Robbins and Cotran

Pathologic Basis of Disease

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Robbins and Cotran

Pathologic Basis of Disease

Eighth Edition

VINAY KUMAR, MBBS, MD, FRCPath
Alice Hogge and Arthur Baer Professor
Chairman, Department of Pathology
Executive Vice Dean, Division of Biologic Sciences and
The Pritzker School of Medicine
The University of Chicago
Chicago, Illinois

ABUL K. ABBAS, MBBS
Professor and Chairman, Department of Pathology
University of California, San Francisco
San Francisco, California

NELSON FAUSTO, MD
Professor and Chairman, Department of Pathology
University of Washington School of Medicine
Seattle, Washington

JON C. ASTESTO, MD
Professor Department of Pathology
Harvard School of Medicine
Brigh Department of Pathology
Bosto School of Medicine

With Illustrations by
James A. Perkins, MS, MFA

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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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

James M. Crawford, MD, PhD
Senior Vice President for Laboratory Services; Chair, Department of Pathology and Laboratory Medicine, North Shore–Long Island Jewish Health System, Manhasset, NY

Liver and Biliary Tract

Umberto De Girolami, MD
Professor of Pathology, Harvard Medical School; Director of Neuropathology, Brigham and Women's Hospital, Boston, MA

Peripheral Nerve and Skeletal Muscle; The Central Nervous System

Lora Hedrick Ellenson, MD
Weill Medical College of Cornell University, Professor of Pathology and Laboratory Medicine; Attending Pathologist, New York Presbyterian Hospital, New York, NY

The Female Genital Tract

Jonathan I. Epstein, MD
Professor of Pathology, Urology, and Oncology; The Reinhard Professor of Urologic Pathology, The Johns Hopkins University School of Medicine; Director of Surgical Pathology, The Johns Hopkins Hospital, Baltimore, MD

The Lower Urinary Tract and Male Genital System

Robert Folberg, MD
Dean, Oakland University William Beaumont School of Medicine, Rochester, MI; Chief Academic Officer, Beaumont Hospitals, Royal Oak, MI

The Eye

Matthew P. Frosch, MD, PhD
Associate Professor of Pathology, Harvard Medical School; Director, 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 Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Baltimore, MD

The Pancreas

Aliya N. Husain, MBBS
Professor, Department of Pathology, Pritzker School of Medicine, The University of Chicago, Chicago, IL

The Lung

Christine A. Iacobuzio-Donahue, MD, PhD
Associate Professor of Pathology and Oncology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Baltimore, MD

The Pancreas

Alexander J.F. Lazar, MD, PhD
Assistant Professor, Department of Pathology and Dermatology, Sections of Dermatopathology and Soft Tissue Sarcoma Pathology, Faculty of Sarcoma Research Center, University of Texas M.D. Anderson Cancer Center, Houston, TX

The Skin

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, Pritzker School of Medicine, The University of Chicago, Chicago, IL

Head and Neck

Chen Liu, MD, PhD
Associate Professor of Pathology, Immunology and Laboratory Medicine; Director, Gastrointestinal and Liver Pathology, The University of Florida College of Medicine, Gainesville, FL

Liver and Biliary Tract

Anirban Maitra, MBBS
Associate Professor of Pathology and Oncology, 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

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; Blood Vessels; The Heart

George F. Murphy, MD
Professor of Pathology, Harvard Medical School; Director of Dermatopathology, Brigham and Women's Hospital, Boston, MA

The Skin

Edyta C. Pirog, MD
Associate Professor of Clinical Pathology and Laboratory Medicine, New York Presbyterian Hospital-Weil Medical College of Cornell University; Associate Attending Pathologist, New York Presbyterian Hospital, New York, NY

The Female Genital Tract

Andrew E. Rosenberg, MD
Professor, Department of Pathology, Harvard Medical School; Pathologist, 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

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

Thomas Stricker, MD, PhD
Orthopedic Pathology Fellow, Department of Pathology, Pritzker School of Medicine, The University of Chicago, Chicago, IL

Neoplasia

Jerrold R. Turner, MD, PhD
Professor and Associate Chair, Department of Pathology, Pritzker School of Medicine, The University of Chicago, Chicago, IL

The Gastrointestinal Tract

Preface: The Golden Jubilee Edition

As we launch the 8th edition of *Pathologic Basis of Disease* we pause to look back 50 years ago, when the first edition of this book, entitled "Pathology with Clinical Correlations" was published. (For those who may not know, the first three editions were published under this name and so the current "8th edition" is really the 11th edition of this book.)

In the preface of the first edition, Stanley Robbins wrote:

- "But the study of morphology is only one facet of pathology. Pathology contributes much to clinical medicine. The pathologist is interested not only in the recognition of structural alterations, but also in their significance, i.e., the effects of these changes on cellular and tissue function and ultimately the effect of these changes on the patient. It is not a discipline isolated from the living patient, but rather a basic approach to a better understanding of disease and therefore a foundation of sound clinical medicine."
- "The why's and how's are as important as the what's."

In today's vocabulary, what Robbins said in 1957 was that pathology is the study of the mechanism of diseases and morphology is a tool (the only one available at that time) to gain insight into pathogenesis and clinical correlations. Over the past 50 years, this focus has not changed and it remains the guiding principle for the current edition. The main difference is that now we have many more tools to supplement morphology, including molecular biology, genetics, and informatics, to name a few. Indeed, it might be said that this book presents the molecular basis of human disease with clinical correlations. This edition, like all previous ones, has been extensively revised, and some areas have been completely rewritten. A few examples of 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.
- Chapter 3, covering tissue repair and wound healing, has been extensively revised to include new and exciting information on stem cell biology, growth factor signaling, and the mechanisms that underlie fibrosis.
- Chapter 5 includes a completely rewritten section on molecular diagnosis that reflects rapid advances in DNA sequencing technology. The principles of genome-wide analysis, now becoming a powerful tool in the study of complex human diseases like cancer and diabetes, have also been added.
- Chapter 9 has been completely revised and reorganized in view of the increasing importance of environmental factors in human diseases.
- Chapter 17 has been completely rewritten and highlights new insights into the pathogenesis of inflammatory bowel disease and gastrointestinal cancers.
- Chapter 22, covering diseases of the female genital tract, includes discussion of the molecular basis of cancer, endometriosis, and preeclampsia.
- In addition to the revision and reorganization of the text, 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 *Robbins Pathology* will find the illustrations and figures sparkling and fresh.

Wherever appropriate, we have blended new discoveries into the discussion of pathogenesis and pathophysiology, while 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 highlighted above, our goals remain the same as those articulated by Robbins and Cotran over the past many years.

- To integrate into the discussion of pathologic processes and disorders the newest established information available—morphologic as well as molecular.
- To organize information into logical and uniform presentations, facilitating readability, comprehension, and learning.
- To maintain the book at a reasonable size and yet provide adequate discussion of the significant lesions, processes, and disorders. Indeed, we have reduced the girth and the weight of this book by trimming out about 80 pages (making it less useful for weight lifting).
- To place great emphasis on clarity of writing and proper use 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 all 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 readers that up-to-datedness is a special feature that makes this book very valuable. We have strived to remain current by providing new information and references from recent literature, many published in 2008 and some from the early part of 2009. However, older classics have also been retained to provide original source material for advanced readers.

We are now into the digital age and so the text will be available online to those who own the print version. Such access gives the reader the ability to search across the entire text, bookmark passages, add personal notes, and use PubMed to view references, and has many other exciting features. In addition, also available online are 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. The cases are designed to enhance and reinforce learning by challenging students to apply their knowledge to solve clinical cases. A virtual microscope feature enables the viewing of selected images at various magnifications.

This edition is also marked by the addition of a new coauthor, Jon Aster. All four of us have reviewed, critiqued, and edited each chapter to ensure the uniformity of style and flow that have been the hallmarks of the book. Together, we hope that we have succeeded in equipping the readers with the scientific basis for the practice of medicine and in whetting their appetite for learning beyond what can be offered in any textbook.

VK
AKA
NF
JCA

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 four of us offer thanks to our contributing authors for their commitment to this textbook. Many are veterans of previous editions; others are new to the eighth 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 Drs. Michelle LeBeau, Jerry Krishnan, Julian Solway, Elyssa Gordon, Ankit Desai, Sue Cohen, Megan McNerney, Peter Pytel, and Tony Chang (at the University of Chicago); Dr. Serdar Bulun (at Northwestern University, Chicago); Drs. Steven Deeks, Sanjay Kakar, Zoltan Laszik, Scott Oakes, Jay Debnath, and Michael Nystrom (at the University of California San Francisco); Dr. Lundy Braun at Brown University and Dr. Peter Byers at the University of Washington; Drs. Frank Bunn, Jeffery Kutok, Helmut Rennke, Fred Wang, Max Loda, and Mark Fleming (at Harvard Medical School); and Dr. Richard Aster (at the Milwaukee Blood Center and Medical College of Wisconsin). Special thanks are due to Dr. Raminder Kumar for updating clinical information and extensive proof-reading of many chapters. Many colleagues provided photographic gems from their collections. They are individually acknowledged in the text.

Our administrative staff needs special mention 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. Valerie Driscoll and Garcia Wilson; at The University of California at San Francisco, Ms. Ana Narvaez; at the University of Washington, Seattle, Greg Lawrence, Joscelyn Rompogren, Stephanie Meleady-Brown, and Jane Norris; at the Brigham and Women's Hospital, Deborah Kutok and Muriel Goutas. Ms. Beverly Shackelford at the University of Texas Southwestern Medical School at Dallas, who has helped one of us (VK) for 26 years, deserves a gold star 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. Almost all 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. 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, Ann DeLancey, and Erin Malone for their patience, love, and support of this venture, and for their tolerance of our absences.

Finally, Vinay Kumar, Abul Abbas, and Nelson Fausto wish to express their deep appreciation to Jon Aster for joining the team. Jon has proved his excellence as a contributor for many years, and now he adds luster to the entire book. Despite differences in our vantage points, opinions, and individual styles, our common vision shared with the late Drs. Stanley Robbins and Ramzi Cotran, has made this an exciting and rewarding partnership.

VK
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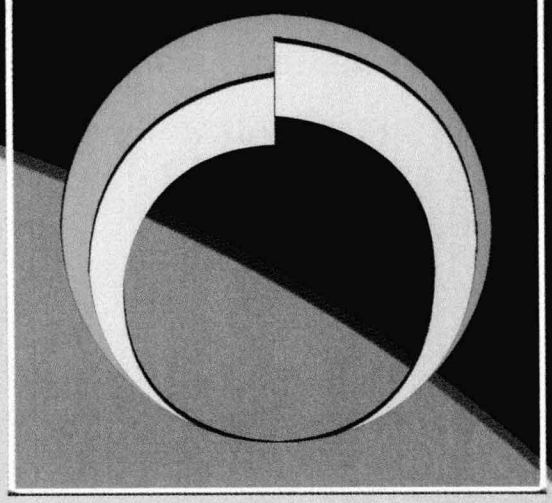
General Pathology

Systemic Pathology: Diseases of Organ Systems

* Chapters without any listed contributors have been written by the editors.



General Pathology

1

Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

Introduction to Pathology

Pathology is the study *(logos)* of disease *(pathos)*. More specifically, it is devoted to the study of the structural, biochemical, 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 rational basis for clinical care and therapy. It thus serves as the bridge between the basic sciences and clinical medicine, and is the scientific foundation for all of medicine.

Traditionally the study of pathology is divided into general pathology and systemic pathology. The former is concerned with the reactions of cells and tissues to abnormal stimuli and to inherited defects, which are the main causes of disease. The latter examines the alterations in specialized organs and tissues that are responsible for disorders that involve these organs. 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 biochemical and structural alterations induced in the cells and organs of the body *(molecular and morphologic changes)*, and the functional consequences of these changes *(clinical manifestations)*.

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 effects of outside agents, such as bad smells, cold, evil spirits, or gods.[1] We now recognize that there are two major classes of etiologic factors: genetic (e.g., inherited mutations and disease-associated gene variants, or polymorphisms) and acquired (e.g., infectious, nutritional, chemical, physical). The idea that one etiologic agent is the cause of one disease—developed from the study of infections and single-gene disorders—is not applicable to the majority of diseases. In fact, most of our common afflictions, such as atherosclerosis and cancer, are multifactorial and arise from the effects of various external triggers on a genetically susceptible individual. The relative contribution of inherited susceptibility and external influences varies in different diseases.

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 cause is known (e.g., infection or mutation), 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 and morphologic events leading to the formation of cysts and fibrosis in the lungs, 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—the pathogenesis—are still often obscure. Technologic advances are making it 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.

Molecular and Morphologic Changes. Morphologic changes refer to the structural alterations in cells or tissues that are either characteristic of a disease or diagnostic of an 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 that look morphologically identical may have widely different courses, therapeutic responses, and prognosis. Molecular analysis by techniques such as DNA microarrays (Chapter 5) has begun to reveal genetic differences that predict the behavior of the tumors as well as their responsiveness to different therapies. Increasingly, such techniques are being used to extend and even supplant traditional morphologic analyses.

Functional Derangements and Clinical Manifestations. The end results of genetic, biochemical, and structural changes in cells and tissues are functional abnormalities, which lead to the clinical manifestations (symptoms and signs) of disease, as well as its progress (clinical course and outcome).

Virtually all forms of disease 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 causes, mechanisms, and morphologic and biochemical correlates of *cell injury*. Injury to cells and to extracellular matrix ultimately leads to *tissue and organ injury*, which determine 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 state of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates. It is nevertheless able to handle physiologic demands, maintaining a steady state called *homeostasis*. *Adaptations* are reversible functional and structural responses to more severe physiologic stresses and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function (Fig. 1–1 and Table 1–1). The adaptive response may consist of an increase in the size of cells (hypertrophy) and functional activity, an increase in their number (hyperplasia), a decrease in the size and metabolic activity of cells (atrophy), or a change in the phenotype of cells (metaplasia). When the stress is eliminated the cell can recover to its original state without having suffered any harmful consequences.

If the limits of adaptive responses are exceeded or if cells are exposed to injurious agents or stress, deprived of essential nutrients, or become compromised by mutations that affect essential cellular constituents, a sequence of events follows that is termed *cell injury* (see Fig. 1–1) Cell injury is *reversible* up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell suffers *irreversible injury* and ultimately *cell death*. *Adaptation, reversible injury*, and *cell death* may be stages of progressive impairment following different types of insults. For instance, in response to increased hemodynamic loads, the heart muscle becomes enlarged, a form of adaptation, and can even undergo injury. If the blood supply to the myocardium is compromised or inadequate, the muscle first suffers reversible injury, manifested by certain

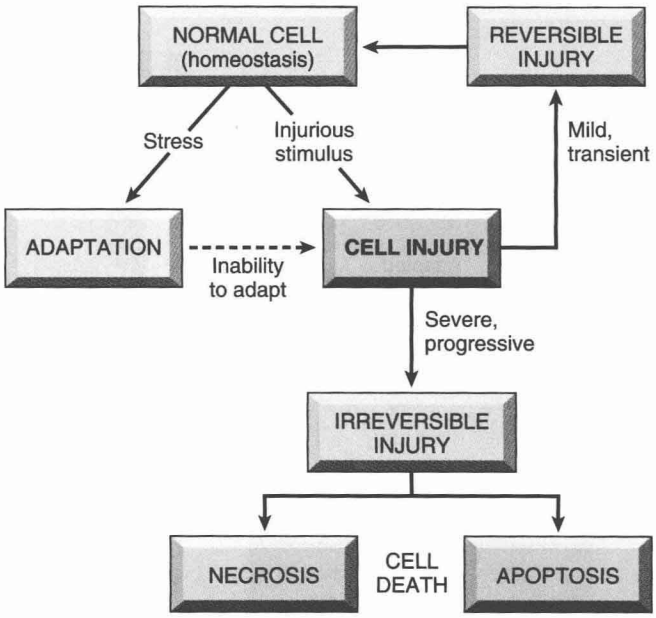


FIGURE 1–1 Stages of the cellular response to stress and injurious stimuli.

cytoplasmic changes (described later). Eventually, the cells suffer irreversible injury and die (Fig. 1–2).

Cell death, the end result of progressive cell injury, is one of the most crucial events in the evolution of disease in any tissue or organ. It results from diverse causes, including ischemia (reduced blood flow), infection, and toxins. Cell death is also a normal and essential process in embryogenesis, the development of organs, and the maintenance of homeostasis. There are two principal pathways of cell death, *necrosis* and *apoptosis*. Nutrient deprivation triggers an adaptive cellular response called *autophagy* that may also culminate in cell death. 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 typical adaptations, cell injury, and death (see Table 1–1). Metabolic derangements in cells and sublethal, chronic injury may be associated with *intracellular*

TABLE 1–1 Cellular Responses to Injury

Nature of Injurious Stimulus	Cellular Response
ALTERED PHYSIOLOGICAL STIMULI; SOME NONLETHAL INJURIOUS STIMULI	**CELLULAR ADAPTATIONS**
• Increased demand, increased stimulation (e.g., by growth factors, hormones) • Decreased nutrients, decreased stimulation • Chronic irritation (physical or chemical)	• Hyperplasia, hypertrophy • Atrophy • Metaplasia
REDUCED OXYGEN SUPPLY; CHEMICAL INJURY; MICROBIAL INFECTION	**CELL INJURY**
• Acute and transient	• Acute reversible injury Cellular swelling fatty change
• Progressive and severe (including DNA damage)	• Irreversible injury → cell death Necrosis Apoptosis
METABOLIC ALTERATIONS, GENETIC OR ACQUIRED; CHRONIC INJURY	**INTRACELLULAR ACCUMULATIONS; CALCIFICATION**
CUMULATIVE SUBLETHAL INJURY OVER LONG LIFE SPAN	**CELLULAR AGING**

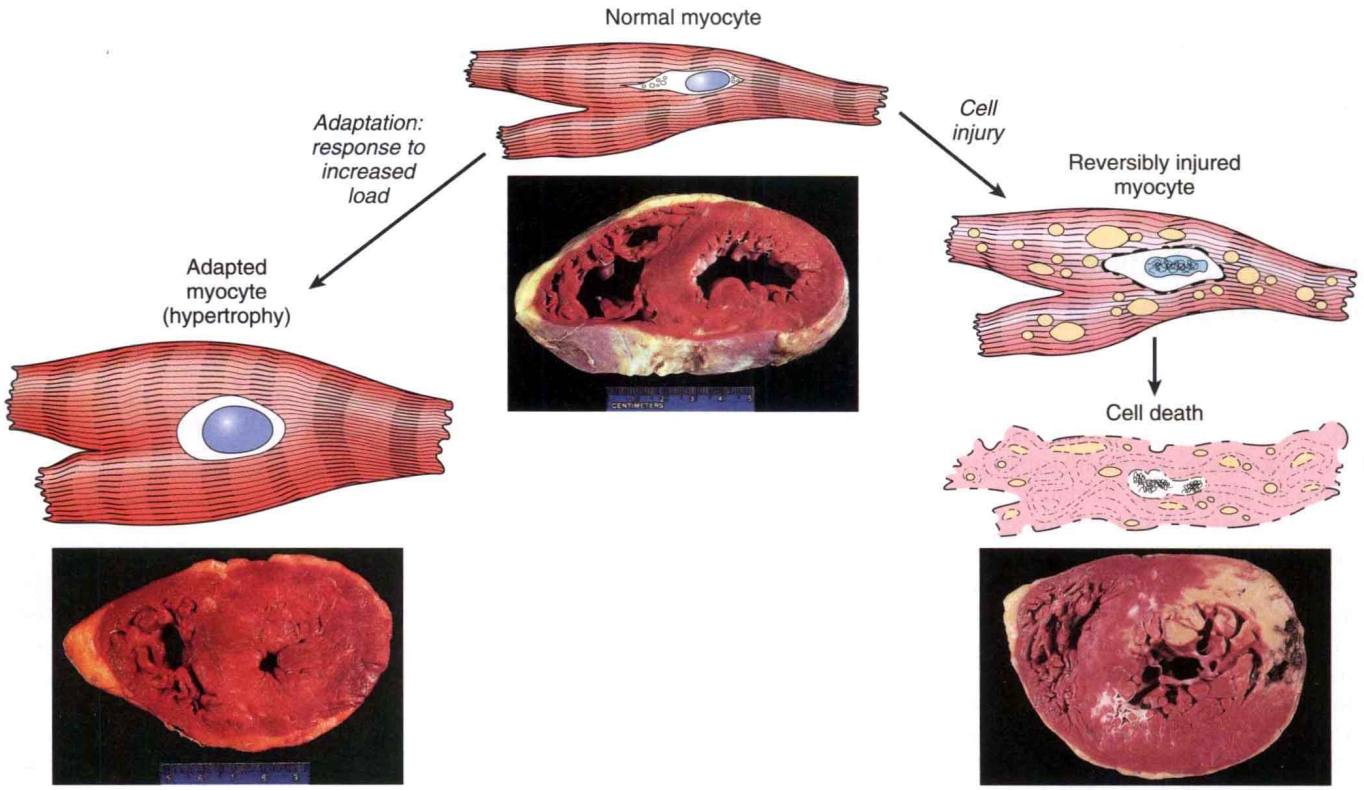


FIGURE 1–2 The relationship between normal, adapted, reversibly injured, and dead myocardial cells. The cellular adaptation is myocardial hypertrophy *(lower left)*, caused by increased blood flow requiring greater mechanical effort by myocardial cells. This adaptation leads to thickening of the left ventricular wall to over 2 cm (normal, 1–1.5 cm). In reversibly injured myocardium (illustrated schematically, *right*) there are generally only functional effects, without any readily apparent gross or even microscopic changes. In the specimen showing necrosis, a form of cell death *(lower right)*, the light area in the posterolateral left ventricle represents an acute myocardial infarction caused by reduced blood flow (ischemia). All three transverse sections of the heart have been stained with triphenyltetrazolium chloride, an enzyme substrate that colors viable myocardium magenta. Failure to stain is due to enzyme loss following cell death.

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, the normal process of *aging* itself is accompanied by characteristic morphologic and functional changes in cells.

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 reversible cell injury, and cell death. We conclude with three other processes that affect cells and tissues: intracellular accumulations, pathologic calcification, and cell aging.

Adaptations of Cellular Growth and Differentiation

Adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment. Such adaptations may take several distinct forms.

HYPERTROPHY

Hypertrophy refers to an increase in the size of cells, resulting in an increase in the size of the organ. The hypertrophied organ has no new cells, just larger cells. The increased size of the cells is due to the synthesis of more structural components of the cells. Cells capable of division may respond to stress by undergoing both hyperplasia (described below) and hypertrophy, whereas in *nondividing cells* (e.g., myocardial fibers) increased tissue mass is due to hypertrophy. In many organs hypertrophy and hyperplasia may coexist and contribute to increased size.

Hypertrophy can be *physiologic* or *pathologic* and is caused by increased functional demand or by stimulation by hormones and growth factors. The striated muscle cells in the heart and skeletal muscles have only a limited capacity for division, and respond to increased metabolic demands mainly by undergoing hypertrophy. *The most common stimulus for hypertrophy of muscle is increased workload.* For example, the bulging muscles of bodybuilders engaged in "pumping iron" result from an increase in size of the individual muscle fibers in response to increased demand. In the heart, the stimulus for hypertrophy is usually chronic hemodynamic overload, resulting from either hypertension or faulty valves (see Fig. 1–2). In both tissue types the muscle cells synthesize more proteins and the number of myofilaments increases. This increases the amount of force each myocyte can generate, and thus increases the strength and work capacity of the muscle as a whole.

The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced increase in the

size of an organ that results mainly from hypertrophy of muscle fibers (Fig. 1–3). The cellular enlargement is stimulated by estrogenic hormones acting on smooth muscle estrogen receptors, eventually resulting in increased synthesis of smooth muscle proteins and an increase in cell size.

Although the traditional view of cardiac and skeletal muscle is that in adults these tissues are incapable of proliferation and, therefore, their enlargement is entirely a result of hypertrophy, there is now accumulating evidence that even these cell types are capable of some proliferation as well as repopulation from precursors, in addition to hypertrophy (Chapter 3).[2]

Mechanisms of Hypertrophy

Hypertrophy is the result of increased production of cellular proteins. Much of our understanding of hypertrophy is based on studies of the heart. Hypertrophy can be induced by the linked actions of mechanical sensors (that are triggered by increased work load), growth factors (including TGF-β, insulin-like growth factor-1 [IGF-1], fibroblast growth factor), and vasoactive agents (such as α-adrenergic agonists, endothelin-1, and angiotensin II). Indeed, mechanical sensors themselves induce production of growth factors and agonists (Fig. 1–4).[3–5] These stimuli work coordinately to increase the synthesis of muscle proteins that are responsible for the hypertrophy. The two main biochemical pathways involved in muscle hypertrophy seem to be the phosphoinositide 3-kinase/Akt pathway (postulated to be most important in physiologic, e.g., exercise-induced, hypertrophy) and signaling downstream of G protein-coupled receptors (induced by many growth factors and vasoactive agents, and thought to be more important in pathologic hypertrophy). Hypertrophy may also be associated with a switch of contractile proteins from adult to fetal or neonatal forms. For example, during muscle hypertrophy the α isoform of myosin heavy chain is replaced by the β isoform, which has a slower, more energetically economical contraction. In addition, some genes that are expressed only during early development are re-expressed in hypertrophic cells, and the products of these genes participate in the cellular response to stress. For example, the gene for atrial natriuretic factor (ANF) is expressed in both the atrium and the ventricle in the embryonic heart, but it is down-regulated after birth. Cardiac hypertrophy, however, is associated with reinduction of ANF gene expression. ANF is a peptide hormone that causes salt secretion by the kidney, decreases blood volume and pressure, and therefore serves to reduce hemodynamic load.

Whatever the exact cause and mechanism of cardiac hypertrophy, it eventually reaches a limit beyond which enlargement of muscle mass is no longer able to compensate for the increased burden. At this stage several regressive changes occur in the myocardial fibers, of which the most important are lysis and loss of myofibrillar contractile elements. In extreme cases myocyte death can occur by either apoptosis or necrosis.[5,6] The net result of these changes is cardiac failure, a sequence of events that illustrates how *an adaptation to stress can progress to functionally significant cell injury if the stress is not relieved.*

Although hypertrophy usually refers to increase in size of cells or tissues, sometimes a subcellular organelle may undergo selective hypertrophy. For instance, individuals treated with drugs such as barbiturates show hypertrophy of the smooth endoplamic reticulum (ER) in hepatocytes, which is an adaptive response that increases the amount of enzymes (cytochrome P-450 mixed function oxidases) available to detoxify the drugs. Over time, the patients respond less to the drug because of this adaptation. Adaptation to one drug may result in an increased capacity to metabolize other drugs. For instance, alcohol intake causes hypertrophy of the smooth ER and may lead to reduced levels of available barbiturates that are being taken at the same time. Although P-450-mediated modification is often thought of as "detoxification," many compounds are rendered *more* injurious by this process. In addition, the products formed by this oxidative metabolism include reactive oxygen species, which can injure the cell. Normal genetic variations (polymorphisms) influence the activity of P-450, and thus the sensitivity of different individuals to various drugs.[7]

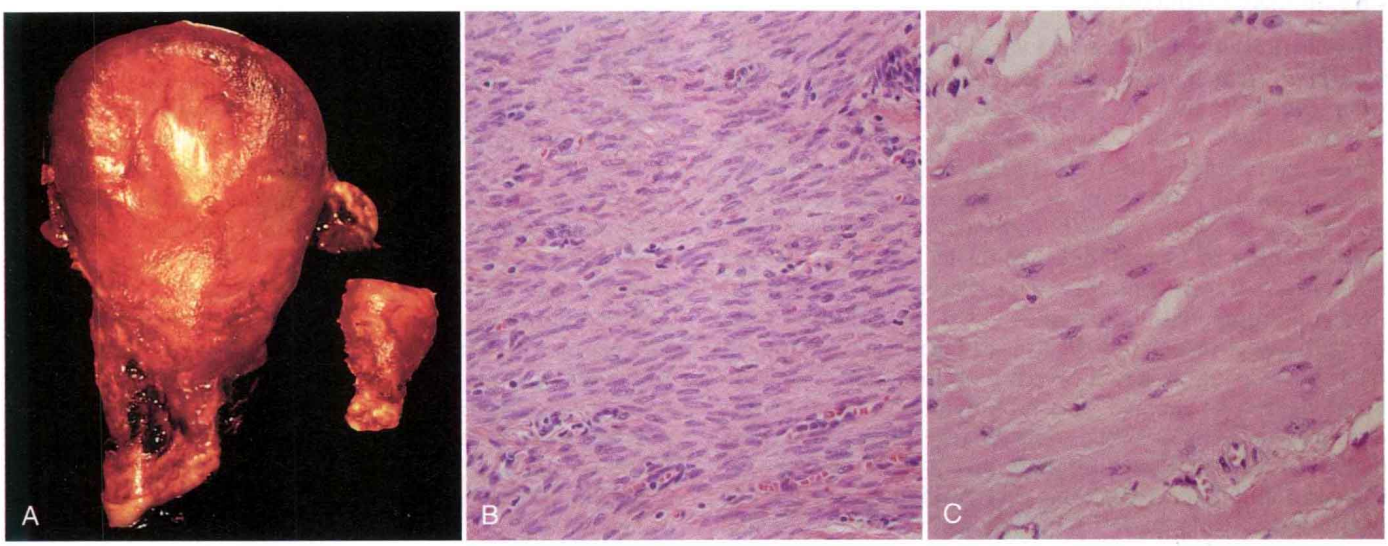


FIGURE 1–3 Physiologic hypertrophy of the uterus during pregnancy. **A,** Gross appearance of a normal uterus *(right)* and a gravid uterus (removed for postpartum bleeding) *(left)*. **B,** Small spindle-shaped uterine smooth muscle cells from a normal uterus, compared with **C,** large plump cells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