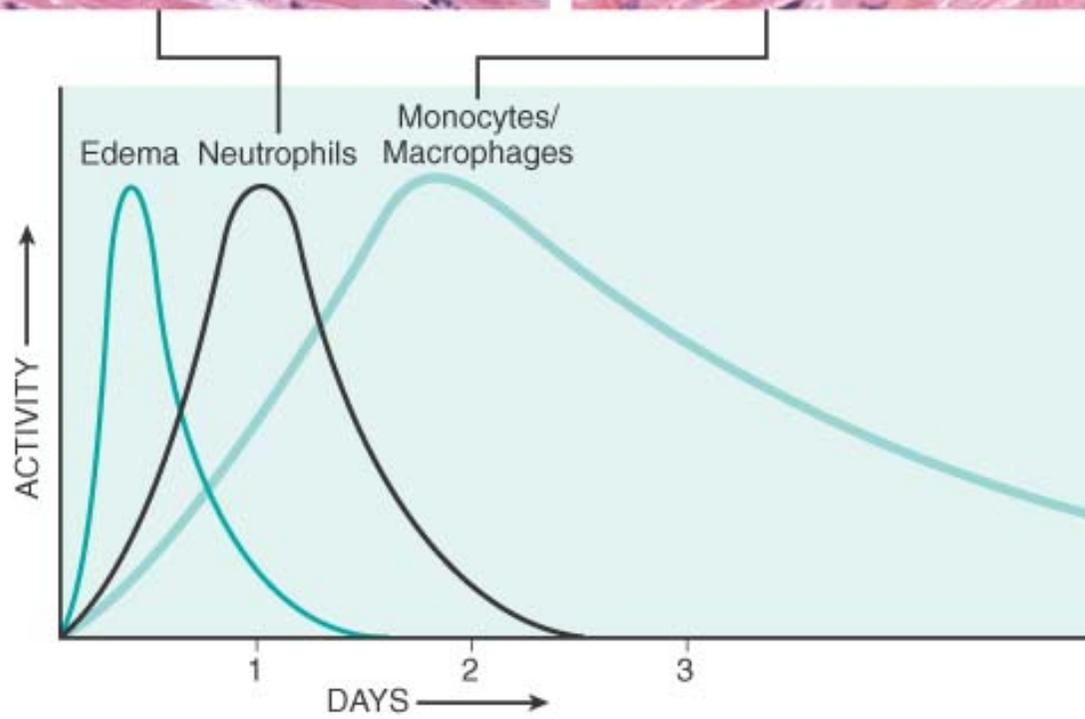
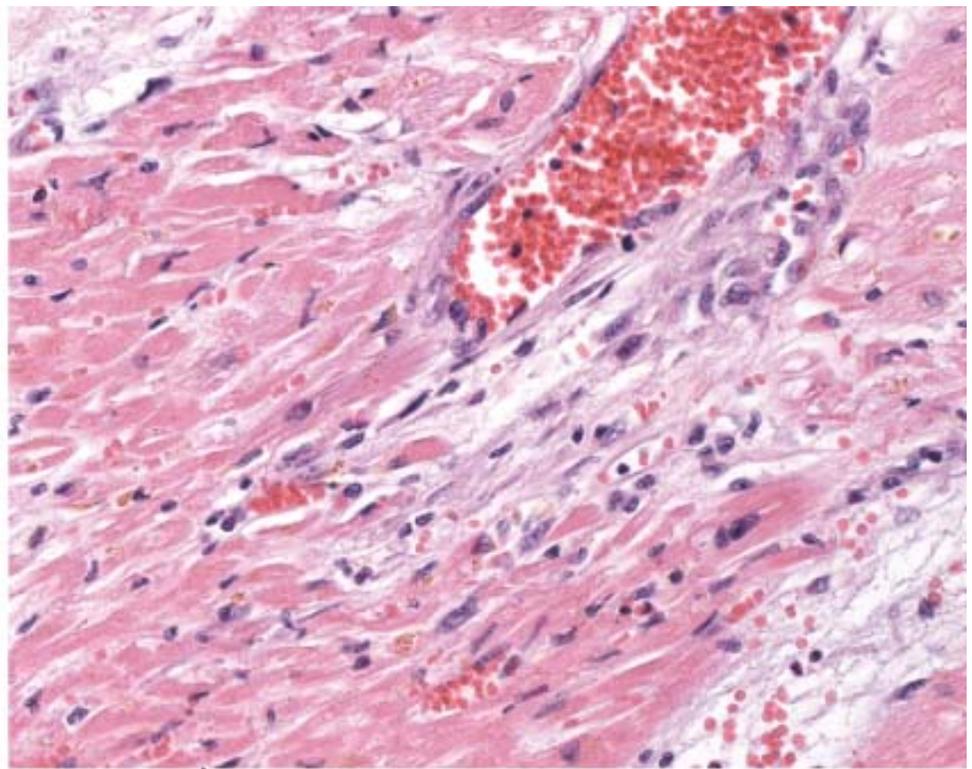
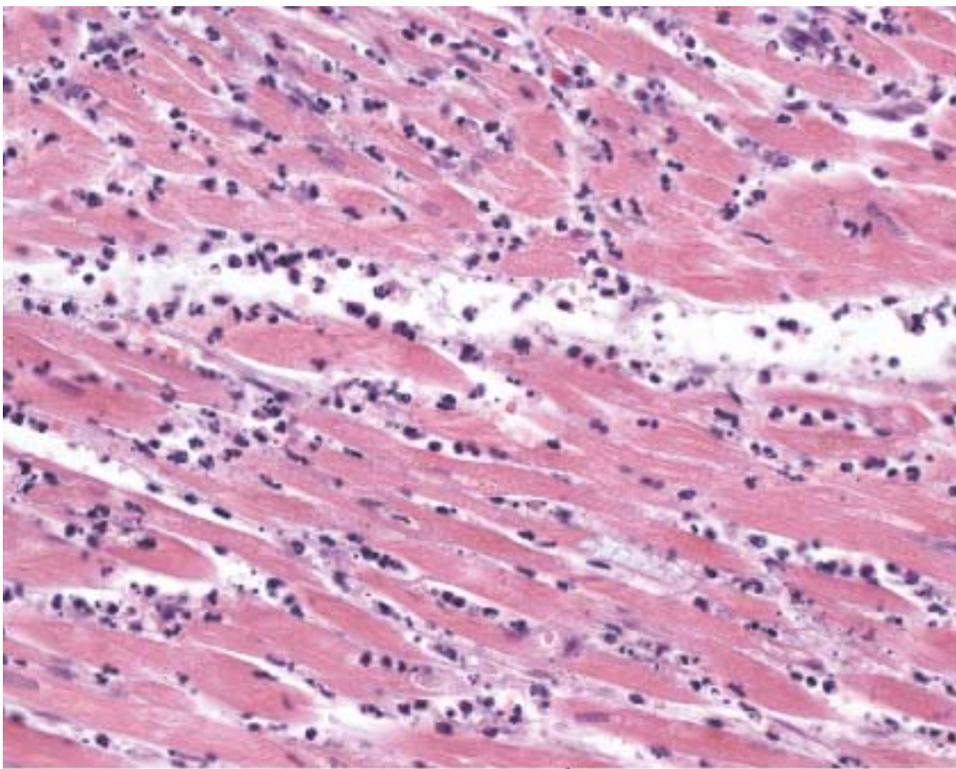


Figure 2-9 Scanning electron micrograph of a moving leukocyte in culture showing a filopodium (*upper left*) and a trailing tail. (*Courtesy of Dr. Morris J. Karnovsky, Harvard Medical School, Boston, MA.*)

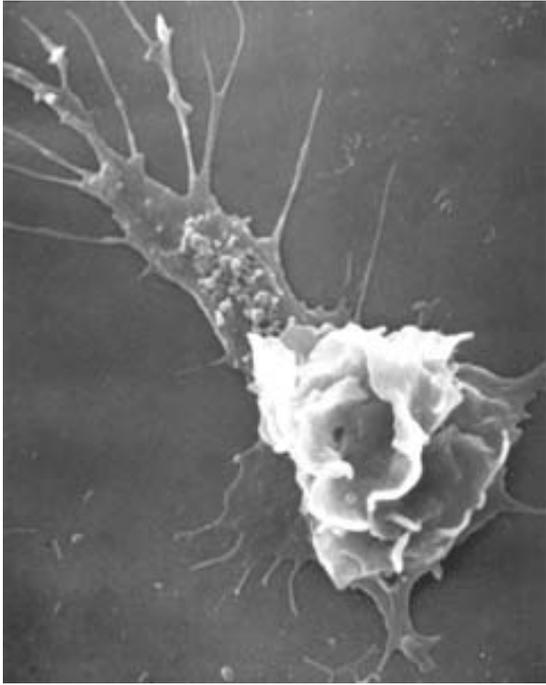


Figure 2-10 Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted (see text for details).

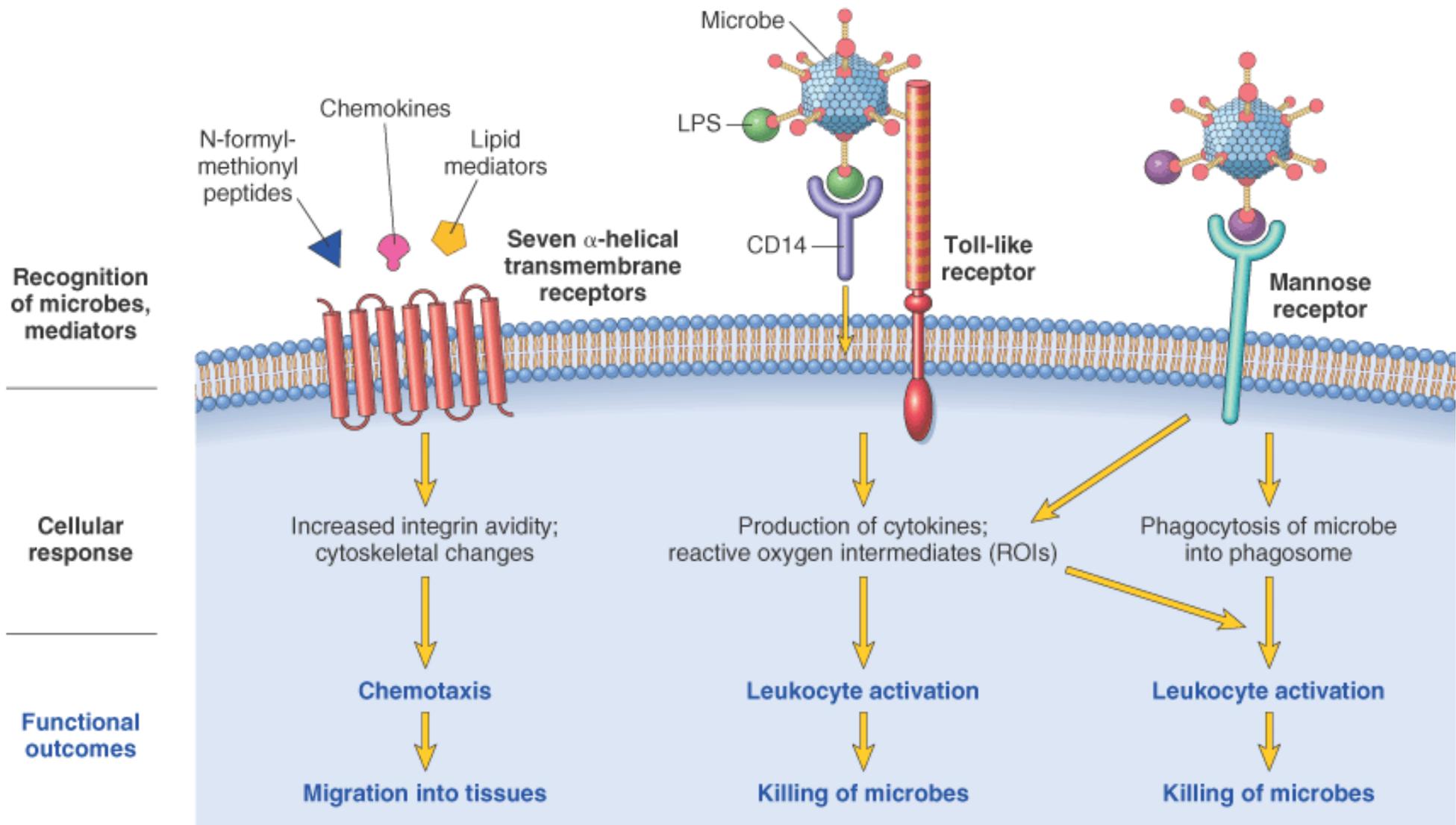
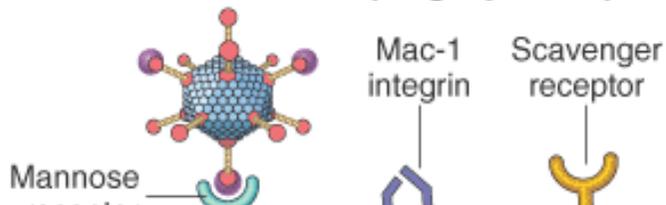


Figure 2-11 A, Phagocytosis of a particle (e.g., bacterium) involves attachment and binding of Fc and C3b to receptors on the leukocyte membrane, engulfment, and fusion of lysosomes with phagocytic vacuoles, followed by destruction of ingested particles within the phagolysosomes. Note that during phagocytosis, granule contents may be released into extracellular tissues. **B**, Production of microbicidal reactive oxygen intermediates within phagocytic vesicles.

1. RECOGNITION AND ATTACHMENT

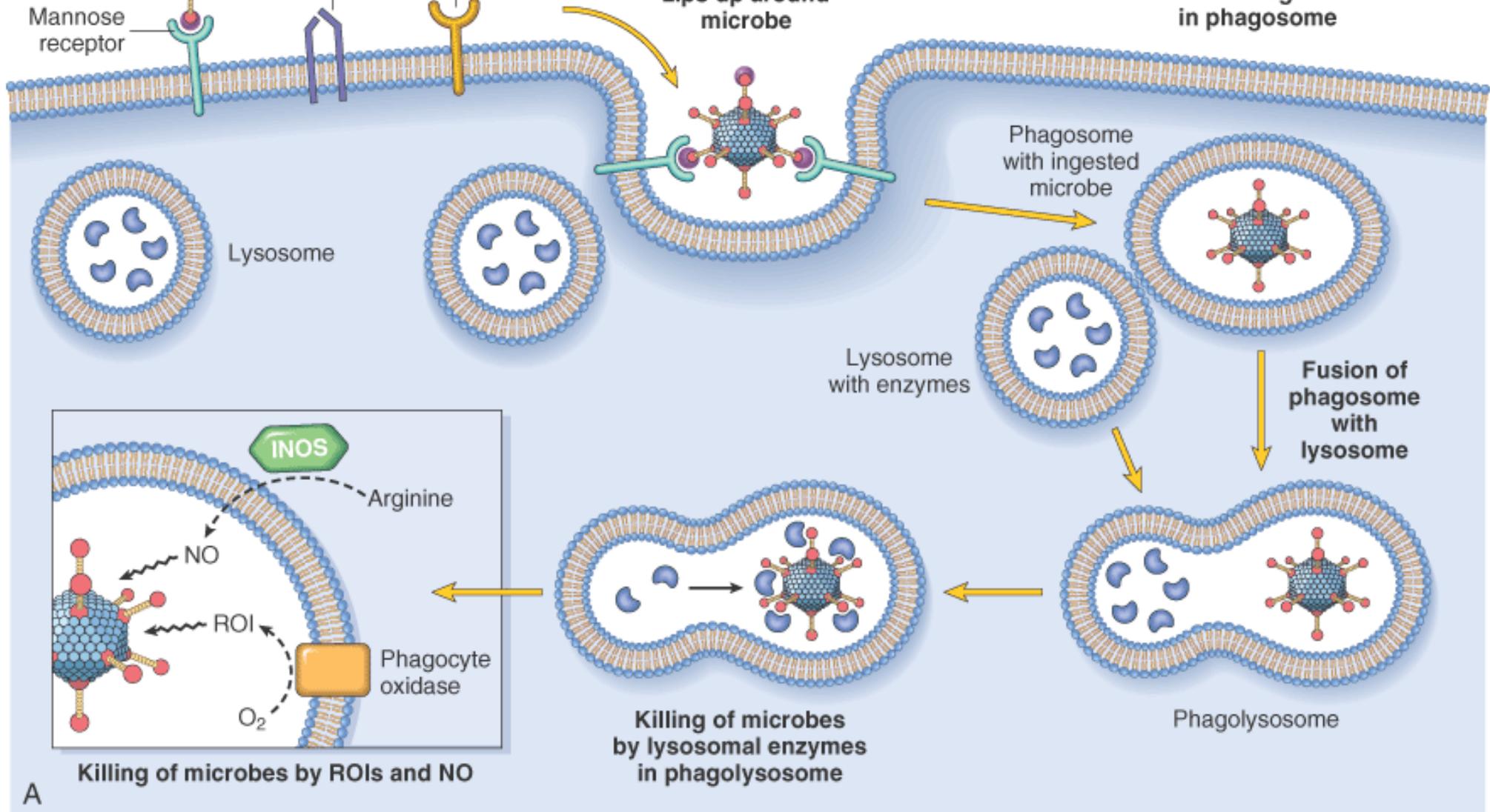
Microbes bind to phagocyte receptors



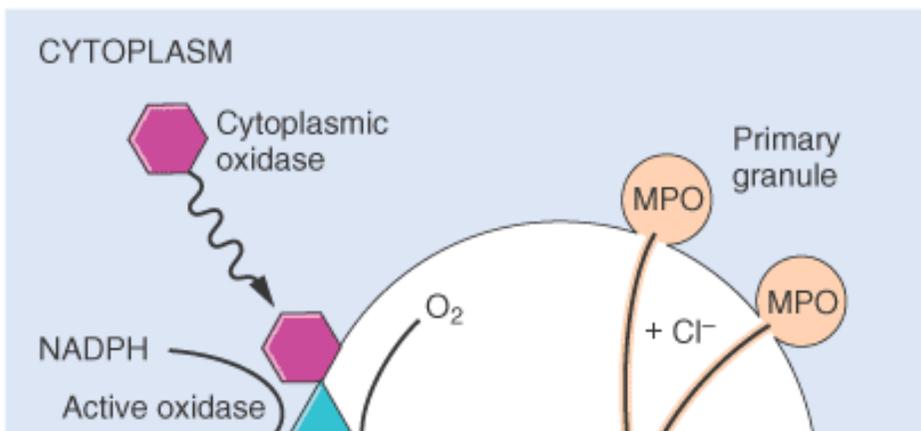
2. ENGULFMENT

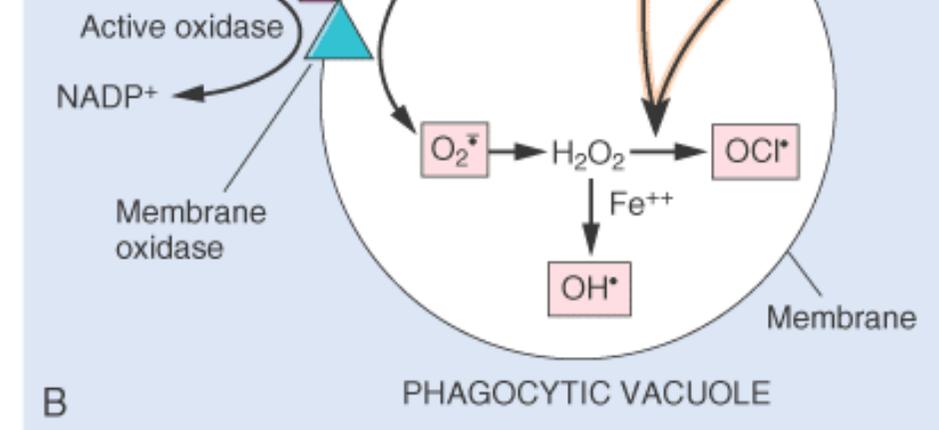
Phagocyte membrane zips up around microbe

Microbe ingested in phagosome



3. KILLING AND DEGRADATION





$O_2^{\bullet -}$). Superoxide is then converted into hydrogen peroxide (H_2O_2), mostly by spontaneous dismutation. Hydrogen peroxide can also be further reduced to the highly reactive hydroxyl radical (OH^{\bullet}). Most of the H_2O_2 is eventually broken down by catalase into H_2O and O_2 , and some is destroyed by the action of glutathione oxidase. This process and its regulation were described in detail in Chapter 1.

NADPH oxidase is an enzyme complex consisting of at least seven proteins.^[32] In resting neutrophils, different NADPH

oxidase protein components are located in the plasma membrane and the cytoplasm. In response to activating stimuli, the cytosolic protein components translocate to the plasma membrane or phagosomal membrane, where they assemble and form the functional enzyme complex (see Fig. 2-11B). Thus, the *reactive oxygen intermediates are produced within the lysosome* where the ingested substances are segregated, and the cell's own organelles are protected from the harmful effects of the ROIs. A similar enzyme system generates reactive nitrogen intermediates, notably nitric oxide, which also helps to kill microbes.

The H_2O_2 generated by the NADPH oxidase system is generally not able to efficiently kill microbes by itself. However, the azurophilic granules of neutrophils contain the enzyme *myeloperoxidase* (MPO), which, in the presence of a halide such as Cl^- , converts H_2O_2 to hypochlorite ($HOCl$). The latter is a potent antimicrobial agent that destroys microbes by *halogenation* (in which the halide is bound covalently to cellular constituents) or by oxidation of proteins and lipids (lipid peroxidation).^[33] *The H_2O_2 -MPO-halide system is the most efficient bactericidal system in neutrophils.* MPO-deficient leukocytes are capable of killing bacteria (albeit more slowly than normal cells), by virtue of the formation of superoxide, hydroxyl radicals, and singlet-oxygen.

Bacterial killing can also occur by *oxygen-independent mechanisms*, through the action of substances in leukocyte granules.^[34] These include *bactericidal permeability increasing protein* (BPI), a highly cationic granule-associated protein that causes phospholipase activation, phospholipid degradation, and increased permeability in the outer membrane of the microorganisms; *lysozyme*, which hydrolyzes the muramic acid-*N*-acetyl-glucosamine bond, found in the glycopeptide coat of all bacteria; *lactoferrin*, an iron-binding protein present in specific granules; *major basic protein*, a cationic protein of eosinophils, which has limited bactericidal activity but is cytotoxic to many parasites; and *defensins*, cationic arginine-rich granule peptides that are cytotoxic to microbes (and certain mammalian cells).^[35] In addition, neutrophil granules contain many *enzymes*, such as elastase, that also contribute to microbial killing (discussed later in the chapter).

After killing, acid hydrolases, which are normally stored in lysosomes, degrade the microbes within phagolysosomes. The pH of the phagolysosome drops to between 4 and 5 after phagocytosis, this being the optimal pH for the action of these enzymes.

Release of Leukocyte Products and Leukocyte-Induced Tissue Injury

During activation and phagocytosis, leukocytes release microbicidal and other products not only within the phagolysosome but also into the extracellular space. The most important of these substances in neutrophils and macrophages are *lysosomal enzymes*, present in the granules; *reactive oxygen intermediates*; and *products of arachidonic acid metabolism*, including prostaglandins and leukotrienes. These products are capable of causing endothelial injury and tissue damage and may thus amplify the effects of the initial injurious agent. Products of monocytes/macrophages and other leukocyte types have additional potentially harmful products, which are described in the discussion of chronic inflammation. Thus, if persistent and unchecked, the leukocyte infiltrate itself becomes the offender,^[36] and leukocyte-dependent tissue injury underlies many acute and chronic human diseases (Table 2-2). This fact becomes evident in the discussion of specific disorders throughout this book.

Regulated secretion of lysosomal proteins is a peculiarity of leukocytes and other hematopoietic cells. (Recall that in most secretory cells, the proteins that are secreted are not stored within lysosomes.) The contents of lysosomal granules are secreted by leukocytes into the extracellular milieu by diverse mechanisms. Release may occur if the phagocytic vacuole remains transiently open to the outside before complete closure of the phagolysosome (*regurgitation during feeding*). If cells are exposed to potentially ingestible materials, such as immune complexes deposited on immovable flat surfaces (e.g., glomerular basement membrane), attachment of leukocytes to the immune complexes triggers leukocyte activation, but the fixed immune complexes cannot be phagocytosed, and lysosomal enzymes are released into the medium (*frustrated phagocytosis*). *Cytotoxic release* occurs after phagocytosis of potentially membranolytic substances, such as urate crystals, which damage the membrane of the phagolysosome. In addition, there is some evidence that proteins in certain granules, particularly the specific (secondary) granules of neutrophils, may be directly secreted by *exocytosis*.^[37] ^[38]

After phagocytosis, neutrophils rapidly undergo *apoptotic cell death* and are ingested by macrophages.

Defects in Leukocyte Function

From the preceding discussion, it is obvious that leukocytes play a central role in host defense. Not surprisingly, therefore, defects in leukocyte function, both genetic and acquired, lead to increased vulnerability to infections (Table 2-3). Impairments of virtually every phase of leukocyte function—from adherence to vascular endothelium to microbicidal activity—have been identified, and the existence of clinical genetic deficiencies in each of the critical steps in the process has been described. These include the following:

- *Defects in leukocyte adhesion.* We previously mentioned the genetic deficiencies in leukocyte adhesion molecules (LAD types 1 and 2). LAD 1 is characterized by recurrent bacterial infections and impaired wound healing. LAD 2 is clinically milder than LAD 1 but is also characterized by recurrent bacterial infections.
- *Defects in phagolysosome function.* One such disorder is *Chédiak-Higashi syndrome*, an autosomal recessive condition

characterized by neutropenia (decreased numbers of neutrophils), defective degranulation, and delayed microbial killing. The neutrophils (and other leukocytes) have *giant granules*, which can be readily seen in peripheral blood smears and which are thought to result from aberrant organelle fusion.^[39] In this syndrome, there is reduced transfer of lysosomal enzymes to phagocytic vacuoles in phagocytes (causing susceptibility to infections) and abnormalities in melanocytes (leading to albinism), cells of the nervous system (associated with nerve defects), and platelets (generating bleeding disorders). The gene associated with this disorder encodes a large cytosolic protein that is apparently involved in vesicular traffic but whose precise function is not yet known. The secretion of granule proteins by cytotoxic T cells is also affected, accounting for part of the immunodeficiency seen in the disorder.

- *Defects in microbicidal activity.* The importance of oxygen-dependent bactericidal mechanisms is shown by the existence of a group of congenital disorders with defects in bacterial killing called *chronic granulomatous disease*, which render patients susceptible to recurrent bacterial infection. Chronic granulomatous disease results from *inherited defects in the genes encoding several components of NADPH oxidase*, which generates superoxide. The most common variants are an *X-linked defect* in one of the plasma membrane-bound

components (gp91phox) and *autosomal recessive* defects in the genes encoding two of the cytoplasmic components (p47phox and p67phox).^[40] ^[41]

- Clinically, the most frequent cause of leukocyte defects is *bone marrow suppression*, leading to reduced production of leukocytes. This is seen following therapies for cancer (radiation and chemotherapy) and when the marrow space is compromised by tumor metastases to bone.

TABLE 2-2 -- Clinical Examples of Leukocyte-Induced Injury

Acute	Chronic
Acute respiratory distress syndrome	Arthritis
Acute transplant rejection	Asthma
Asthma	Atherosclerosis
Glomerulonephritis	Chronic lung disease
Reperfusion injury	Chronic rejection
Septic shock	
Vasculitis	

TABLE 2-3 -- Defects in Leukocyte Functions

Disease	Defect
<i>Genetic</i>	
Leukocyte adhesion deficiency 1	β chain of CD11/CD18 integrins
Leukocyte adhesion deficiency 2	Fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectin)
Chronic granulomatous disease	Decreased oxidative burst
••X-linked	••NADPH oxidase (membrane component)
••Autosomal recessive	••NADPH oxidase (cytoplasmic components)
Myeloperoxidase deficiency	Absent MPO-H ₂ O ₂ system
Chédiak-Higashi syndrome	Protein involved in organelle membrane docking and fusion
<i>Acquired</i>	
Thermal injury, diabetes, malignancy, sepsis, immunodeficiencies	Chemotaxis
Hemodialysis, diabetes mellitus	Adhesion
Leukemia, anemia, sepsis, diabetes, neonates, malnutrition	Phagocytosis and microbicidal activity

Data from Gallin JI: Disorders of phagocytic cells. In Gallin JI, et al (eds): Inflammation: Basic Principles and Clinical Correlates, 2nd ed. New York, Raven Press, 1992, pp 860, 861.

Although we have emphasized the role of leukocytes recruited from the circulation in the acute inflammatory response, *cells resident in tissues also serve important functions in initiating acute inflammation*. The two most important of these cell types are *mast cells* and *tissue macrophages*. Mast cells react to physical trauma, breakdown products of complement, microbial products, and neuropeptides. The cells release histamine, leukotrienes, enzymes, and many cytokines (including TNF, IL-1, and chemokines), all of which contribute to inflammation. The functions of mast cells are discussed in more detail in Chapter 6. Macrophages recognize microbial products and secrete most of the cytokines important in acute inflammation. These cells are stationed in tissues to rapidly recognize potentially injurious stimuli and initiate the host defense reaction.

TERMINATION OF THE ACUTE INFLAMMATORY RESPONSE

It is predictable that such a powerful system of host defense, with its inherent capacity to cause tissue damage, needs tight controls to minimize the damage. In part, inflammation declines simply because the mediators of inflammation have short half-lives, are degraded after their release, and are produced in quick bursts, only as long as the stimulus persists. In addition as inflammation develops, the process also triggers a variety of stop signals that serve to actively terminate the reaction.^[42] These active mechanisms include a switch in the production of pro-inflammatory leukotrienes to anti-inflammatory lipoxins from arachidonic acid (described below); the liberation of an anti-inflammatory cytokine, transforming growth factor- β (TGF- β), from macrophages and other cells; and neural impulses (cholinergic discharge) that inhibit the production of TNF in macrophages.^[43] There are, in addition, many other controls whose existence is suspected from the phenotypes of mice in which genes encoding putative regulatory molecules have been knocked out—these mice develop uncontrolled inflammation, but precisely how the regulation works normally is not yet defined.^[42] Not surprisingly, there is great interest in defining the molecular basis

of the brakes on inflammation, since this knowledge could be used to design powerful anti-inflammatory drugs.

Chemical Mediators of Inflammation

Having described the events in acute inflammation, we can now turn to a discussion of the chemical mediators that are responsible for the events. Many mediators have been identified, and how they function in a coordinated manner is still not fully understood. Here we review general principles and highlight some of the major mediators (Fig. 2-12).

- *Mediators originate either from plasma or from cells.* Plasma-derived mediators (e.g., complement proteins, kinins) are present in plasma in *precursor forms that must be activated*, usually by a series of proteolytic cleavages, to acquire their biologic properties. Cell-derived mediators are normally *sequestered in intracellular granules* that need to be secreted (e.g., histamine in mast cell granules) or are *synthesized de novo* (e.g., prostaglandins, cytokines) in response to a stimulus. The major cellular sources are platelets, neutrophils, monocytes/macrophages, and mast cells, but mesenchymal cells (endothelium, smooth muscle, fibroblasts) and most epithelia can also be induced to elaborate some of the mediators.
- *The production of active mediators is triggered by microbial products or by host proteins, such as the proteins of the complement, kinin, and coagulation systems, that are themselves activated by microbes and damaged tissues.*
- Most mediators perform their biologic activity by initially *binding to specific receptors on target cells*. Some, however, have direct enzymatic activity (e.g., lysosomal proteases) or mediate oxidative damage (e.g., reactive oxygen and nitrogen intermediates).
- *One mediator can stimulate the release of other mediators by target cells themselves.* These secondary mediators may be identical or similar to the initial mediators but may also have opposing activities. They provide mechanisms for amplifying—or in certain instances counteracting—the initial mediator action.
- Mediators can act on one or few target cell types, have diverse targets, or may even have differing effects on different types of cells.
- *Once activated and released from the cell, most of these mediators are short-lived.* They quickly decay (e.g., arachidonic acid metabolites) or are inactivated by enzymes (e.g., kinase inactivates bradykinin), or they are otherwise scavenged (e.g., antioxidants scavenge toxic oxygen metabolites) or inhibited (e.g., complement regulatory proteins break up and degrade activated complement components). There is thus a system of checks and balances in the regulation of mediator actions.
- Most mediators have the potential to cause harmful effects.

Figure 2-12 Chemical mediators of inflammation. EC, endothelial cells.

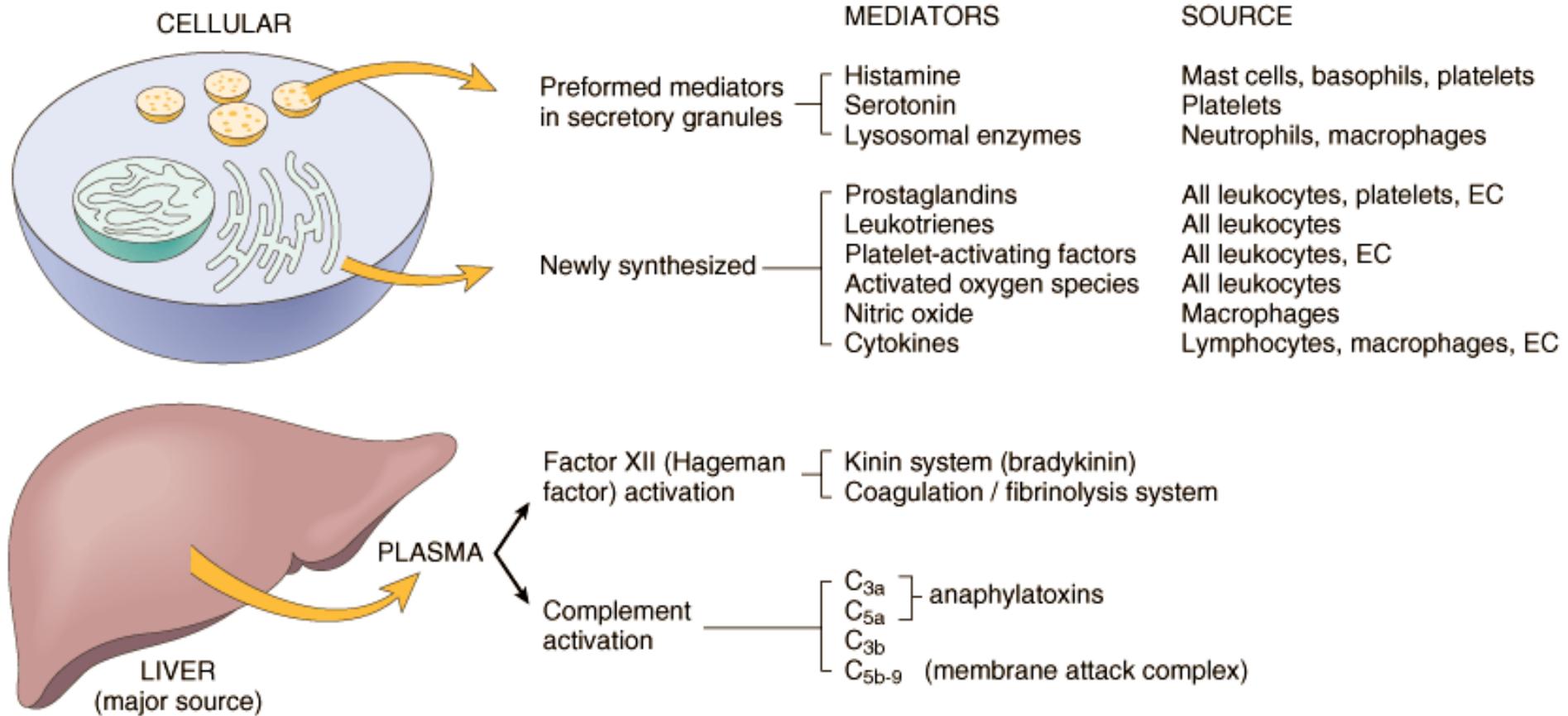
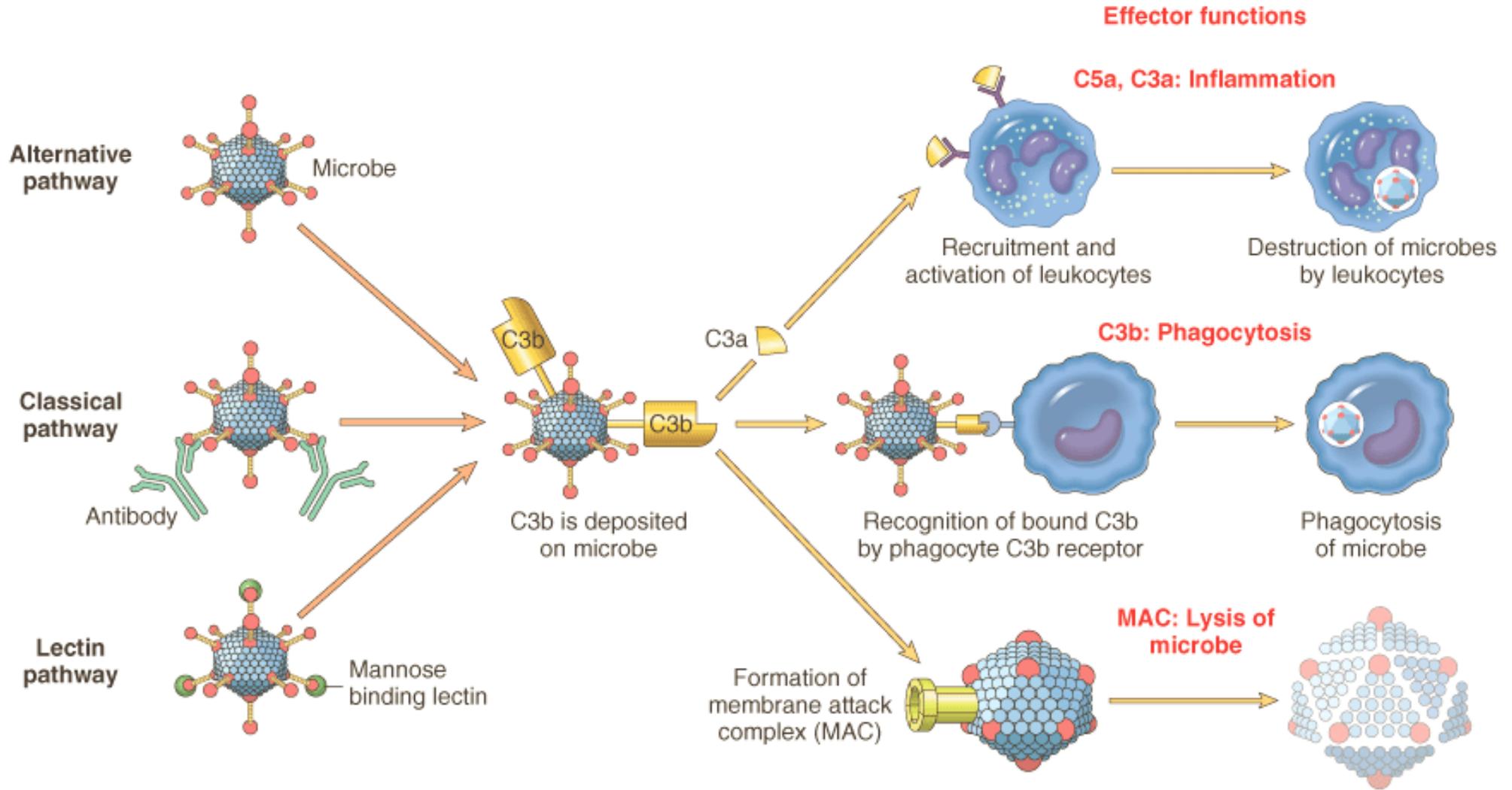


Figure 2-13 A flat spread of omentum showing mast cells around blood vessels and in the interstitial tissue. Stained with metachromatic stain to identify the mast cell granules (dark blue or purple). The red structures are fat globules stained with fat stain. (Courtesy of Dr. G. Majno, University of Massachusetts Medical School, Worcester, MA.)



Figure 2-14 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC). The steps in the activation and regulation of complement are described in Box 2-2 .



Box 2-2. The Complement System in Health and Disease

The activation of the complement cascade may be divided into early and late steps. In the early steps, three different pathways lead to the proteolytic cleavage of C3. In the late steps, all three pathways converge, and the major breakdown product of C3, C3b, activates a series of other complement components.

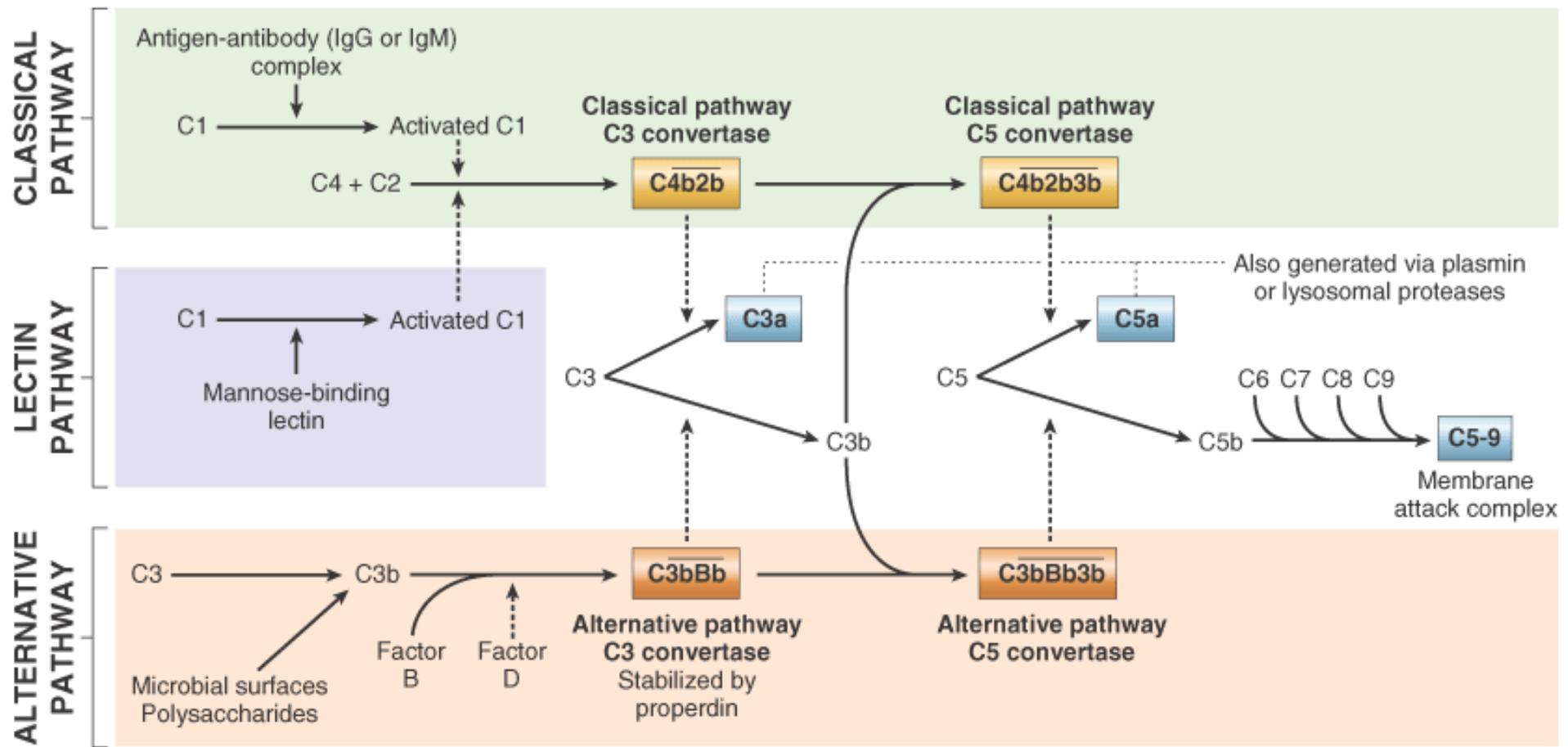
The Early Steps of Complement Activation

The pathways of early complement activation are the following (see Figure): The *classical pathway* is triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen, and proteolysis of C2 and C4, and subsequent formation of a C4b2b complex that functions as a C3 convertase. The *alternative pathway* can be triggered by microbial surface molecules (e.g., endotoxin, or LPS), complex polysaccharides, and cobra venom. It involves a distinct set of plasma components (properdin, and factors B and D). In this pathway, the spontaneous cleavage of C3 that occurs normally is enhanced and stabilized by a complex of C3b and a breakdown product of Factor B called Bb; the C3bBb complex is a C3 convertase. In the *lectin pathway*, mannose-binding lectin, a plasma collectin, binds to carbohydrate-containing proteins on bacteria and viruses and directly activates C1; the remaining steps are as in the classical pathway. The C3 convertases break down C3 into C3b, which remains attached to the surface where complement is activated, and a smaller C3a fragment that diffuses away.

The Late Steps of Complement Activation

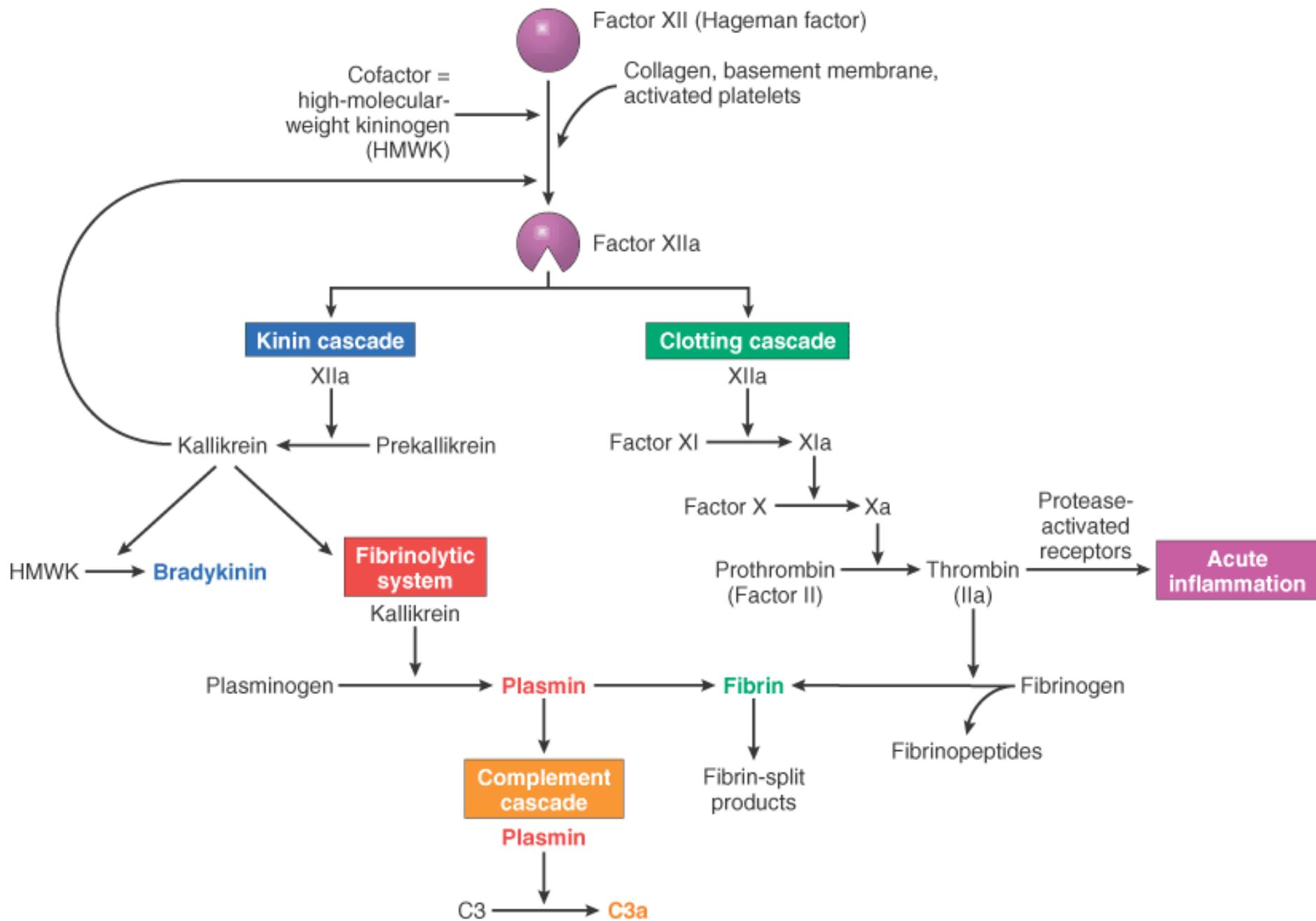
The C3b that is generated by any of the pathways binds to the C3 convertase and produces a C5 convertase, which cleaves C5. C5b remains attached to the complex and forms a substrate for the subsequent binding of the C6-C9 components. Polymerized C9 forms a channel in lipid membranes, called the

Figure 2-



receptors (PARs) because they bind multiple trypsin-like serine proteases in addition to thrombin.^[49] These receptors are seven-transmembrane G protein-coupled receptors that are expressed on platelets, endothelial and smooth muscle cells, and many other cell types. Engagement of the so-called type

Figure 2-15 Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor). Note that thrombin induces inflammation by binding to protease-activated receptors (principally PAR-1) on platelets, endothelium, smooth muscle cells, and other cells.



The prostaglandins are also involved in the pathogenesis of *pain* and *fever* in inflammation. PGE₂ is hyperalgesic in that it makes the skin hypersensitive to painful stimuli. It causes a marked increase in pain produced by intradermal injection of suboptimal concentrations of histamine and bradykinin and is involved in cytokine-induced fever during infections (described later). PGD₂ is the major metabolite of the cyclooxygenase pathway in mast cells;

along with PGE₂ and PGF_{2α} (which are more widely distributed), it causes vasodilation and increases the permeability of postcapillary venules, thus potentiating edema formation.

There has been great interest in the COX-2 enzyme because it is induced by a variety of inflammatory stimuli and is absent in most tissues under normal "resting" conditions. COX-1, by contrast, is produced in response to inflammatory stimuli and is also constitutively expressed in most tissues. This difference has led to the notion that *COX-1 is responsible for the production of prostaglandins that are involved in inflammation but also serve a homeostatic function* (e.g., fluid and electrolyte balance in the kidneys, cytoprotection in the gastrointestinal tract). In contrast, *COX-2 stimulates the production of the prostaglandins that are involved in inflammatory reactions*.

- In the *lipoxygenase pathway*, the initial products are generated by three different lipoxygenases, which are present in only a few types of cells. 5-lipoxygenase (5-LO) is the predominant enzyme in neutrophils. The main product, 5-HETE, which is chemotactic for neutrophils, is converted into a family of compounds collectively called *leukotrienes*. *LTB₄* is a potent chemotactic agent and activator of neutrophil functional responses, such as aggregation and adhesion of leukocytes to venular endothelium, generation of oxygen free radicals, and release of lysosomal enzymes. The cysteinyl-containing leukotrienes C₄, D₄, and E₄ (*LTC₄*, *LTD₄*, and *LTE₄*) cause intense vasoconstriction, bronchospasm, and increased vascular permeability. The vascular leakage, as with histamine, is restricted to venules. Leukotrienes are several orders of magnitude more potent than histamine in increasing vascular permeability and causing bronchospasm. Leukotrienes mediate their actions by binding to cysteinyl leukotriene 1 (CysLT1) and CysLT2 receptors. They are important in the pathogenesis of bronchial asthma.

- *Lipoxins* are a recent addition to the family of bioactive products generated from AA, and transcellular biosynthetic mechanisms (involving two cell populations) are key to their production. Leukocytes, particularly neutrophils, produce intermediates in lipoxin synthesis, and these are converted to lipoxins by platelets interacting with the leukocytes. Lipoxins A₄ and B₄ (*LXA₄*, *LXB₄*) are generated by the action of platelet 12-lipoxygenase on neutrophil-derived LTA₄ (Fig. 2-17). Cell-cell contact enhances transcellular metabolism, and blocking adhesion inhibits lipoxin

production. *The principal actions of lipoxins are to inhibit leukocyte recruitment and the cellular components of inflammation*. They inhibit neutrophil chemotaxis and adhesion to endothelium.^[55] There is an inverse relationship between the amount of lipoxin and leukotrienes formed, suggesting that the lipoxins may be endogenous negative regulators of leukotriene action and may thus play a role in the resolution of inflammation.

- A new class of arachidonic acid-derived mediators, called *resolvins*, have been identified in experimental animals treated with aspirin.^[54] These mediators inhibit leukocyte recruitment and activation, in part by inhibiting the production of cytokines. Thus, the anti-inflammatory activity of aspirin is likely attributable to its ability to inhibit cyclooxygenases (see below) and, perhaps, to stimulate the production of resolvins.

Figure 2-16 Generation of arachidonic acid metabolites and their roles in inflammation. The molecular targets of action of some anti-inflammatory drugs are indicated by a red X. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.

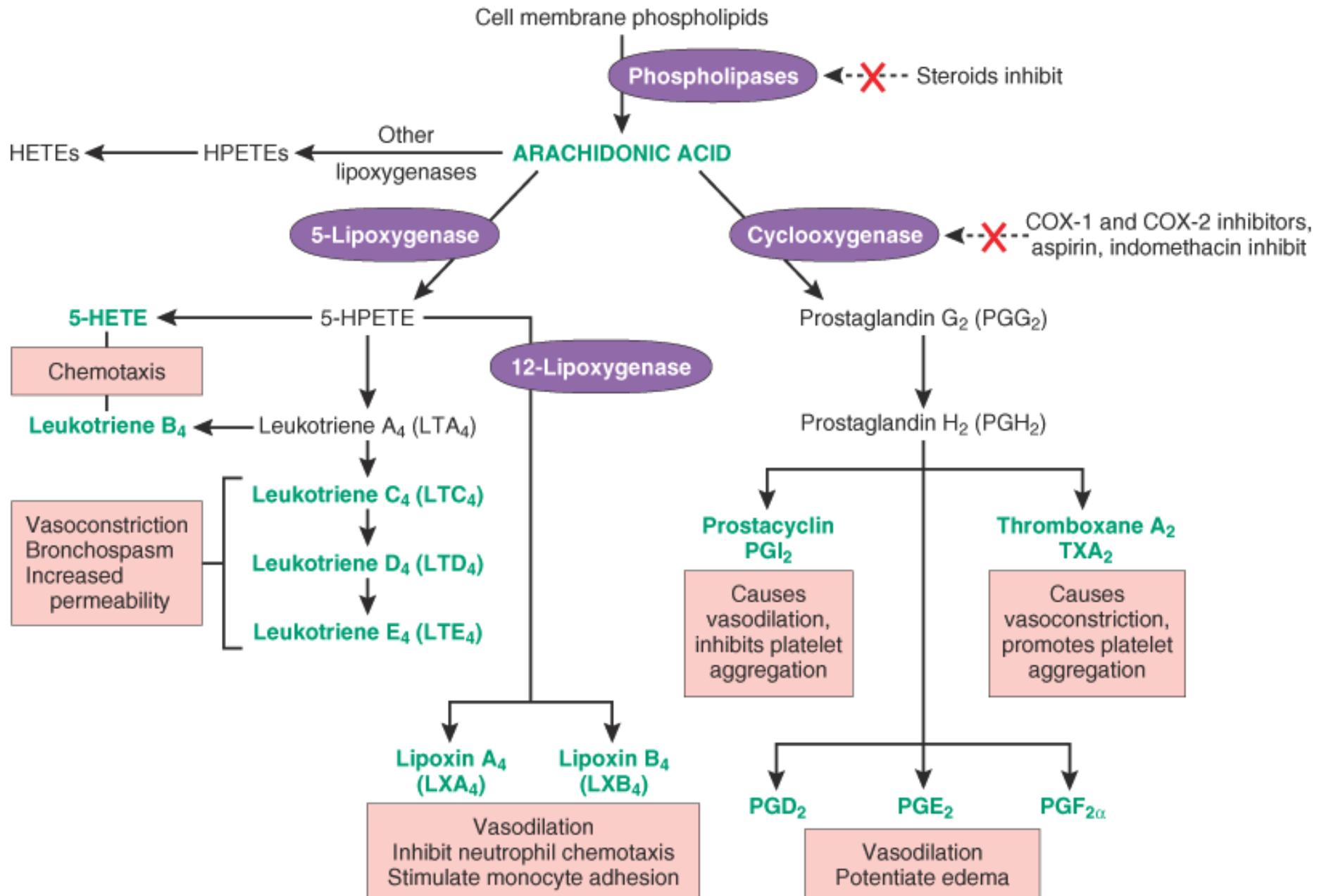


TABLE 2-4 -- Inflammatory Actions of Eicosanoids

Action	Metabolite
Vasoconstriction	Thromboxane A ₂ , leukotrienes C ₄ , D ₄ , E ₄

Vasodilation	PGI ₂ , PGE ₁ , PGE ₂ , PGD ₂
Increased vascular permeability	Leukotrienes C ₄ , D ₄ , E ₄
Chemotaxis, leukocyte adhesion	Leukotriene B ₄ , HETE, lipoxins

Figure 2-17 Biosynthesis of leukotrienes and lipoxins by cell-cell interaction. Activated neutrophils generate LTB₄ from arachidonic acid-derived LTA₄ by the action of 5-lipoxygenase, but they do not possess LTC₄ -synthase activity and consequently do not produce LTC₄ . In contrast, platelets cannot form LTC₄ from endogenous substrates, but they can generate LTC₄ and lipoxins from neutrophil-derived LTA₄ . (Courtesy of Dr. C. Serhan, Brigham and Women's Hospital, Boston, MA.)

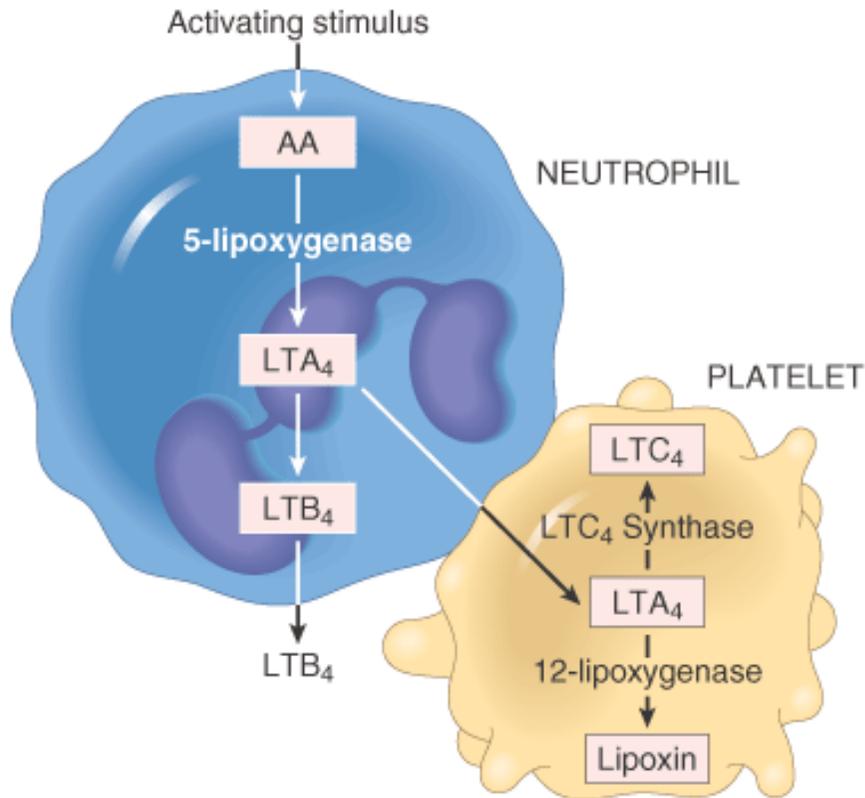


Figure 2-18 Major effects of interleukin-1 (IL-1) and tumor necrosis factor (TNF) in inflammation.

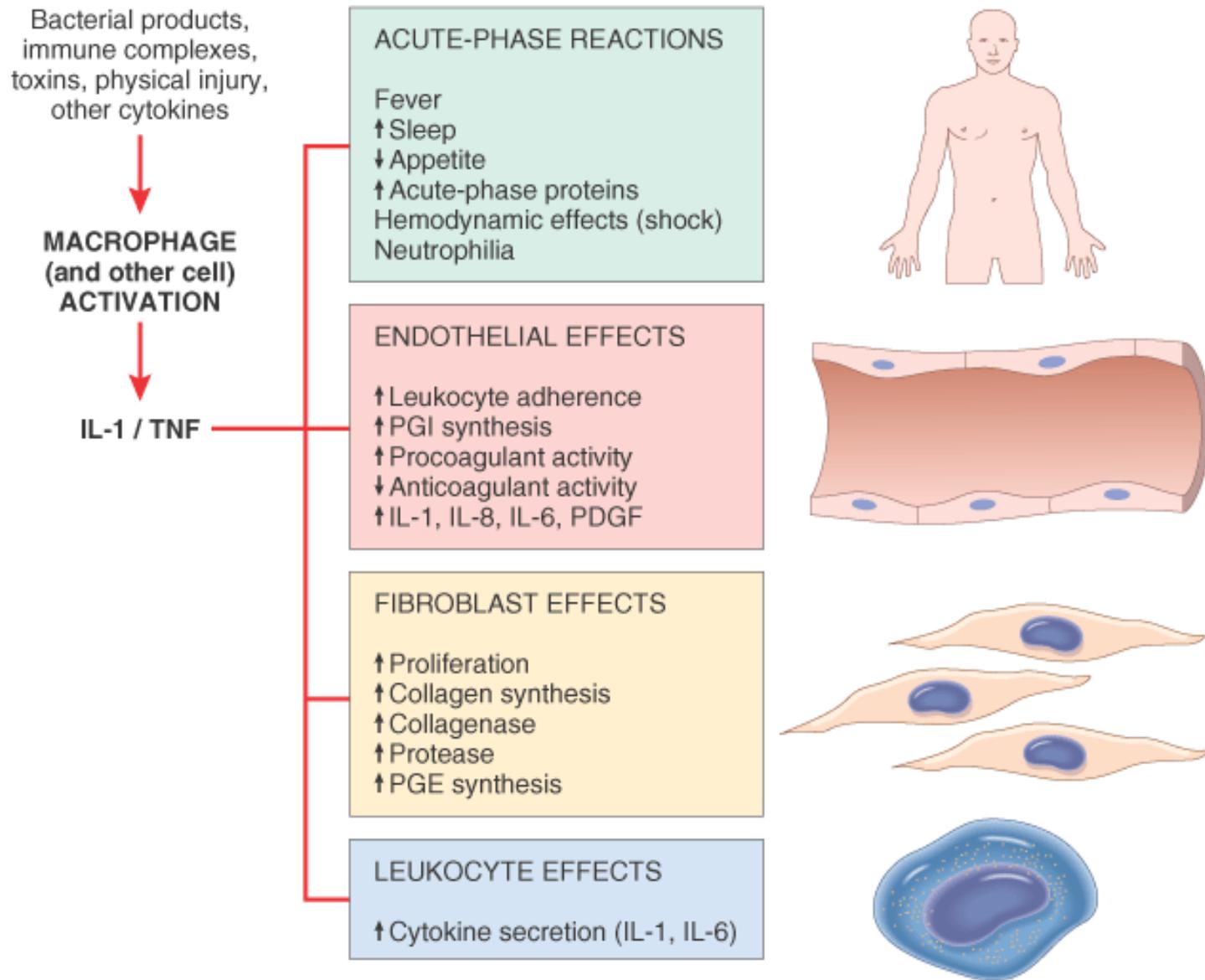


Figure 2-19 Functions of nitric oxide (NO) in blood vessels and macrophages, produced by two NO synthase enzymes. NO causes vasodilation, and NO free radicals are toxic to microbial and mammalian cells. NOS, nitric oxide synthase.

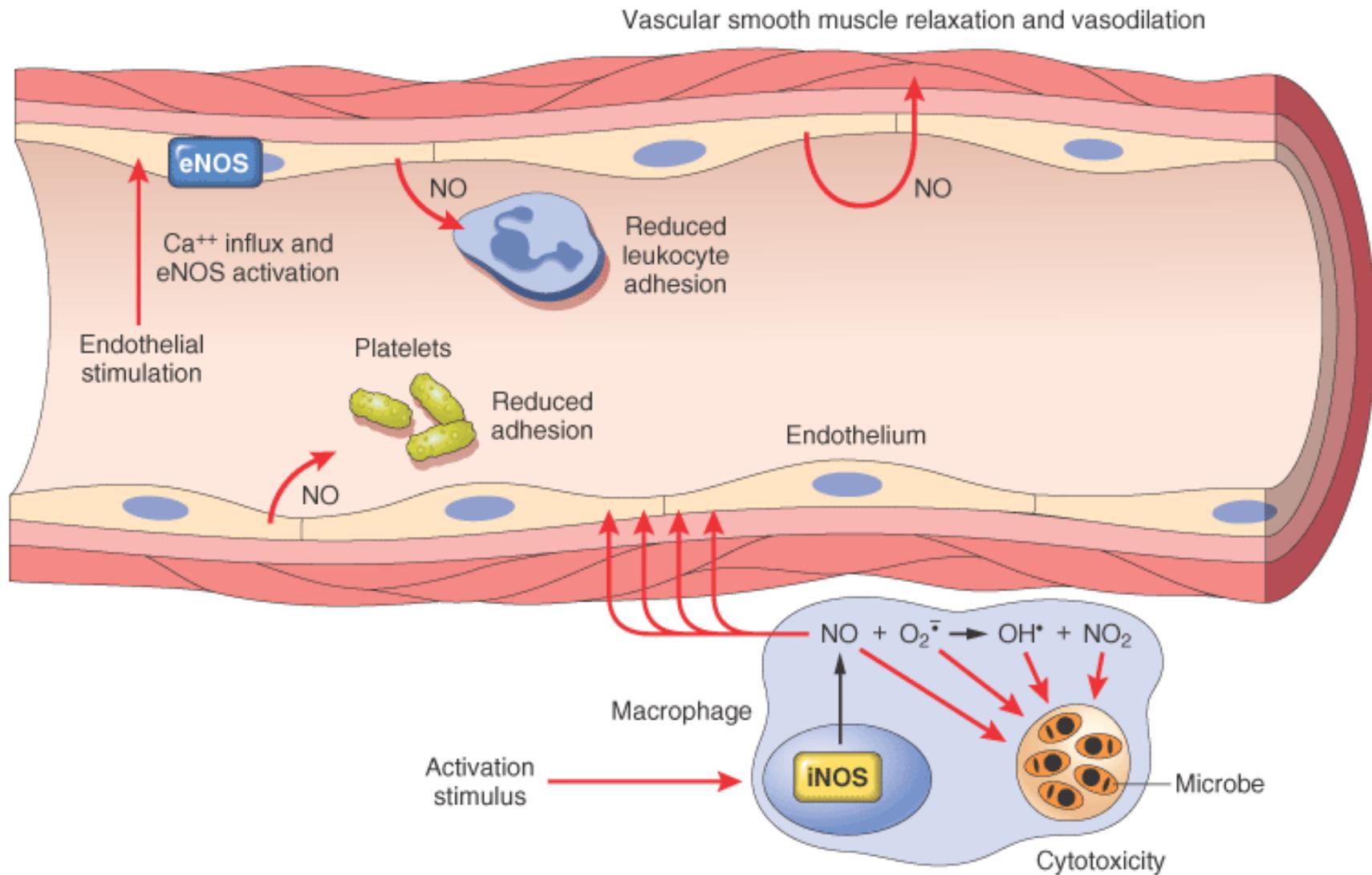
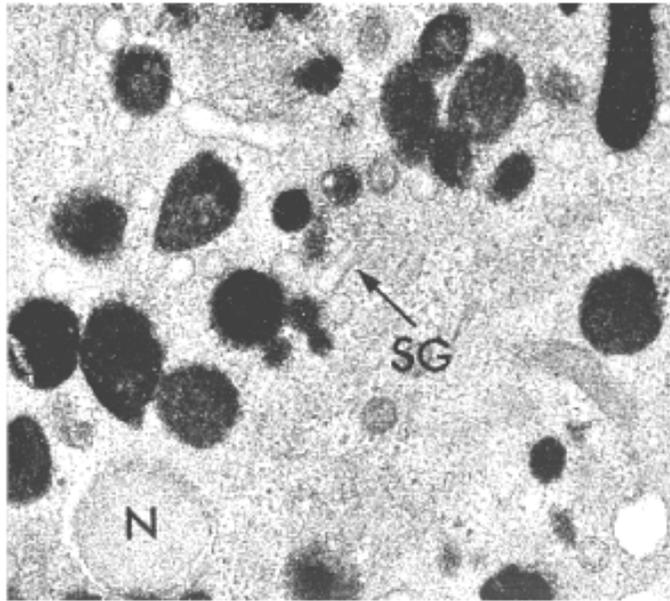


Figure 2-20 Ultrastructure and contents of neutrophil granules, stained for peroxidase activity. The large peroxidase-containing granules are the azurophil granules; the smaller peroxidase-negative ones are the specific granules (SG). N, portion of nucleus; BPI, bactericidal permeability increasing protein.



SPECIFIC GRANULES

Lactoferrin
 Lysozyme
 Alkaline phosphatase
 Type IV collagenase
 Leukocyte adhesion molecules
 Plasminogen activation
 Phospholipase A₂

AZUROPHIL GRANULES

Myeloperoxidase
 Lysozyme → Bactericidal factors
 Cationic proteins
 Acid hydrolases
 Elastase
 Nonspecific collagenase
 BPI
 Defensins
 Cathepsin G
 Phospholipase A₂

O₂⁻

), hydrogen peroxide (H₂O₂), and hydroxyl radical (OH) are the major species produced within the cell, and these metabolites can combine with NO to form other reactive nitrogen intermediates.^[70] Extracellular release of low levels of these potent mediators can increase the expression of chemokines (e.g., IL-8), cytokines, and endothelial leukocyte adhesion molecules, amplifying the cascade that elicits the inflammatory response.^[71] As mentioned earlier, the physiologic function of these reactive oxygen intermediates is to destroy phagocytosed microbes. At higher levels, release of

these potent mediators can be *damaging* to the host. They are implicated in the following responses:

- *Endothelial cell damage, with resultant increased vascular permeability.* Adherent neutrophils, when activated, not only produce their own toxic species, but also stimulate xanthine oxidation in endothelial cells themselves, thus elaborating more superoxide.
- *Inactivation of antiprotease*, such as α₁-antitrypsin. This leads to unopposed protease activity, with increased destruction of extracellular matrix.
- *Injury to other cell types* (parenchymal cells, red blood cells).

Serum, tissue fluids, and host cells possess *antioxidant mechanisms* that protect against these potentially harmful oxygen-derived radicals. These antioxidants were discussed in Chapter 1 ; they include: (1) the copper-containing serum protein *ceruloplasmin*; (2) the iron-free fraction of serum, *transferrin*; (3) the enzyme *superoxide dismutase*, which is found or can be activated in a variety of cell types; (4) the enzyme *catalase*, which detoxifies H₂O₂ ; and (5) *glutathione peroxidase*, another powerful H₂O₂ detoxifier.

Thus, the influence of oxygen-derived free radicals in any given inflammatory reaction depends on the *balance* between the production and the inactivation of these metabolites by cells and tissues.

NEUROPEPTIDES

Neuropeptides, similar to the vasoactive amines and the eicosanoids previously discussed, play a role in the initiation and propagation of an inflammatory response. The small peptides, such as *substance P* and neurokinin A, belong to a family of tachykinin neuropeptides produced in the central and peripheral nervous systems.^[72] Nerve fibers containing substance P are prominent in the lung and gastrointestinal tract. Substance P has many biologic functions, including the transmission of pain signals, regulation of blood pressure,

TABLE 2-5 -- Summary of Mediators of Acute Inflammation

Mediator	Source	Action		
		Vascular Leakage	Chemotaxis	Other
Histamine and serotonin	Mast cells, platelets	+	-	
Bradykinin	Plasma substrate	+	-	Pain
C3a	Plasma protein via liver	+	-	Opsonic fragment (C3b)
C5a	Macrophages	+	+	Leukocyte adhesion, activation
Prostaglandins	Mast cells, from membrane phospholipids	Potentiate other mediators	-	Vasodilation, pain, fever
Leukotriene B ₄	Leukocytes	-	+	Leukocyte adhesion, activation
Leukotriene C ₄ , D ₄ , E ₄	Leukocytes, mast cells	+	-	Bronchoconstriction, vasoconstriction
Oxygen metabolites	Leukocytes	+	-	Endothelial damage, tissue damage
PAF	Leukocytes, mast cells	+	+	Bronchoconstriction, leukocyte priming
IL-1 and TNF	Macrophages, other	-	+	Acute-phase reactions, endothelial activation
Chemokines	Leukocytes, others	-	+	Leukocyte activation
Nitric oxide	Macrophages, endothelium	+	+	Vasodilation, cytotoxicity

stimulation of secretion by endocrine cells, and increasing vascular permeability.^[73] Sensory neurons appear to produce other pro-inflammatory molecules, which are thought to link the sensing of dangerous stimuli to the development of protective host responses.^[74]

OTHER MEDIATORS

The mediators described above account for inflammatory reactions to microbes, toxins, and many types of injury, but may not explain why inflammation develops in some specific situations. Recent studies are providing clues about the mechanisms of inflammation in two frequently encountered pathologic conditions.

- *Response to hypoxia.* In Chapter 1 we described the role of hypoxia in causing cell injury and necrosis. Hypoxia by itself is also an inducer of the inflammatory response. This response is mediated largely by a protein called hypoxia-induced factor 1 α , which is produced by cells deprived of oxygen and activates many genes involved in inflammation, including VEGF, which increases vascular permeability.^[75]
- *Response to necrotic cells.* Although it has been known for many years that necrotic cells elicit inflammatory reactions that serve to eliminate these cells, the molecular basis of this reaction has been largely unknown. One participant may be uric acid, which is a product of DNA breakdown, and crystallizes when present at sufficiently high concentrations in extracellular tissues. Uric acid crystals stimulate inflammation and subsequent immune response.^[76] This proinflammatory action of uric acid is the basis of the disease gout, in which excessive amounts of uric acid are produced and crystals deposit in joints and other tissues.

SUMMARY OF CHEMICAL MEDIATORS OF ACUTE INFLAMMATION

Table 2-5 summarizes the major actions of the principal mediators. When Lewis discovered the role of histamine in

inflammation, one mediator was thought to be enough. Now, we are wallowing in them! Yet, from this menu of substances we can emphasize a few mediators that may be particularly relevant in vivo (Table 2-6). Vasodilation, an early event in inflammation, is caused by histamine, prostaglandins, and nitric oxide. Increased vascular permeability is caused by histamine; the anaphylatoxins (C3a and C5a); the kinins; leukotrienes C, D, and E; PAF; and substance P. For chemotaxis, the most likely contributors are complement fragment C5a, lipoxygenase products (LTB₄), and chemokines. Prostaglandins play an important role in vasodilation, pain, and fever, and in potentiating edema. IL-1 and TNF are critical for endothelial-leukocyte interactions and subsequent leukocyte recruitment, and for the production of acute-phase reactants. Lysosomal products and oxygen-derived radicals are the most likely candidates responsible for the ensuing tissue destruction. NO is involved in vasodilation and also causes tissue damage.

Outcomes of Acute Inflammation

The discussion of mediators completes the description of the basic, relatively uniform pattern of the inflammatory reaction encountered in most injuries. Although hemodynamic, permeability, and leukocyte changes have been described sequentially and may be initiated in this order, all these phenomena may be concurrent in the fully evolved reaction to injury. As might be expected, many variables may modify this basic process, including the nature and intensity of the injury,

Figure 2-21 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation (see text).

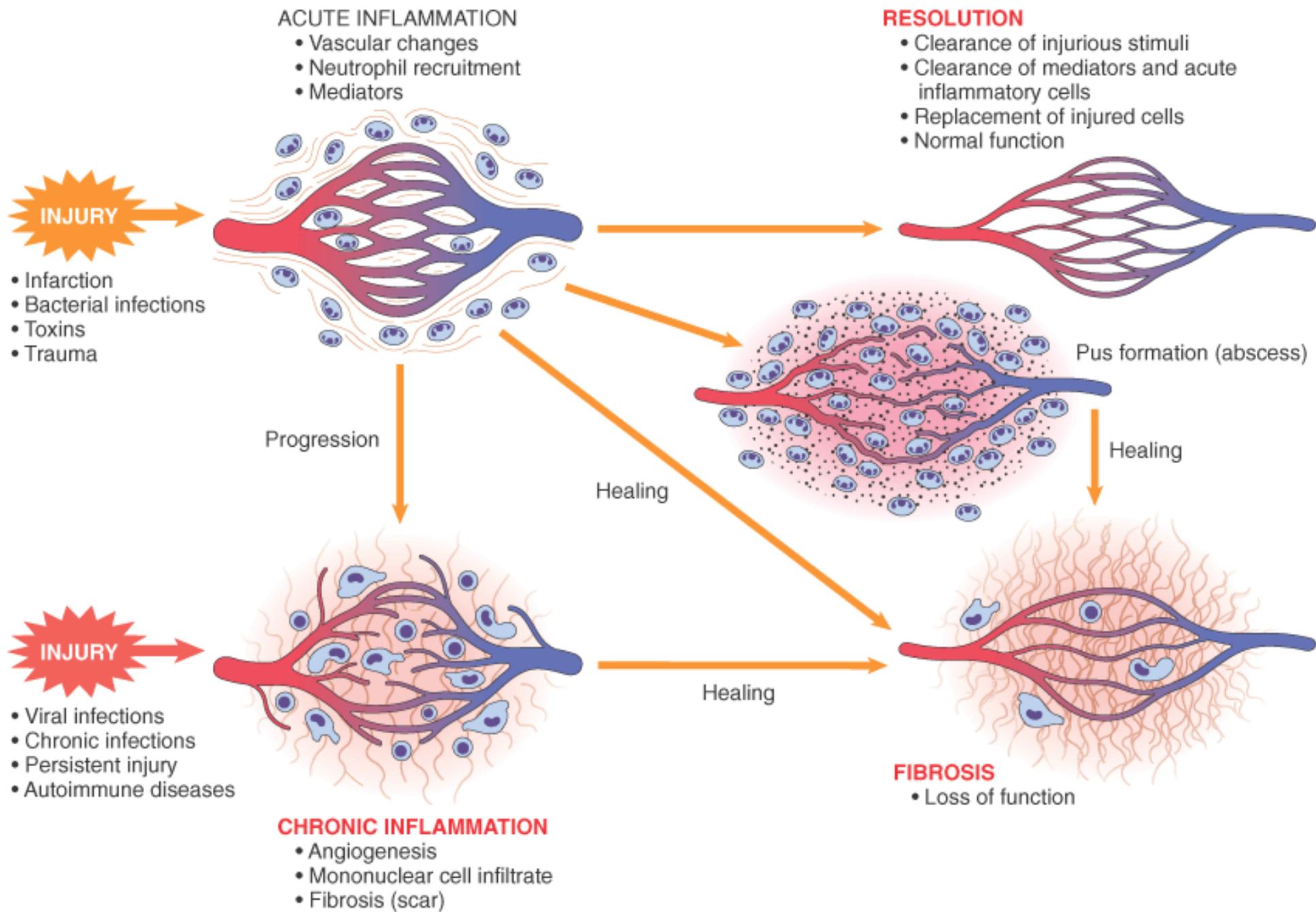


TABLE 2-6 -- Role of Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins
	Nitric oxide

	Histamine
Increased vascular permeability	Vasoactive amines
	C3a and C5a (through liberating amines)
	Bradykinin
	Leukotrienes C ₄ , D ₄ , E ₄
	PAF
	Substance P
Chemotaxis, leukocyte recruitment and activation	C5a
	Leukotriene B ₄
	Chemokines
	IL-1, TNF
	Bacterial products
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes
	Oxygen metabolites
	Nitric oxide

the site and tissue affected, and the responsiveness of the host. In general, however, *acute inflammation may have one of three outcomes* (Fig. 2-21):

1. *Complete resolution.* In a perfect world, all inflammatory reactions, once they have succeeded in neutralizing and eliminating the injurious stimulus, should end with restoration of the site of acute inflammation to normal. This is called *resolution* and is the usual outcome when the injury is limited or short-lived or when there has been little tissue destruction and the damaged parenchymal cells can regenerate. Resolution involves neutralization or spontaneous decay of the chemical mediators, with subsequent return of normal vascular permeability, cessation of leukocytic infiltration, death (largely by apoptosis) of neutrophils, and finally removal of edema fluid and protein, leukocytes, foreign agents, and necrotic debris from the site (Fig. 2-22). Lymphatics and phagocytes play a role in these events, as described later in this Chapter and in Chapter 3 .
2. *Healing by connective tissue replacement (fibrosis).* This occurs after substantial tissue destruction, when the inflammatory injury involves tissues that are incapable of regeneration, or when there is abundant fibrin exudation. When the fibrinous exudate in tissue or serous cavities (pleura, peritoneum) cannot be adequately cleared, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue—a process also called *organization*. In many pyogenic infections there may be intense neutrophil infiltration and

liquefaction of tissues, leading to pus formation. The destroyed tissue is resorbed and eventually replaced by fibrosis.

3. Progression of the tissue response to *chronic inflammation* (discussed below). This may follow acute inflammation, or the response may be chronic almost from the onset. Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, owing either to the persistence of the injurious agent or to some interference with the normal process of healing. For example, bacterial infection of the lung may begin as a focus of acute inflammation (pneumonia), but its failure to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to a chronic lung abscess. Another example of chronic inflammation with a persisting stimulus is peptic ulcer of the duodenum or stomach. Peptic ulcers may persist for months or years and, as discussed below, are manifested by both acute and chronic inflammatory reactions.

Figure 2-22 Events in the resolution of inflammation: (1) return to normal vascular permeability; (2) drainage of edema fluid and proteins into lymphatics or (3) by pinocytosis into macrophages; (4) phagocytosis of apoptotic neutrophils and (5) phagocytosis of necrotic debris; and (6) disposal of macrophages. Macrophages also produce growth factors that initiate the subsequent process of repair. Note the central role of macrophages in resolution. (Modified from Haslett C, Henson PM: In Clark R, Henson PM (eds): *The Molecular and Cellular Biology of Wound Repair*. New York, Plenum Press, 1996.)

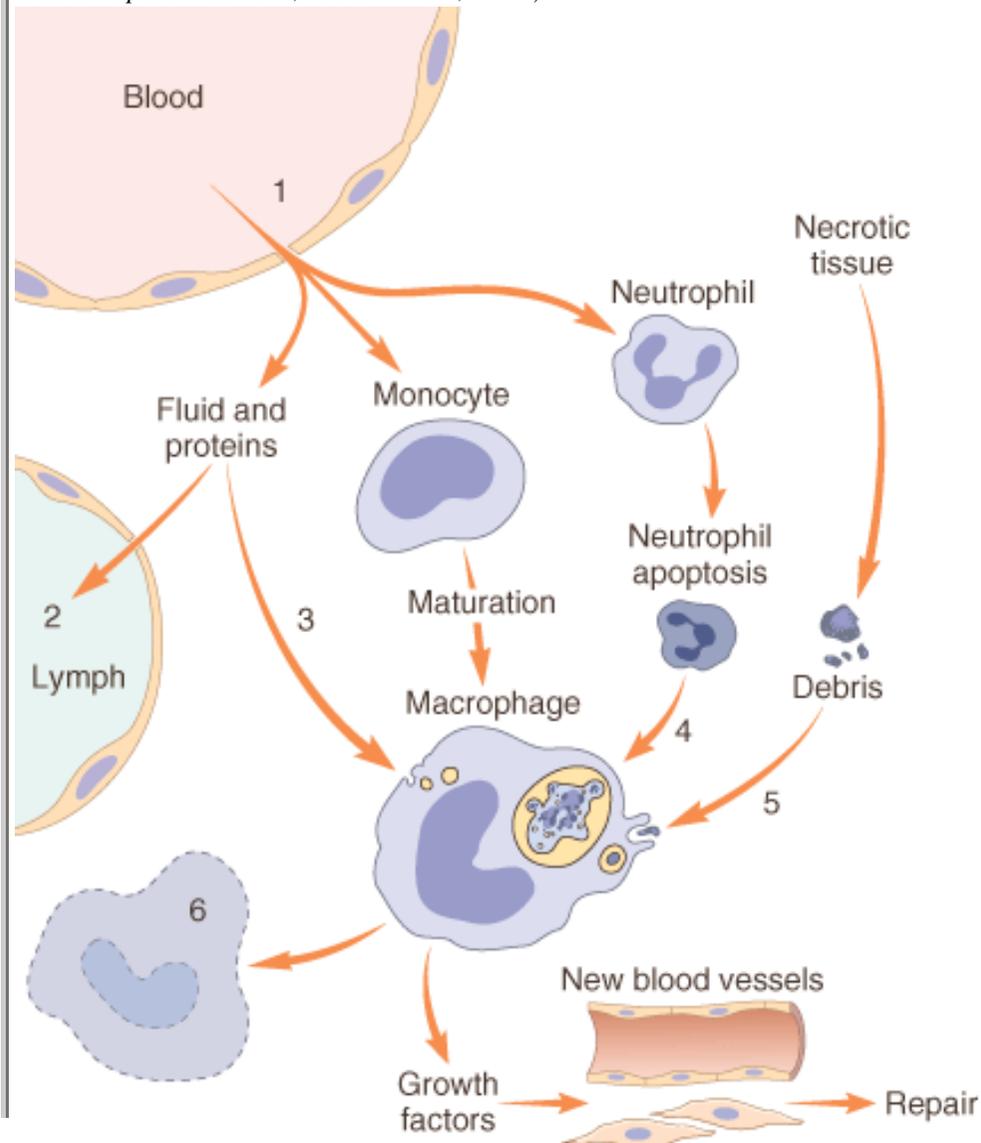




Figure 2-23 Serous inflammation. Low-power view of a cross-section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

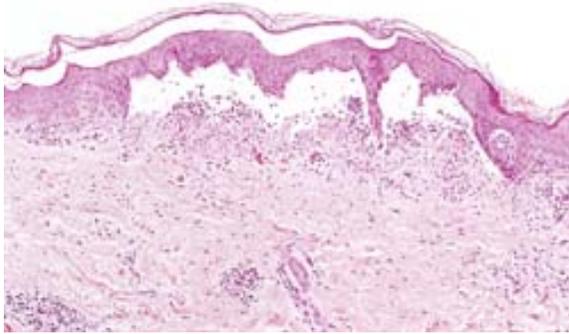


Figure 2-24 Fibrinous pericarditis. *A*, Deposits of fibrin on the pericardium. *B*, A pink meshwork of fibrin exudate (F) overlies the pericardial surface (P).

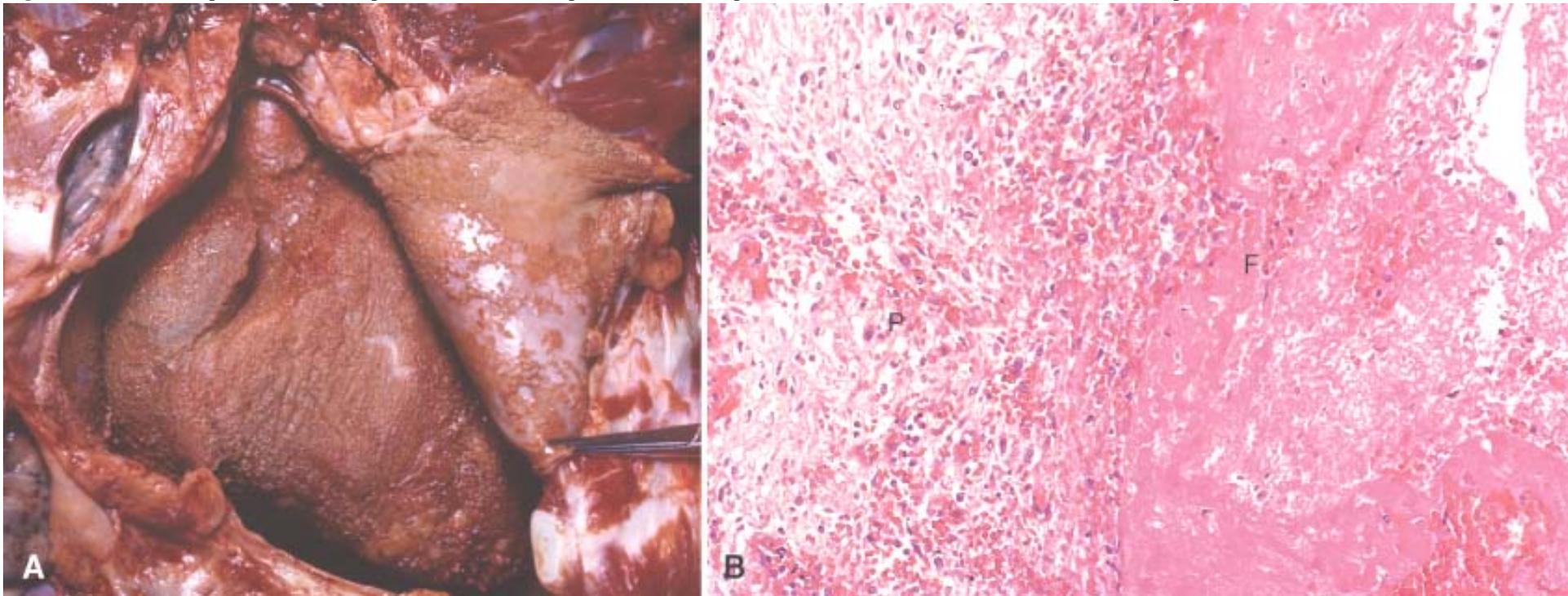


Figure 2-25 Suppurative inflammation. *A*, A subcutaneous bacterial abscess with collections of pus. *B*, The abscess contains neutrophils, edema fluid, and cellular debris.

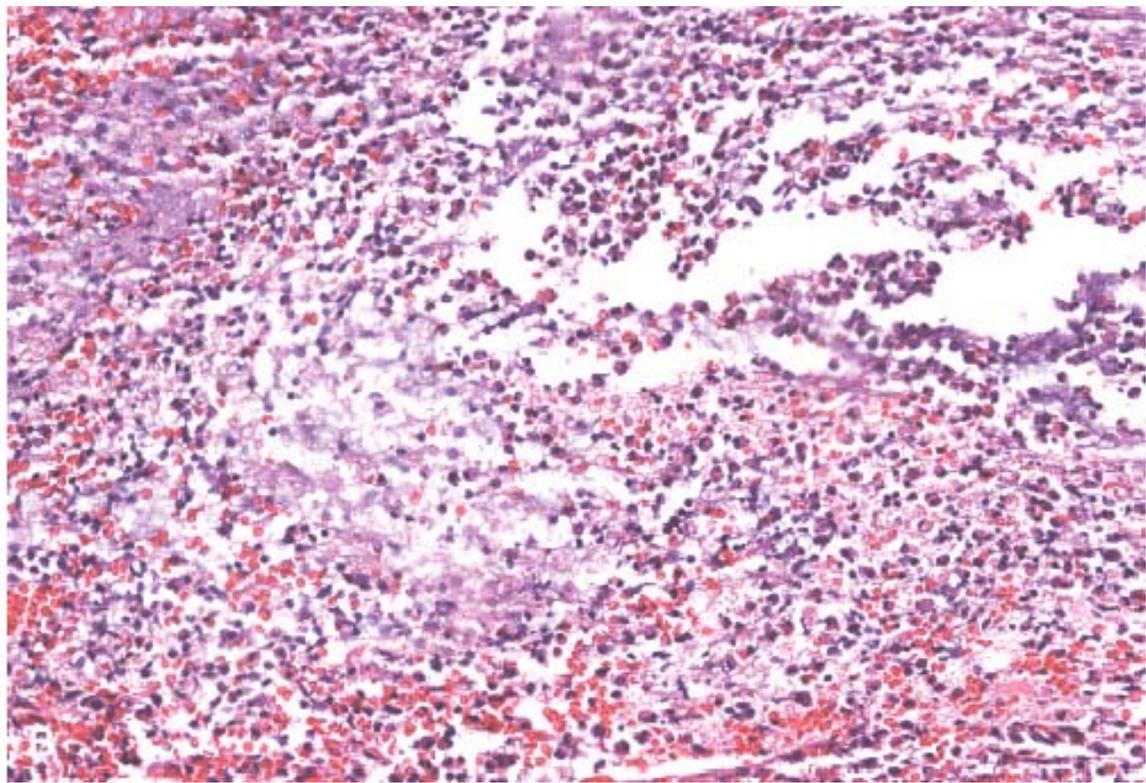


Figure 2-26 The morphology of an ulcer. *A*, A chronic duodenal ulcer. *B*, Low-power cross-section of a duodenal ulcer crater with an acute inflammatory exudate in the base.

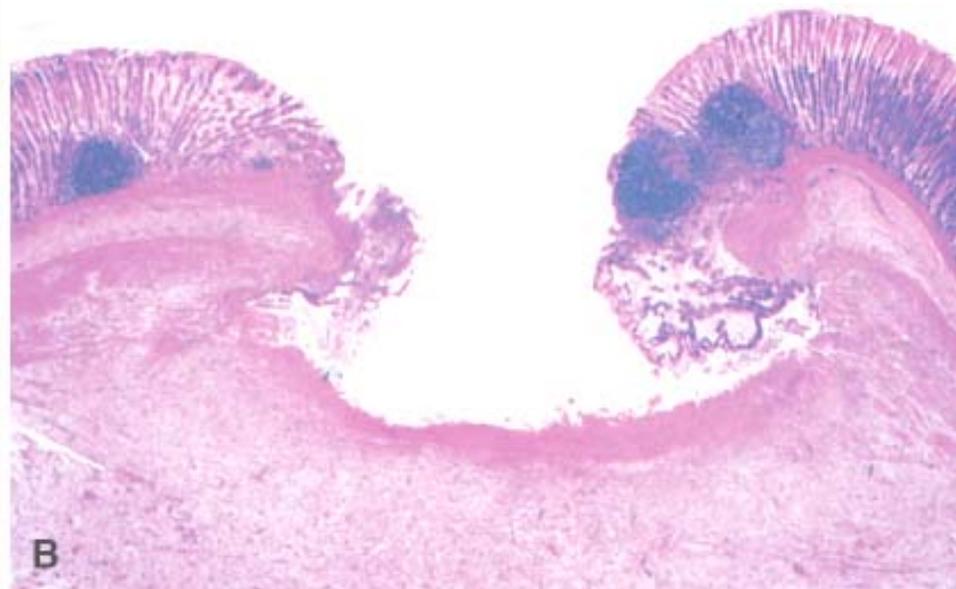


Figure 2-27 Maturation of mononuclear phagocytes. (From Abbas AK, et al: *Cellular and Molecular Immunology*, 5th ed. Philadelphia, Saunders, 2003.)

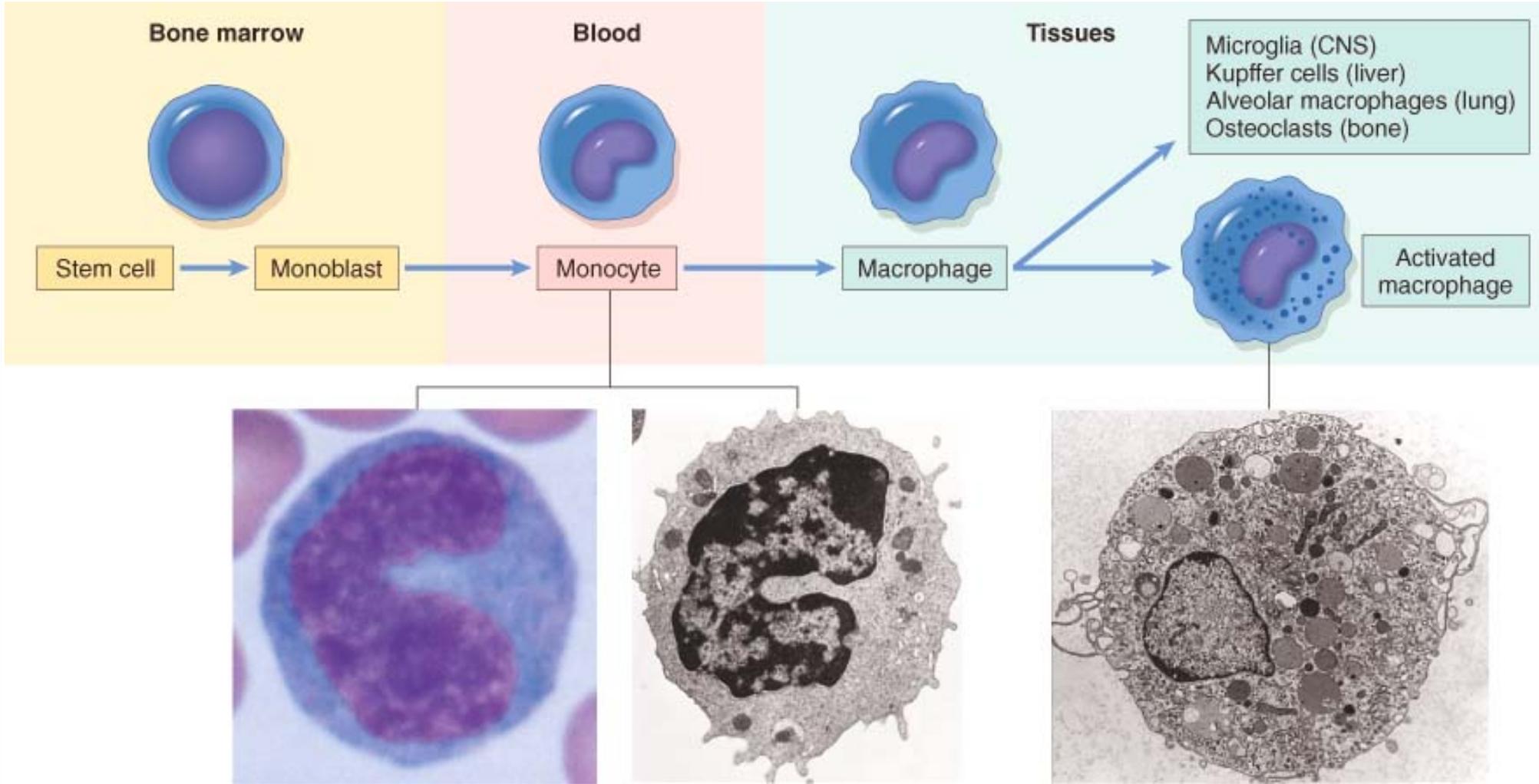


Figure 2-28 The roles of activated macrophages in chronic inflammation. Macrophages are activated by cytokines from immune-activated T cells (particularly IFN- γ) or by nonimmunologic stimuli such as endotoxin. The products made by activated macrophages that cause tissue injury and fibrosis are indicated. AA, arachidonic acid; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; TGF β , transforming growth factor β .

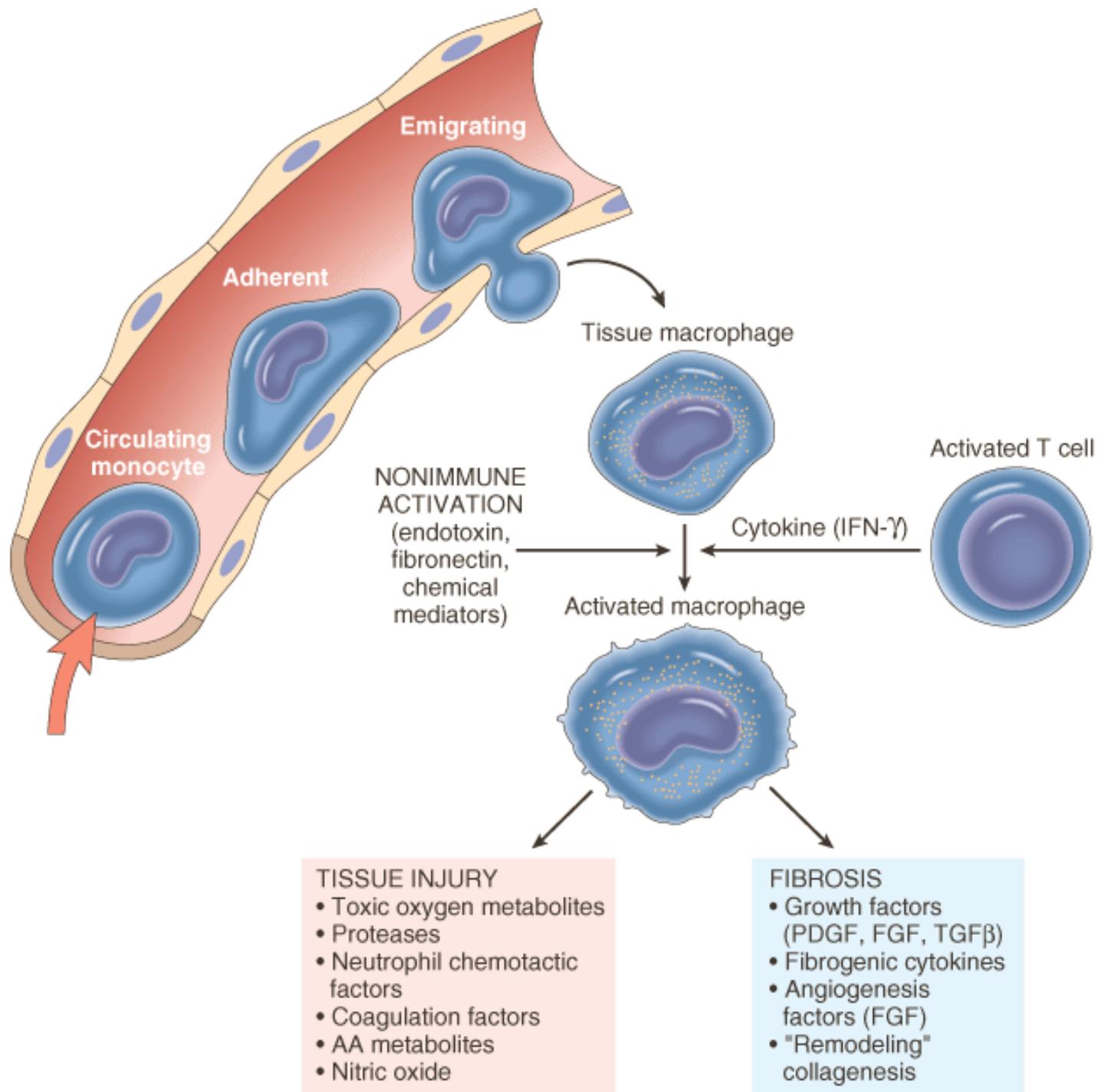


Figure 2-29 A, Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, *arrowheads*), and (3) replacement by connective tissue (fibrosis, *arrows*). B, By contrast, in acute inflammation of the lung (acute

bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

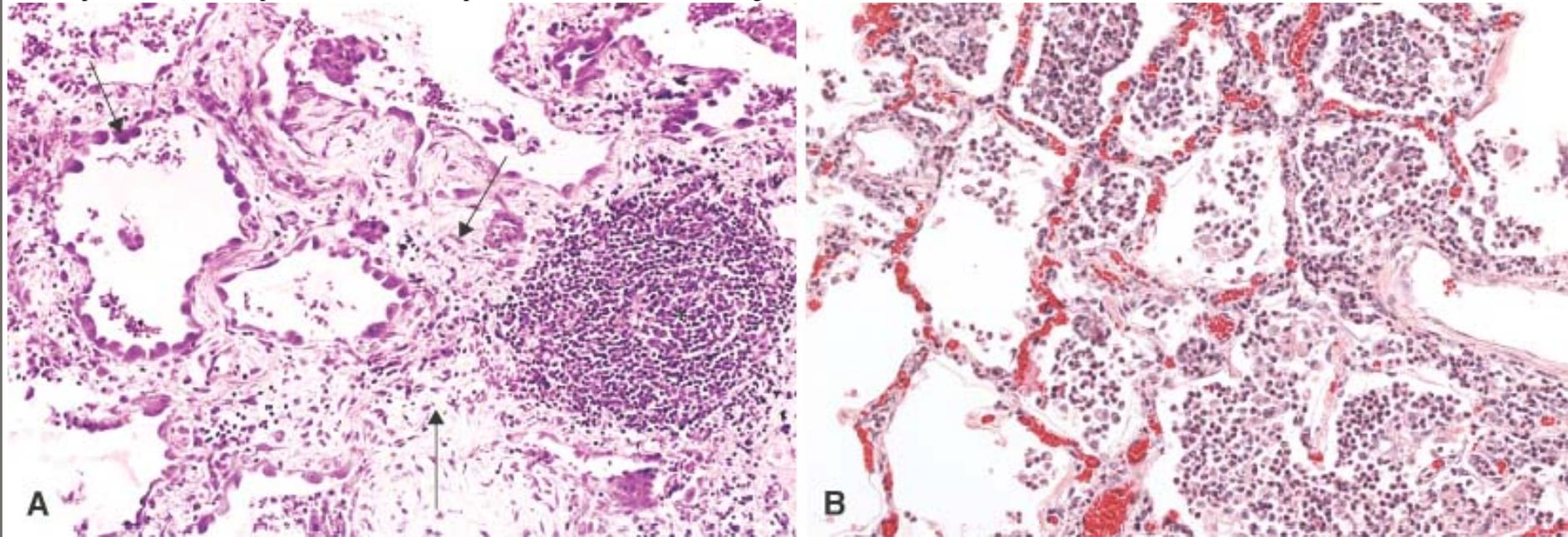
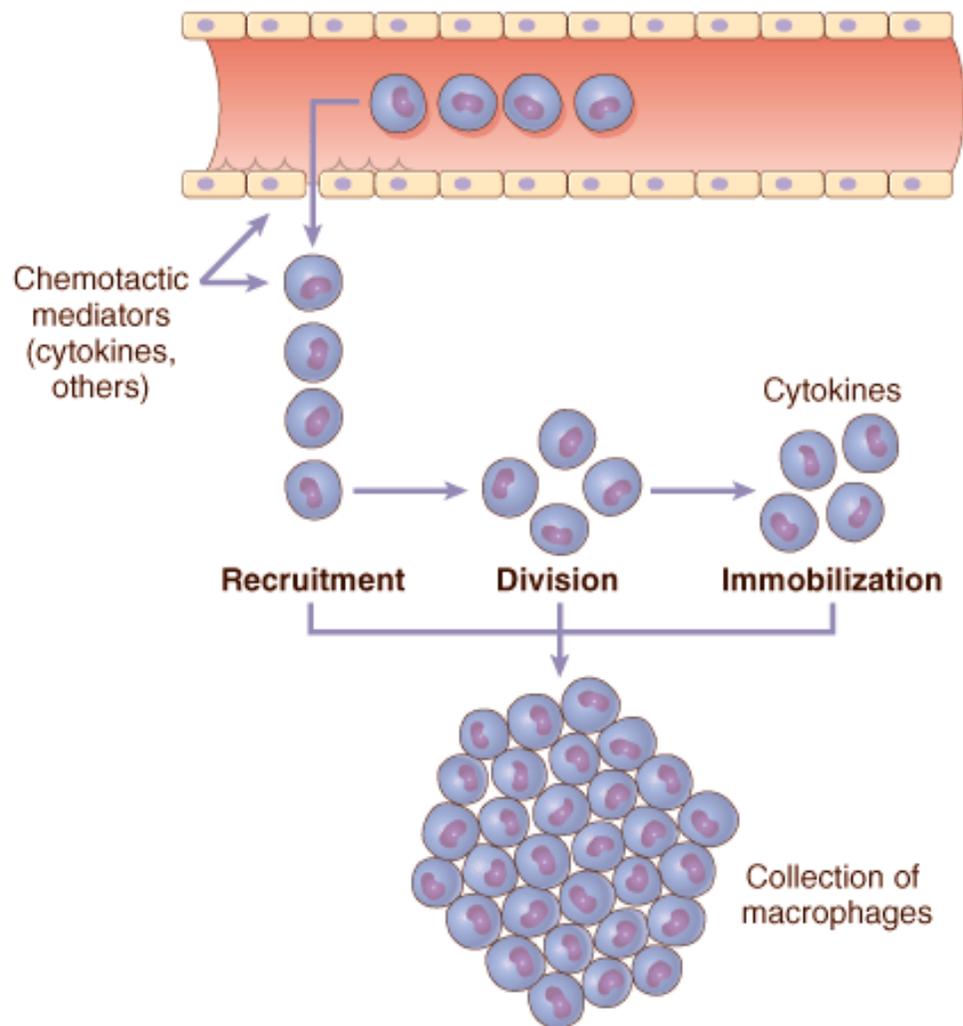


Figure 2-30 Mechanisms of macrophage accumulation in tissues. The most important is continued recruitment from the microcirculation. (*Adapted from Ryan G, Majno G: Inflammation. Kalamazoo, MI, Upjohn, 1977.*)



Lymphocytes and macrophages interact in a bidirectional way, and these reactions play an important role in chronic inflammation (Fig. 2-31). Macrophages display antigens to T cells, and produce membrane molecules (costimulators) and cytokines (notably IL-12) that stimulate T-cell responses (Chapter 6). Activated T lymphocytes produce cytokines, and one of these, IFN- γ , is a major activator of macrophages. *Plasma cells* develop from activated B lymphocytes and produce antibody directed either against persistent antigen in the inflammatory site or against altered tissue components. In some strong chronic inflammatory reactions, the accumulation of lymphocytes, antigen-presenting cells, and

plasma cells may assume the morphologic features of lymphoid organs, particularly lymph nodes, even containing well-formed germinal centers. This pattern of *lymphoid organogenesis* is often seen in the synovium of patients with long-standing rheumatoid arthritis.

- *Eosinophils* are abundant in immune reactions mediated by IgE and in parasitic infections (Fig. 2-32). The recruitment of eosinophils involves extravasation from the blood and their migration into tissue by processes similar to those for other leukocytes. One of the chemokines that is especially important for eosinophil recruitment is eotaxin. Eosinophils have granules that contain *major basic protein*, a highly cationic protein that is toxic to parasites but also causes lysis of mammalian epithelial cells. They may thus be of benefit in controlling

parasitic infections but they contribute to tissue damage in immune reactions (Chapter 6).^[79]

• *Mast cells* are widely distributed in connective tissues and participate in both acute and persistent inflammatory reactions. Mast cells express on their surface the receptor that binds the Fc portion of IgE antibody (FcεRI). In acute reactions, IgE antibodies bound to the cells' Fc receptors specifically recognize antigen, and the cells degranulate and release mediators, such as histamine and products of AA oxidation (Chapter 6). This type of response occurs during anaphylactic reactions to foods, insect venom, or drugs, frequently with catastrophic results. When properly regulated, this response can benefit the host. Mast cells are also present in chronic inflammatory reactions, and may produce cytokines that contribute to fibrosis.

Figure 2-31 Macrophage-lymphocyte interactions in chronic inflammation. Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

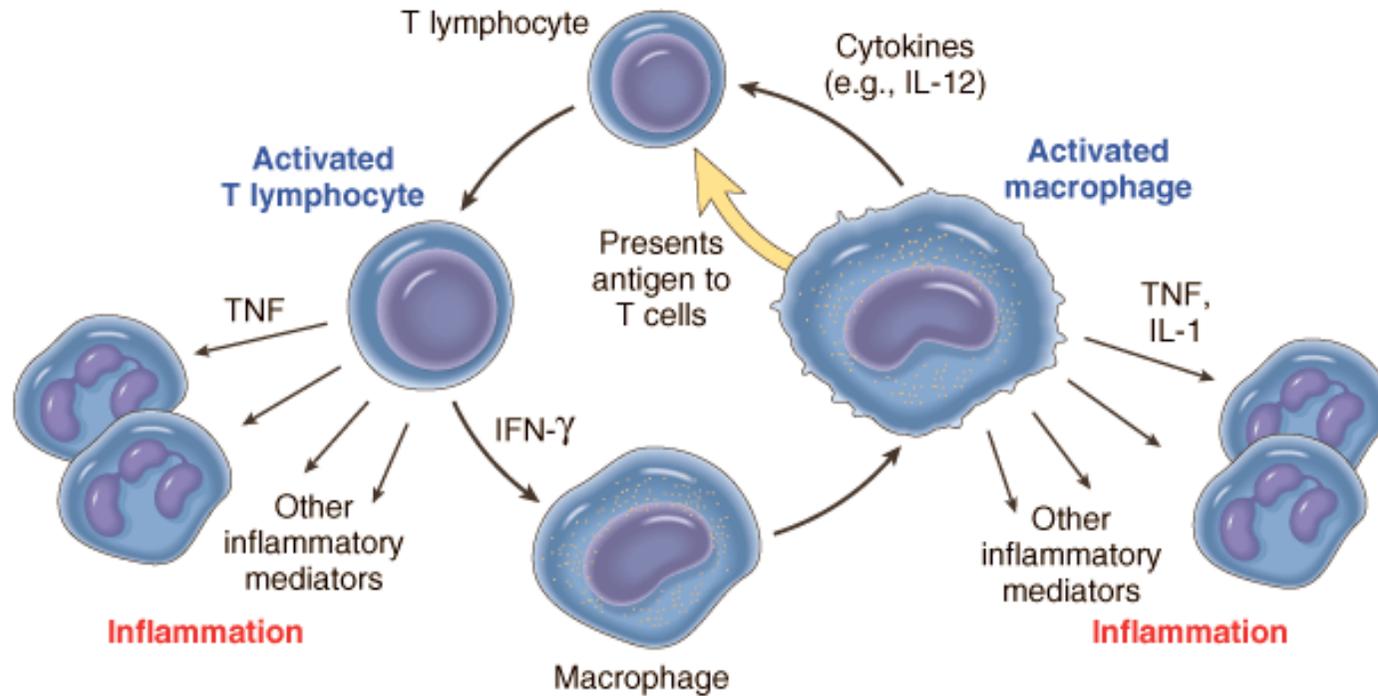


Figure 2-32 A focus of inflammation showing numerous eosinophils.

