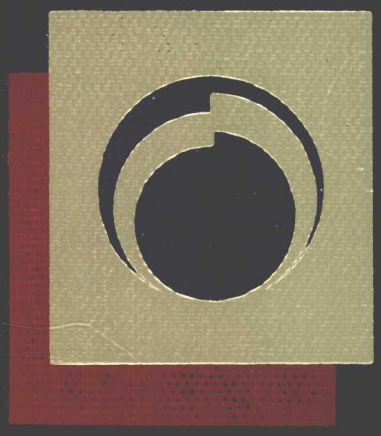
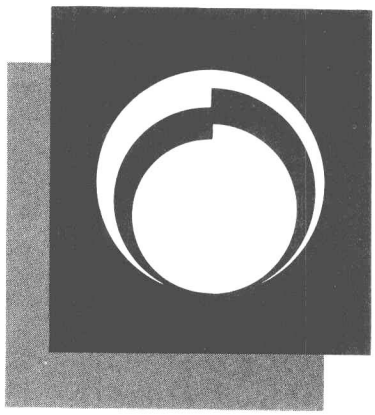
Robbins Pathologic Basis of Disease



Cotran
Kumar
Robbins

4th Edition

ROBBINS PATHOLOGIC BASIS OF DISEASE



RAMZI S. COTRAN, M.D.
Frank Burr Mallory Professor of Pathology
Harvard Medical School
Chairman, Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

VINAY KUMAR, M.D.
Charles T. Ashworth Professor of Pathology
Southwestern Medical School
The University of Texas
Southwestern Medical Center at Dallas
Dallas, Texas

STANLEY L. ROBBINS, M.D.
Visiting Professor of Pathology
Harvard Medical School
Senior Pathologist
Brigham and Women's Hospital
Boston, Massachusetts

4th Edition

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
Philadelphia ■ London ■ Toronto ■ Montreal ■ Sydney ■ Tokyo

W.B. SAUNDERS COMPANY
A Division of
Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data
Robbins, Stanley L. (Stanley Leonard), 1915–
[Pathologic basis of disease]
Robbins' pathologic basis of disease.—4th ed./Ramzi S.
Cotran, Vinay Kumar, Stanley L. Robbins.
p. cm.
Rev. ed. of: Pathologic basis of disease. 3rd ed./Stanley L.
Robbins, Ramzi S. Cotran, Vinay Kumar. 1984.
Includes bibliographies and index.
ISBN 0-7216-2302-6
1. Pathology. I. Cotran, Ramzi S., 1932– . II. Kumar, Vinay.
III. Title. IV. Title: Pathologic basis of disease.
[DNLM:- 1. Pathology. QZ 4 R634p]
RB111.R62 1989
616.07—dc20
DNLM/DLC
for Library of Congress 89-6261
CIP

Listed here are the latest translated editions of this book together with the language of the translation and the publisher.

Portuguese *(4th edition)*—Editora Guanabara Koogan S.A., Rio de Janeiro, Brazil

Spanish *(4th edition)*—2 volumes, McGraw-Hill Interamericana de Espana, Madrid, Spain

Yugoslavian *(1st edition)*—Serbo-Croat, Skolska Knjiga, Zagreb, Yugoslavia

Italian *(3rd edition)*—Piccin Nuova Libraria S.p.A., Padova, Italy

French *(2nd edition)*—Piccin Nuova Libraria S.p.A., Padova, Italy

Persian *(3rd edition)*—Sherkat Sahami TCHEHR, Tehran, Iran

Editor: W. B. Saunders Staff
Developmental Editor: Linda Mills
Designer: W. B. Saunders Staff
Production Manager: Carolyn Naylor
Manuscript Editor: Constance Burton
Staff Illustrators: Karen Giacomucci, Risa Clow, Glenn Edelmayer, Sharon Iwanczuk
Illustration Coordinator: Brett MacNaughton
Indexer: Ann Cassar

Robbins Pathologic Basis of Disease ISBN 0-7216-2302-6

Last digit is the print number: 9 8 7

To
Kerstin
To
Raminder
and to
Elly
with love

Preface

THE DATABASE OF biomedical knowledge, as all interested observers know, is expanding at an astonishing rate. Witness the growth of molecular genetics and its rapid application to the understanding and diagnosis of disease; the growing awareness of the complexity of regulatory circuits governing the immune response and inflammation; and the penetrations that have been made into the roles of oncogenes and antioncogenes in the origins of cancer. Any textbook of pathology, then, requires revision periodically if it is to keep abreast of this deluge of new information.

Our major goals for this edition are:

- To bring to the bedside the remarkable advances that have been made in the understanding of the biomolecular origins of disease, drawing on the most recent reports (as the abundant references will attest) as well as the standard classics.
- To present accurately and clearly the dynamics and development of clinical diseases from their very beginnings (i.e., etiology and pathogenesis), through the dysfunctions caused by lesions, to the clinical implications.
- To devote space to subjects in proportion to their clinical importance or biologic relevance to fundamental processes, providing complete discussions of the significant conditions without permitting the book to become unwieldy.
- To maintain the essential morphologic descriptions that represent the backbone of pathology, incorporating the current molecular, immunologic, and other techniques that enhance accurate interpretation of the pathogenesis and diagnosis of lesions.
- Above all, to be meticulous about the organization and clarity of the writing, recognizing that readability illuminates a text and enhances understanding and learning.

Only the users of this book can tell to what extent these goals have been met, but such shortfalls as may exist surely cannot stem from lack of trying.

This book is written primarily as a teaching text. With recognition of the constraints on a student's time, rigorous efforts have been made to achieve as much brevity as is compatible with thoroughness

and sufficient discussion to permit easy understanding. We reasoned that it is better to unfold a rounded, full story rather than attempt to achieve brevity by short, more difficult to comprehend telegraphic condensations. Topics, be they cell injury, inflammation, or systemic disorders such as amyloidosis, systemic lupus erythematosus, and AIDS, are discussed as a piece rather than dispersed into parts based on particular tissue or organ involvements. Detailed outlines are given at the beginning of each chapter, offering the student an immediate overview of the content and organization and facilitating a teacher's selection of specific segments for course instruction.

Effort has been made to maintain an organization of the subject matter compatible with most teaching programs. Thus, about the first third of the book is devoted to general pathology, i.e., cell injury, inflammation, hemodynamic derangements including thrombosis and infarction, the role of immunity in producing disease, and a general discussion of neoplasia. The remainder of the text is a systematic presentation of disorders divided into rational categories, e.g., environmental disease, pediatric diseases, vascular disease, heart disease, and pulmonary disease. Because this is designed as a teaching text, the coverage is not intended to be encyclopedic, but it is sufficiently broad and detailed, we believe, to be helpful to pathologists, residents in training, and biomedical and basic scientists and to clinicians who wish to review and refresh their understanding of the origins of clinical dysfunctions.

It may fairly be asked, "How does this edition differ from its predecessor?" The simple and, we believe, valid answer is—greatly. Aside from the extensive rewriting, which involves in many instances complete chapters and careful reconsideration of previous text, the changes are wide ranging. New chapters and sections have been added on aging, the head and neck, the eye, and soft tissue tumors. Many lesions and disorders that were poorly understood at the time of the previous edition have now been detailed in much greater depth—for example, the basic defects in diabetes mellitus, the origins of neoplasia, and the etiology and immunopathogenesis of AIDS. The improved diagnostic accuracy provided by immunocytochemical and molecular techniques has been amply detailed. Encouraged by the positive response to the use of schematic illustrations in our "smaller" book, *Basic Pathology*, colored diagrams, drawings, and flow charts have been introduced to the extent that they enhance the understanding of the text matter. Numerous illustrations have been replaced and many added to better document the nature of anatomic changes. The writing is liberally referenced to provide guidance to those who wish to pursue subjects of particular interest. The same three authors of previous editions prepared most of this text to ensure uniformity and continuity of writing. But however seasoned in teaching and however broad their interests, the advice of specialist consultants was sought to bring expertise to particular fields, thus enhancing accuracy and authenticity.

We only hope that we have succeeded in transmitting to the reader the excitement of our greatly increased understanding of the pathologic basis of disease.

Acknowledgments

THE COMPLETION OF this edition brings us to the time to express our thanks to all those who helped along the way. Our only regret is our inability, because of limitations of space or lapses of memory, to mention by name each and every one of our "samaritans," because all made contributions to the progress and are deserving of our gratitude. To those wittingly or unwittingly unsung, our apologies and thanks.

Foremost among those to whom we are deeply indebted are our editorial assistants and secretaries — Ms. Cathleen Curtin (RC), Ms. Beverly Shackelford and Ms. Mary Helen Solano (VK), and Ms. Robin Lee (SLR). Without their expert help in library research, preparation of reams of manuscript, patient proofing of immeasurable "miles" of writing, and unobtrusive organization of their "bosses," there would be no text.

Special thanks are owed to our contributors of individual chapters; some participated in the previous edition, and a few joined us afresh. They are cited in the following pages as well as with their specific chapters. The depth of their knowledge and clarity of their writing are documented in their contributions.

New to this edition is a Board of Consultants, experts in particular fields, whose knowledge, perspectives, and suggestions we sought to enhance the clarity and accuracy of the writing. Their names are listed below, but here we wish to express our gratitude for their help because, however broadly experienced writers may be, they cannot be expert in all areas.

Consultants

Dr. Max Goodman, Massachusetts Eye and Ear Infirmary, Harvard Medical School.

Dr. Jose Hernandez, University of Texas Southwestern Medical School.

Dr. Lester Kobzik, Brigham and Women's Hospital – Harvard Medical School.

Dr. Janice Lage, Brigham and Women's Hospital – Harvard Medical School.

Dr. Robert W. McKenna, University of Texas Southwestern Medical School.

Dr. Joseph Rutledge, Children's Hospital and Medical Center, University of Washington School of Medicine.

Dr. Frederick Schoen, Brigham and Women's Hospital–Harvard Medical School.

Dr. Arlene Sharpe, Brigham and Women's Hospital–Harvard Medical School.

Dr. Ricardo Uauy, University of Texas Southwestern Medical School.

Dr. Noel Weidner, Brigham and Women's Hospital–Harvard Medical School.

Many colleagues, senior and relatively junior, have been extremely helpful in many ways, including enlightening us with their thoughts about controversial or emerging areas, offering critiques of the writing, or providing us with choice illustrative material. In alphabetical order, from Brigham and Women's Hospital–Harvard Medical School they are: Drs. Jon Aster, Gilbert Brodsky, Joseph Corson, James Crawford, Mark Flomenbaum, John Godleski, Nabila Haikal, Morris Karnovsky, Lester Kobzik, Richard Mitchell, Helmut Rennke, Marcel Seiler, Joseph Semple, Charles Serhan, Sandor Szabo, and William Welch; from the University of Texas Southwestern Medical School: Drs. Maximilian Buja, Dennis Burns, Edwin Eigenbrodt, Pam Jensen, Mary Lipscomb, Julie Sandstad, Nancy Schneider, Fred Silva, and Patrick Stout; as well as Drs. Jag Bhawan (Boston University School of Medicine), Loren Borud (Harvard Medical School), Robert Jennings (Duke University School of Medicine), Manjeri Venkatachalam (University of Texas School of Medicine at San Antonio), and Patrick Ward (University of Minnesota School of Medicine at Duluth). VK also wishes to thank Dr. Michael Bennett and his other colleagues for their support in the research laboratory during his absence.

Our publisher, W.B. Saunders, also deserves recognition and thanks. They were most generous in their commitment of resources and efforts to produce the best book possible. Ms. Linda Mills, our developmental editor, must be singled out in particular. Throughout the sometimes arduous and hectic "gestation" of this text, she was an unflappable tower of strength and unfailing source of good humor. Her dedication to this edition went far beyond duty. Many other individuals contributed unstintingly, among them Ms. Carolyn Naylor, Ms. Constance Burton, and Mr. Lewis Reines, President of W.B. Saunders, who graciously and gracefully acceded to virtually all our requests and consistently offered encouragement and support.

Similarly, we wish the W. B. Saunders Illustration Department, Ms. Lynn Waltman, and Ms. Amy Boches, to know how grateful we are for their skill and help. Their artistry has undoubtedly embellished these pages. Special thanks go to Mr. Anthony Merola and Ms. Linda Bolding for their invaluable help with the photography.

Not to be forgotten are our wives, Kerstin Cotran, Raminder Kumar, and Elly Robbins, to whom it must have appeared that we

would never be done with the writing. Their reading of these words is proof that "we have indeed finished," and we thank them for their unending tolerance of our "compulsion."

Finally, each of us wishes to express to his two coauthors gratitude for their patience and good humor, respect for their dedication to the common effort, and appreciation for their collegiality. Although we did not always agree on every point, we always listened carefully, and we finished the writing still good friends.

R.C.
V.K.
S.R.

Contents

1

Cellular Injury and Adaptation

Translated literally, pathology is the study (logos) of suffering (pathos). As a science, pathology focuses on the structural and functional consequences of injurious stimuli on cells, tissues, and organs and ultimately the consequences on the entire organism.

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 will 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 (1) its cause (etiology), (2) the mechanisms of its development (pathogenesis), (3) the structural alterations induced in the cells and organs of the body (morphologic changes), and (4) the functional consequences of the morphologic changes (clinical significance).

1. **Etiology or Cause.** The concept that certain abnormal symptoms or diseases are "caused" is as ancient as recorded history. For the Acadians (2500 BC), if someone became ill, it was either his own fault (for having sinned) or the makings of outside agents, such as bad smells, cold, evil spirits, or gods.[1] In more modern terms, there are the two major classes of etiologic factors: *genetic* and *acquired* (infectious, nutritional, chemical, physical, etc.). Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, or a treatment developed. But the concept of *one cause* leading to *one disease*—developed largely from the discovery of specific infectious agents as the causes of specific diseases—is no longer sufficient. Although it is true that there would be no malaria without malarial parasites, no tuberculosis without tubercle bacilli, and no gout without a derangement in urate metabolism, not all individuals infected with these organisms or born with the metabolic abnormality develop the disease, or develop it at the same rate and with the same severity. Genetic factors clearly affect environmentally induced maladies, and the environment may have profound influences on genetic diseases.

2. **Pathogenesis.** Pathogenesis refers to the sequence of events in the response of the cells or tissues, or the whole organism, to the cause—from the initial stimulus to the ultimate expression of the manifestations of the disease. *The study of pathogenesis remains one of the main domains of the science 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 gout is to know not only the molecular pathways of uric acid metabolism, but also the biochemical and morphologic events leading to a painful toe or a kidney stone. Although from the late nineteenth century up to the 1950s, pathology was largely limited to the study of the morphologic consequences of disease, chemical, immunologic, and molecular mechanisms clearly underlie the morphologic changes and these, fortunately, have become the domain of modern pathology.

3. **Morphologic Changes.** The morphologic changes refer to the structural and associated functional alter-

ations in cells or tissues that are either characteristic of the disease or diagnostic of the etiologic process.
4. **Functional Derangements and Clinical Significance.** 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 tissue injury start with molecular or structural alterations in *cells*, a concept first put forth in the 19th century by Rudolf Virchow, known as the "father" of modern pathology. We will therefore begin our consideration of pathology by the study of the origins, molecular mechanisms, and structural changes of cell injury.

DEFINITION AND CAUSES OF CELLULAR INJURY AND ADAPTATION

The normal cell is confined to a fairly narrow range of function and structure by its genetic programs of differentiation and specialization, constraints of neighboring cells, the availability of metabolic substrates, and the finite capacities of its primary and alternative metabolic pathways. It is said to be in a homeostatic "*steady state*," able to handle normal physiologic demands. Somewhat more excessive physiologic stresses or some pathologic stimuli may bring about a number of *cellular adaptations* in which a new but altered steady state is achieved, preserving the viability of the cell. For example, the bulging muscles of the "muscle men" and women engaged in "pumping iron" are cellular adaptations. The increase in muscle mass reflects the increase in size of the individual muscle fibers. The workload is thus shared by a greater mass of cellular components, and each muscle fiber is spared excess work and so escapes injury. The enlarged muscle cell achieves a new equilibrium, permitting it to survive at a higher level of metabolic activity. This adaptive response is called *hypertrophy*. Conversely, *atrophy* is an adaptive response in which there is a decrease in the size and function of cells. Other cell adaptations occur and these are considered later in this chapter.

If the limits of adaptive capability are exceeded, or when no adaptive response is possible, a sequence of events follows, loosely termed *cell injury*. Cell injury is *reversible* up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell reaches the point of no return, and suffers *irreversible cell injury* and cell death. For example, if the blood supply to a segment of the heart is cut off for 10 to 15 minutes and is then restored, the myocardial cells experience injury but can recover and function normally. However, if blood flow is not restored until one hour later, the myocardial fiber dies. *Adaptation, reversible injury,* and *cell death,* then, should be considered states along a continuum of progressive encroachment on the cell's normal function and structure (Fig. 1–1). Whether specific types of stress induce an adaptive response, reversible injury, or cell death depends on the nature and severity of the stress and on many other variables relating to the intrinsic state of the cell itself.

The causes of reversible cell injury and cell death range from the external gross physical violence of an automobile accident to internal endogenous causes, such as a subtle genetic lack of a vital enzyme that impairs normal metabolic function. Most adverse influences can be grouped into the following broad categories.

HYPOXIA. Hypoxia, an extremely important and common cause of cell injury and cell death, impinges on aerobic oxidative respiration. Loss of blood supply (ischemia), which occurs when arterial flow is impeded by arteriosclerosis or by thrombi, is the most common cause of hypoxia. Another cause is inadequate oxygenation of the blood due to cardiorespiratory failure. Loss of the oxygen-carrying *capacity* of the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage), is a third, less frequent basis for oxygen deprivation. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if the femoral artery is narrowed, the skeletal muscle cells of the leg may shrink in size (atrophy). This reduction in cell mass achieves a balance between metabolic needs and the available oxygen supply. More severe hypoxia will induce injury and cell death.

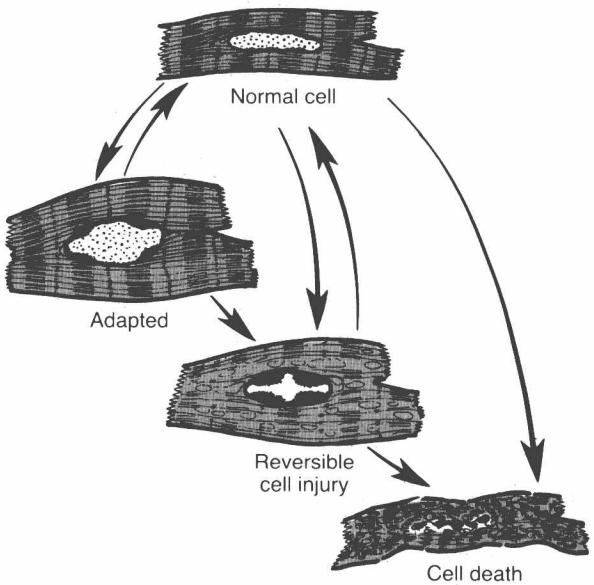


Figure 1–1. The relationships among normal, adapted, reversibly injured, and dead myocardial cells. The cellular adaptation depicted here is hypertrophy, and the type of cellular injury is ischemic necrosis.

PHYSICAL AGENTS. Physical agents include mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock (see Chapter 9, Environmental Pathology).

CHEMICAL AGENTS AND DRUGS. The list of chemicals that may produce cell injury defies compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury by deranging the fluid and electrolyte homeostasis of cells. Even oxygen, in high concentrations, is severely toxic. Trace amounts of agents known as *poisons,* such as arsenic, cyanide, or mercuric salts, may destroy sufficient numbers of cells within minutes to hours to cause death. Other substances, 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 causes injury are diverse and are discussed in greater detail in Chapter 7 (Infectious Diseases).

IMMUNOLOGIC REACTIONS. These may be lifesaving or lethal. Although the immune system serves in the defense against biologic agents, 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 thought to be responsible for a number of so-called autoimmune diseases (see Chapter 5).

GENETIC DERANGEMENTS. Genetic defects as causes of cellular injury are of major interest to biologists today (see Chapter 4). The genetic injury may result in as gross a defect as the congenital malformations associated with Down's syndrome or in subtle alterations in the coding of hemoglobin responsible for the production of hemoglobin S in sickle cell anemia. The many inborn errors of metabolism arising from enzymic abnormalities, usually an enzyme lack, are excellent examples of cell damage due to subtle alterations at the level of DNA.

NUTRITIONAL IMBALANCES. Even today nutritional imbalances continue to be major causes of cell injury. Protein-calorie deficiencies cause an appalling number of deaths, chiefly among underprivileged populations. Deficiencies in specific vitamins are found throughout the world (see Chapter 8). Ironically, nutritional excesses have become important causes of cell injury among the overprivileged. Excesses of lipids predispose to atherosclerosis, and obesity is an extraordinary manifestation of the overloading of some cells in the body with fats. Atherosclerosis is virtually endemic in the United States, and as any look down the street reveals, obesity is rampant.

MECHANISMS OF CELL INJURY

The molecular mechanisms responsible for cell injury are complex. As we have seen, injury to cells may have many causes, and probably there is no common final pathway of cell death. There are, however, a number of considerations that are useful to remember.

1. Although it is not always possible to determine the precise biochemical site of action of an injurious agent, four intracellular systems are particularly vulnerable: (a) *maintenance of the integrity of cell membranes,* upon which the ionic and osmotic homeostasis of the cell and its organelles is dependent, (b) *aerobic respiration* involving oxidative phosphorylation and production of ATP, (c) *synthesis of enzymic and structural proteins,* and (d) *preservation of the integrity of the genetic apparatus* of the cell.
2. *The structural and biochemical elements of the cell are so closely related that whatever the precise point of initial attack by the damaging agent, injury at one locus leads to wide-ranging secondary effects.* For example, impairment of aerobic respiration disrupts the energy-dependent sodium pump that maintains the ionic and fluid balance of the cell, resulting in alterations in the intracellular content of ions and water.
3. *The morphologic changes of cell injury become apparent only after some critical biochemical system within the cell has been deranged.* As would be expected, the morphologic manifestations of lethal damage take more time to develop than those of reversible damage. For example, cell swelling is a reversible morphologic change, and this may occur in a matter of minutes; however, unmistakable light microscopic changes characteristic of cell death do not occur in the myocardium until 10 to 12 hr after total ischemia, yet we know that irreversible injury occurs within 20 to 60 min. Obviously, ultrastructural alterations occur earlier than light microscopic changes.
4. *Reactions of the cell to injurious stimuli depend on the type of injury, its duration, and its severity;* thus, small doses of a chemical toxin or ischemia of short duration may induce reversible injury, whereas large doses of the same toxin or more prolonged ischemia might lead either to instantaneous cell death or to slow, irreversible injury leading in time to cell death.
5. *The consequences of cell injury depend not only on the type, duration, and severity of the stimulus but also on the type, state, and adaptability of the cell.* The cell's nutritional and hormonal status and its metabolic needs are important in its response to injury. How vulnerable is a cell, for example, to loss of blood supply and hypoxia? The striated muscle cell in the leg can be placed entirely at rest when deprived of its blood supply; not so, the striated muscle of the heart (Table 1–1). Exposure of two individuals to identical concentrations of a toxin, such as tetrachloride, may

Table 1-1. Susceptibility of Cells to Ischemic Necrosis

High	Neurons (3-5 min)
Intermediate	Myocardium, hepatocytes, renal epithelium (30 min-2 hr)
Low	Fibroblasts, epidermis, skeletal muscle (many hours)

be without effect in one and may produce cell death in the other. This may be due, as we shall see, to the amounts of hepatic enzymes that convert carbon tetrachloride to toxic by-products. Differences in the nutritional state or in potentiating factors, such as alcohol consumption, influence the ability of the two individuals and their cells to withstand injury.

With certain injurious agents, the mechanisms and loci of attack are well defined. Cyanide represents an intracellular asphyxiant in that it inactivates cytochrome oxidase. Certain anaerobic bacteria, such as *Clostridium perfringens,* elaborate phospholipases, which attack phospholipids in cell membranes. Other isolated examples exist, but the modes of action of many injurious agents are more complex. Recent work, however, suggests a central role for *oxygen* in cell injury (Fig. 1-2). Lack of oxygen clearly underlies the pathogenesis of cell injury in ischemia, but it also is clear that *partially reduced activated oxygen species* are important mediators of cell death in many pathologic conditions. As we shall see, these free radical species cause lipid peroxidation and other deleterious effects on cell structure. In the following discussions, we shall concentrate on four of the common causes and mechanisms of cell injury: (1) *hypoxic injury,* (2) *injury induced by free radicals, including activated oxygen species,* (3) some forms of *chemical injury,* and (4) injury induced by *viruses.*

ISCHEMIC AND HYPOXIC INJURY

Sequence of Events and Ultrastructural Changes

The sequence of morphologic and biochemical changes following acute hypoxic injury has been studied extensively in humans, in experimental animals, and in culture systems,[2-5] and reasonable schemes concerning the mechanisms underlying these changes have emerged (Fig. 1-3). A useful model for hypoxic injury has been occlusion of one of the main coronary arteries and examination of the cardiac muscle in the areas supplied by the artery. Besides the relevance of this model to human myocardial infarction, the cellular changes in the heart can also be correlated with physiologic and electrophysiologic alterations.

REVERSIBLE CELL INJURY. *The first point of attack of hypoxia is the cell's aerobic respiration, i.e., oxidative phosphorylation by mitochondria.*[2] As the oxygen tension within the cell decreases, there is loss of oxidative phosphorylation, and the generation of adenosine triphosphate (ATP) slows down or stops.

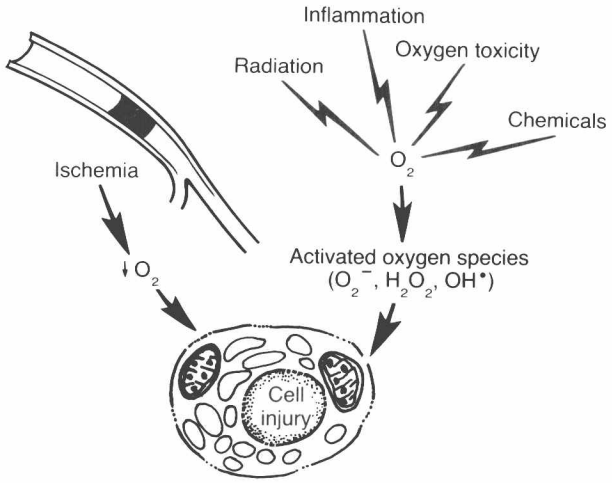


Figure 1-2. The critical role of oxygen in cell injury. Ischemia causes cell injury by reducing cellular oxygen supplies, whereas other stimuli, such as radiation, induce damage via toxic activated oxygen species.

This loss of ATP—the energy source—has widespread effects on many systems within the cell. Heart muscle, for example, ceases to contract within 60 sec of coronary occlusion. (Note, however, that noncontractility does not mean cell death.) The decrease in cellular ATP and associated increase in adenosine monophosphate (AMP) stimulate phosphofructokinase and phosphorylase activities. This results in an increased rate of *anaerobic glycolysis* designed to maintain the cell's energy sources by generating ATP from glycogen. Glycogen is thus rapidly depleted, a phenomenon that can be appreciated histologically if tissues are stained for glycogen (such as with the periodic acid-Schiff [PAS] stain). ATP is also generated anaerobically from creatine phosphate, through the action of the enzyme *creatine kinase.* Glycosis results in the accumulation of lactic acid and inorganic phosphates from the hydrolysis of phosphate esters. *This reduces the intracellular pH.* At this early period there is also *early clumping of nuclear chromatin,* apparently caused by the reduced pH.[5]

One of the earliest and most common manifestations of ischemic injury (and for that matter, other types of injury) is *acute cellular swelling* (cellular edema) (Figs. 1-4 and 1-5), caused by an impairment of cell volume regulation by the plasma membrane. You will recall that mammalian cells possess a high intracellular osmotic colloidal pressure, exerted by a greater intracellular than extracellular concentration of protein. To balance this, sodium is maintained at a lower intracellular than extracellular concentration by an energy-dependent sodium pump (ouabain sensitive Na^+, K^+-ATPase), which also keeps the concentration of potassium significantly higher intracellularly than extracellularly. *Failure of this active transport, owing to diminished ATP and ATPase, causes sodium to accumulate intracellularly with diffusion of potassium out of the cell.* The net gain of

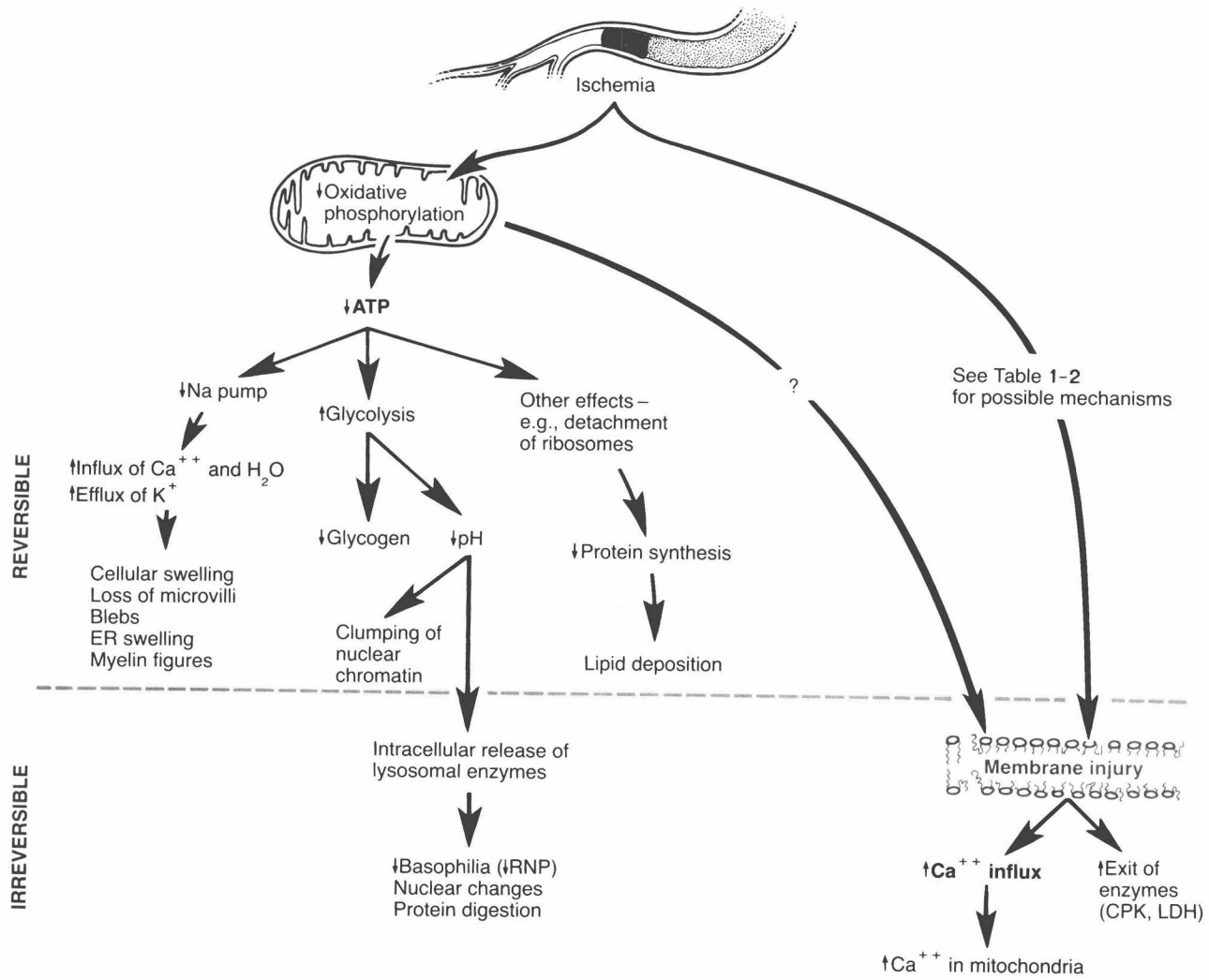


Figure 1-3. Postulated sequence of events in ischemic injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia causes direct membrane damage by mechanisms outlined in Table 1-2.

solute is accompanied by an isosmotic gain of water and consequent cell swelling. The movement of fluid and ions into the cell is associated with *early dilation of the endoplasmic reticulum.* A second mechanism for cell swelling in ischemia is the increased intracellular osmotic load, engendered by the accumulation of catabolites such as inorganic phosphates, lactate, and purine nucleosides.[5]

The next phenomenon to occur is *detachment of ribosomes from the granular endoplasmic reticulum* and *dissociation of polysomes into monosomes,* probably due to disruption of the energy-dependent interactions between the membranes of the endoplasmic reticulum and its ribosomes. If hypoxia continues, other alterations take place and, again, are reflections of increased membrane permeability and diminished mitochondrial function. *Blebs* may form at the cell surface (Figs. 1-5 and 1-6), and cells that possess microvilli (such as proximal tubular epithelial cells) begin to lose their normal microvillous structure. "Myelin figures," derived from plasma as well as organellar membranes, may be seen within the cytoplasm or extracellularly. They are thought to result from dissociation of lipoproteins with unmasking of phosphatide groups, promoting the uptake and intercalation of water between the lamellar stacks of membranes. At this time the mitochondria are usually swollen, owing to loss of volume control by these organelles; the endoplasmic reticulum remains dilated; and the entire cell is markedly swollen, with increased concentrations of water, sodium, and chloride and a decreased concentration of potassium. Up to a certain time, *all the above disturbances are reversible if oxygenation is restored.*

IRREVERSIBLE INJURY. If ischemia persists, irreversible injury ensues. As will be detailed later, *there is no universally accepted biochemical explanation for the transition from reversible injury to cell death.* However, irreversible injury is associated morpho-

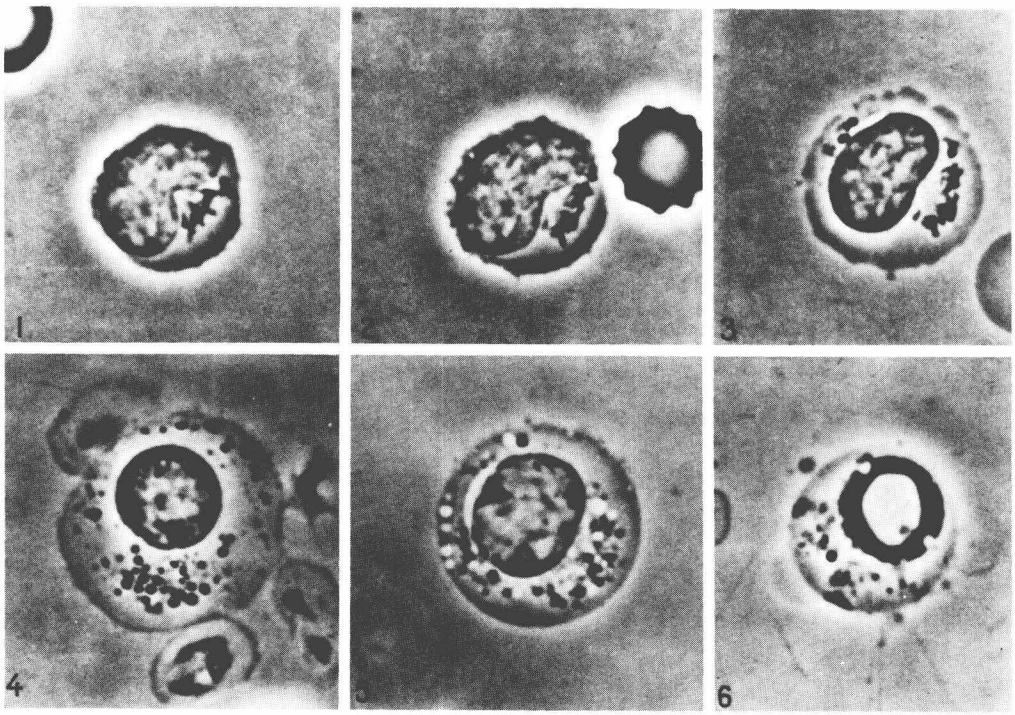
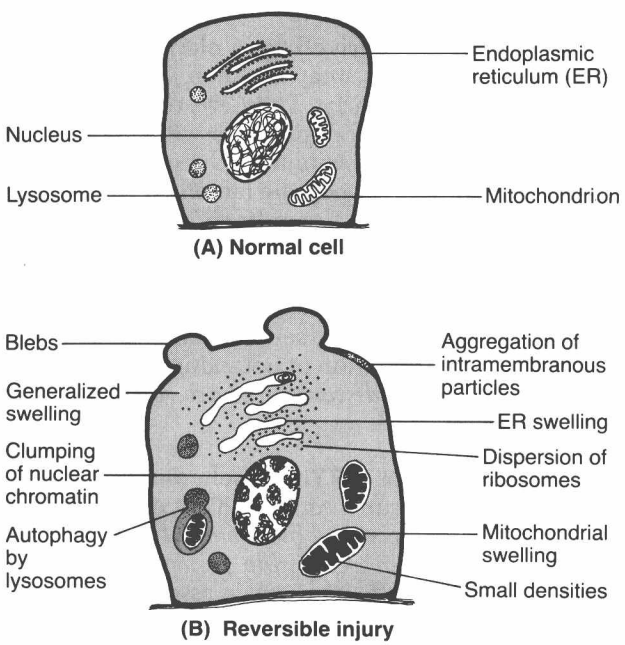


Figure 1–4. Phase micrographs depicting stages of cell death in blood lymphocyte. *1,* Normal lymphocyte; *2,* slight cytoplasmic edema; *3,* increasing cytoplasmic edema; *4* and *5,* disappearance of the nuclear depression; *6,* nuclear pyknosis. (From Bessis, M.: Living Blood Cells and Their Ultrastructure. New York, Springer-Verlag, 1972.)

logically with severe vacuolization of the mitochondria (Figs. 1–5 and 1–7), including their cristae; extensive damage to plasma membranes; swelling of lysosomes; and—particularly if the ischemic zone is reperfused—massive calcium influx into the cell. Large flocculent amorphous densities develop in the mitochondrial matrix (Fig. 1–7). In the myocardium, these are indications of irreversible injury and can be seen as early as 30 to 40 min after ischemia. There is continued loss of proteins, essential coenzymes, and



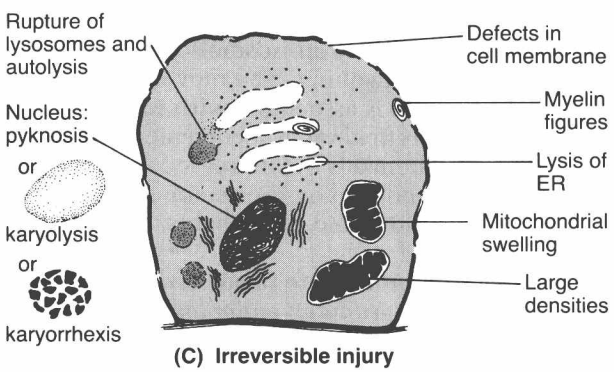


Figure 1–5. Schematic representation of a normal cell (A) and the ultrastructural changes in reversible (B) and irreversible (C) cell injury (see text).