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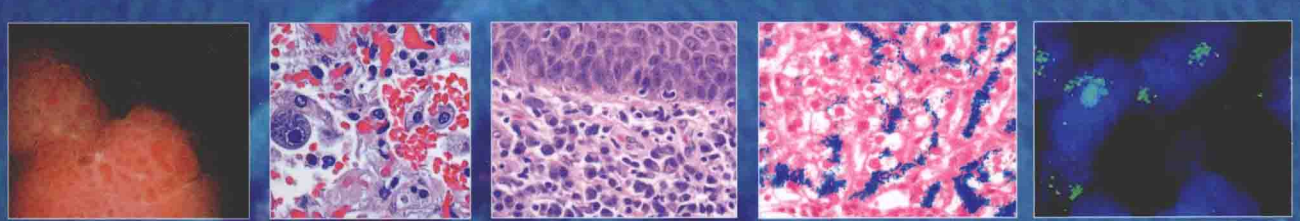

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Basic Pathology

NINTH EDITION

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DEDICATION

To
Our children and a special grandchild
Kiera Chapman Kumar

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Preface

FORTY YEARS OF BASIC PATHOLOGY

As we reach the 40th year of the publication of *Robbins Basic Pathology,* it is useful to quote Stanley Robbins from the Preface of the first edition (1971):

"Of books as well as men, it may be observed that fat ones contain thin ones struggling to get out. In a sense, this book bears such a relationship to its more substantial progenitor, *Robbins Pathology*. It arose from an appreciation of the modern medical student's dilemma. As the curriculum has become restructured to place greater emphasis on clinical experience, time for reading is correspondingly curtailed. ... In writing this book, rare and esoteric lesions are omitted without apology, and infrequent or trivial ones described only briefly. We felt it important, however, to consider rather fully the major disease entities."

The goals of this edition of "baby Robbins" remain true to this vision of Stanley Robbins.

This is an exciting time for students of medicine because the fundamental mechanisms of disease are being unveiled at a breathtaking pace. Pathology is central to understanding the molecular basis of disease, and we have tried to capture the essence of this new knowledge in the ninth edition of *Robbins Basic Pathology*. We firmly believe that pathology forms the scientific foundation of medicine, and advances in the basic sciences ultimately help us in understanding diseases in the individual patient. Thus, while many of the new discoveries in genomics and personalized medicine are covered in the initial chapters on general pathology, we have strived to include the impact of scientific advances on diseases of organ systems described throughout the text. To emphasize the importance of disease mechanisms in the practice of medicine, we have highlighted sections dealing with pathogenesis. In recent years an understanding of the molecular basis of disease has led to the development of "targeted therapies." These are highlighted in the form of "Targeted Therapy" boxes in the online edition of this book. We hope that this new feature will provide examples of "bench-to-bedside" medicine. Although many of the "breakthroughs" in the laboratory have not yet reached the bedside, we have included them in measured "doses" so that students can begin to experience the excitement that is ahead in their careers.

Realizing that the modern medical student feels inundated in trying to synthesize the essentials with the "state of the art," we have continued the use of Summary boxes designed to provide the students with key "take home" messages. These have been retained at the risk of adding a few additional pages to the book since students have uniformly told us that they find them useful.

Many new pieces of four-color art—schematics, flow charts, and diagrammatic representations of disease—have been added to facilitate the understanding of difficult concepts such as the control of the cell cycle, functions of cancer genes, interactions of HIV with its receptors, and the biochemical basis of apoptotic cell death. More illustrations have been added, bringing the total to more than 1,000. Formatting and color palettes of the tables have been changed for greater clarity.

Despite the extensive changes and revisions, our goals remain essentially unaltered. Although we have entered the genomic era, the time-honored tools of gross and microscopic analysis remain useful and morphologic changes are highlighted for ready reference. The strong emphasis on clinicopathologic correlations is maintained, and wherever understood, the impact of molecular pathology on the practice of medicine is emphasized. We are pleased that all of this was accomplished without any "bulge" in the waistline of the text.

We continue to firmly believe that clarity of writing and proper use of language enhance comprehension and facilitate the learning process. Generations of students have told us that they enjoy reading this book. We hope that this edition will be worthy of and possibly enhance the tradition of its forebears.

Acknowledgments

First and foremost, we wish to thank and acknowledge our long-time friend and colleague Dr. Nelson Fausto for his contributions to the previous edition of this book. We continue to benefit from his writing and editing.

Any large endeavor of this type cannot be completed without the help of many individuals. We thank the contributors of various chapters. Many are veterans of the older sibling of this text, the so-called "Big Robbins," and they are listed in the table of contents. To each of them a special thanks. We are fortunate to continue our collaboration with Jim Perkins, whose illustrations bring abstract ideas to life and clarify difficult concepts, and we welcome Dr. Raminder Kumar who edited several chapters for accuracy and appropriateness of the clinical content.

Our assistants, Valerie Driscoll from Chicago, Ana Narvaez from San Francisco, and Muriel Goutas from Boston, deserve thanks for coordinating the tasks.

Many colleagues have enhanced the text by providing helpful critiques in their areas of interest. These include Dr. Rick Aster, who provided "late-breaking news" in the area of climate change science. Many others offered critiques of various chapters. They include Drs. Tony Chang and Neeraj Jolly at the University of Chicago; Drs. Ryan Gill, Andrew Horvai, Marta Margeta, Arie Perry, and Mike Rosenblum of the University of California at San Francisco; Dr. John Stone from Massachusetts General Hospital, Harvard Medical School; Dr. Diego H. Castrillon at UT Southwestern Medical School; and Dr. Victor J. Thannickal of the University of Alabama at Birmingham. Others have provided us with photographic gems from their personal collections. They are individually acknowledged in the credits for their contribution(s). For any unintended omissions we offer our apologies.

Many at Elsevier deserve recognition for their roles in the production of this book. This text was fortunate to be in the hands of Rebecca Gruliow (Manager, Content Development) who has been our partner for several editions. Others deserving of our thanks are Sarah Wunderly (Senor Project Manager) and Lou Forgione (Senior Book Designer). Bill Schmitt, Executive Content Strategist, continues to be our cheerleader and friend. We are especially grateful to the entire production team for tolerating our sometimes next to "impossible" demands and for putting up with our idiosyncrasies during the periods of extreme exhaustion that afflict all authors who undertake what seems like an endless task. We are thankful to the entire Elsevier team for sharing our passion for excellence.

Ventures such as this exact a heavy toll from the families of the authors. We thank them for their tolerance of our absences, both physical and emotional. We are blessed and strengthened by their unconditional support and love, and for their sharing with us the belief that our efforts are worthwhile and useful. We are especially grateful to our wives Raminder Kumar, Ann Abbas, and Erin Malone, who continue to provide steadfast support.

And finally, Vinay Kumar and Abul Abbas welcome Jon Aster, who cut his teeth on the eighth edition of *Pathologic Basis of Disease*, as a co-author and editor. Our partnership thrives because of a shared vision of excellence in teaching despite differences in opinions and individual styles.

VK
AKA
JCA

Contents

Chapters without author names were written by the editors.

See Targeted Therapy available online at
studentconsult.com

CHAPTER 1

Cell Injury, Cell Death, and Adaptations

CHAPTER CONTENTS

INTRODUCTION TO PATHOLOGY

Literally translated, *pathology* is the study (*logos*) of disease (*pathos,* suffering). It involves the investigation of the causes of disease and the associated changes at the levels of cells, tissues, and organs, which in turn give rise to the presenting signs and symptoms of the patient. There are two important terms that students will encounter throughout their study of pathology and medicine:

- *Etiology* is the origin of a disease, including the underlying causes and modifying factors. It is now clear that most common diseases, such as hypertension, diabetes, and cancer, are caused by a combination of inherited genetic susceptibility and various environmental triggers. Understanding the genetic and environmental factors underlying diseases is a major theme of modern medicine.
- *Pathogenesis* refers to the steps in the development of disease. It describes how etiologic factors trigger cellular and molecular changes that give rise to the specific functional and structural abnormalities that characterize the disease. Whereas etiology refers to *why* a disease arises, pathogenesis describes *how* a disease develops.

Defining the etiology and pathogenesis of disease not only is essential for understanding a disease but is also the basis for developing rational treatments. Thus, by explaining the causes and development of disease *pathology provides the scientific foundation for the practice of medicine.*

To render diagnoses and guide therapy in clinical practice, pathologists identify changes in the gross or microscopic appearance (*morphology*) of cells and tissues, and biochemical alterations in body fluids (such as blood and urine). Pathologists also use a variety of morphologic, molecular, microbiologic, and immunologic techniques to define the biochemical, structural, and functional changes that occur in cells, tissues, and organs in response to injury. Traditionally, the discipline is divided into general pathology and systemic pathology; the former focuses on the cellular and tissue alterations caused by pathologic stimuli in most tissues, while the latter examines the reactions and abnormalities of different specialized organs. In this book we first cover the broad principles of general pathology and then progress to specific disease processes in individual organs.

OVERVIEW OF CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI

Cells are active participants in their environment, constantly adjusting their structure and function to accommodate changing demands and extracellular stresses. Cells normally maintain a steady state called *homeostasis* in which the intracellular milieu is kept within a fairly narrow range of physiologic parameters. As cells encounter physiologic stresses or pathologic stimuli, they can undergo

adaptation, achieving a new steady state and preserving viability and function. The principal adaptive responses are *hypertrophy, hyperplasia, atrophy,* and *metaplasia.* If the adaptive capability is exceeded or if the external stress is inherently harmful, *cell injury* develops (Fig. 1-1). Within certain limits, injury is *reversible,* and cells return to a stable baseline; however, if the stress is severe, persistent and rapid in onset, it results in *irreversible injury* and death of the affected cells. *Cell death* is one of the most crucial events in the evolution of disease in any tissue or organ. It results from diverse causes, including ischemia (lack of blood flow), infections, toxins, and immune reactions. Cell death also is a normal and essential process in embryogenesis, the development of organs, and the maintenance of homeostasis.

The relationships among normal, adapted, and reversibly and irreversibly injured cells are well illustrated by the responses of the heart to different types of stress (Fig. 1-2). Myocardium subjected to persistent increased load, as in hypertension or with a narrowed (stenotic) valve, adapts by undergoing *hypertrophy*—an increase in the size of the individual cells and ultimately the entire heart—to generate the required higher contractile force. If the increased demand is not relieved, or if the myocardium is subjected to reduced blood flow (*ischemia*) from an occluded coronary artery, the muscle cells may undergo injury. Myocardium may be reversibly injured if the stress is mild or the arterial occlusion is incomplete or sufficiently brief, or it may undergo irreversible injury and cell death (*infarction*) after complete or prolonged occlusion. Also of note, stresses

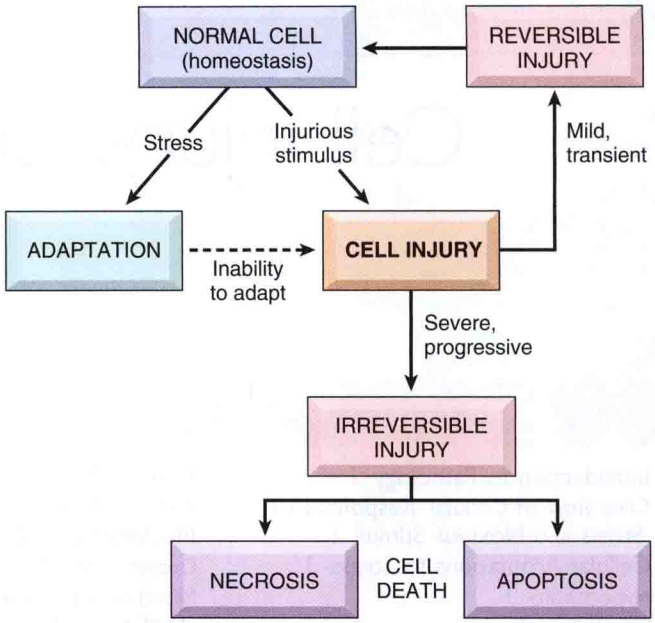

Figure 1–1 Stages in the cellular response to stress and injurious stimuli.

and injury affect not only the morphology but also the functional status of cells and tissues. Thus, reversibly injured myocytes are not dead and may resemble normal myocytes morphologically; however, they are transiently noncontractile, so even mild injury can have a significant

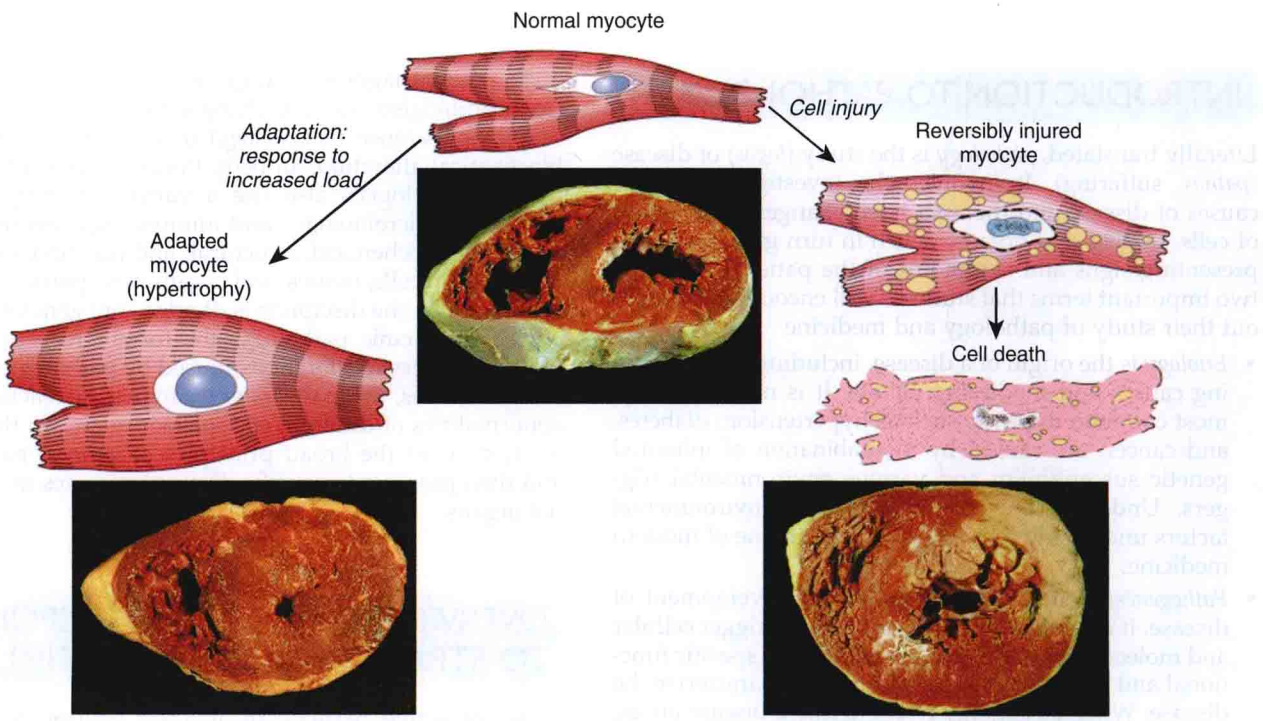

Figure 1–2 The relationship among normal, adapted, reversibly injured, and dead myocardial cells. The cellular adaptation depicted here is hypertrophy, the type of reversible injury is ischemia, and the irreversible injury is ischemic coagulative necrosis. In the example of myocardial hypertrophy (*lower left*), the left ventricular wall is thicker than 2 cm (normal, 1–1.5 cm). Reversibly injured myocardium shows functional effects without any gross or light microscopic changes, or reversible changes like cellular swelling and fatty change (*shown here*). In the specimen showing necrosis (*lower right*) the transmural light area in the posterolateral left ventricle represents an acute myocardial infarction. All three transverse sections of myocardium have been stained with triphenyltetrazolium chloride, an enzyme substrate that colors viable myocardium magenta. Failure to stain is due to enzyme loss after cell death.

clinical impact. Whether a specific form of stress induces adaptation or causes reversible or irreversible injury depends not only on the nature and severity of the stress but also on several other variables, including basal cellular metabolism and blood and nutrient supply.

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

CELLULAR ADAPTATIONS TO STRESS

Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment. *Physiologic adaptations* usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy). *Pathologic adaptations* are responses to stress that allow cells to modulate their structure and function and thus escape injury. Such adaptations can take several distinct forms.

Hypertrophy

Hypertrophy is an increase in the size of cells resulting in increase in the size of the organ. In contrast, hyperplasia (discussed next) is characterized by an increase in cell number because of proliferation of differentiated cells and replacement by tissue stem cells. Stated another way, in pure hypertrophy there are no new cells, just bigger cells containing increased amounts of structural proteins and organelles. Hyperplasia is an adaptive response in cells capable of replication, whereas hypertrophy occurs when cells have a limited capacity to divide. Hypertrophy and hyperplasia also can occur together, and obviously both result in an enlarged (*hypertrophic*) organ.

Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or by growth factor or hormonal stimulation.

- The massive physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogen-stimulated smooth muscle hypertrophy and smooth muscle hyperplasia (Fig. 1–3). In contrast, in response to increased demand the striated muscle cells in both the skeletal muscle and the heart can undergo only hypertrophy because adult muscle cells have a limited capacity to divide. Therefore, the chiseled physique of the avid weightlifter stems solely from the hypertrophy of individual skeletal muscles.
- An example of pathologic cellular hypertrophy is the cardiac enlargement that occurs with hypertension or aortic valve disease (Fig. 1–2).

The mechanisms driving cardiac hypertrophy involve at least two types of signals: *mechanical triggers,* such as stretch, and *trophic triggers,* which typically are soluble mediators that stimulate cell growth, such as growth factors and adrenergic hormones. These stimuli turn on signal transduction pathways that lead to the induction of a number of genes, which in turn stimulate synthesis of many cellular proteins, including growth factors and structural proteins. The result is the synthesis of more proteins and myofilaments per cell, which increases the force generated with each contraction, enabling the cell to meet increased work demands. There may also be a switch of contractile proteins from adult to fetal or neonatal forms. For example, during muscle hypertrophy, the α-myosin heavy chain is replaced by the β form of the myosin heavy chain, which produces slower, more energetically economical contraction.

Whatever the exact mechanisms of hypertrophy, a limit is reached beyond which the enlargement of muscle mass

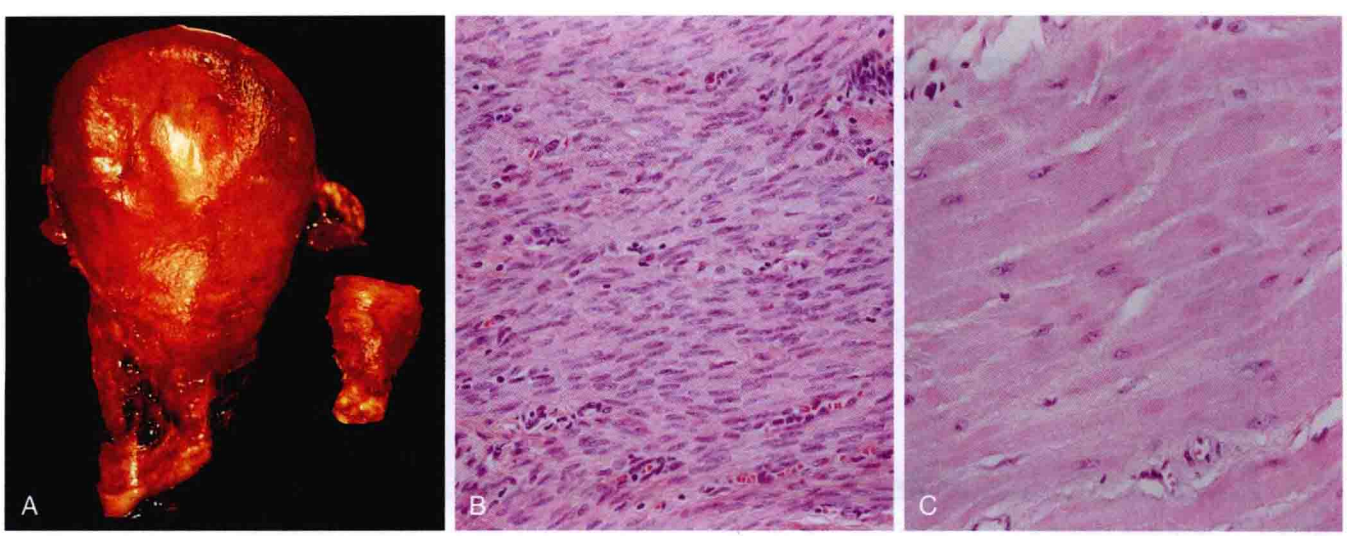

Figure 1–3 Physiologic hypertrophy of the uterus during pregnancy. **A,** Gross appearance of a normal uterus (*right*) and a gravid uterus (*left*) that was removed for postpartum bleeding. **B,** Small spindle-shaped uterine smooth muscle cells from a normal uterus. **C,** Large, plump hypertrophied smooth muscle cells from a gravid uterus; compare with **B.** (**B** and **C,** Same magnification.)

can no longer compensate for the increased burden. When this happens in the heart, several "degenerative" changes occur in the myocardial fibers, of which the most important are fragmentation and loss of myofibrillar contractile elements. The variables that limit continued hypertrophy and cause the regressive changes are incompletely understood. There may be finite limits of the vasculature to adequately supply the enlarged fibers, of the mitochondria to supply adenosine triphosphate (ATP), or of the biosynthetic machinery to provide the contractile proteins or other cytoskeletal elements. The net result of these changes is ventricular dilation and ultimately 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.*

Hyperplasia

As discussed earlier, hyperplasia takes place if the tissue contains cell populations capable of replication; it may occur concurrently with hypertrophy and often in response to the same stimuli.

Hyperplasia can be physiologic or pathologic. In both situations, cellular proliferation is stimulated by growth factors that are produced by a variety of cell types.

- The two types of *physiologic hyperplasia* are (1) *hormonal hyperplasia,* exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy, and (2) *compensatory hyperplasia,* in which residual tissue grows after removal or loss of part of an organ. For example, when part of a liver is resected, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal weight. The stimuli for hyperplasia in this setting are polypeptide growth factors produced by uninjured hepatocytes as well as nonparenchymal cells in the liver (Chapter 2). After restoration of the liver mass, cell proliferation is "turned off" by various growth inhibitors.
- Most forms of *pathologic hyperplasia* are caused by excessive hormonal or growth factor stimulation. For example, after a normal menstrual period there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by inhibition through progesterone. However, a disturbed balance between estrogen and progesterone causes endometrial hyperplasia, which is a common cause of abnormal menstrual bleeding. Hyperplasia also is an important response of connective tissue cells in wound healing, in which proliferating fibroblasts and blood vessels aid in repair (Chapter 2). In this process, growth factors are produced by white blood cells (leukocytes) responding to the injury and by cells in the extracellular matrix. Stimulation by growth factors also is involved in the hyperplasia that is associated with certain viral infections; for example, papillomaviruses cause skin warts and mucosal lesions composed of masses of hyperplastic epithelium. Here the growth factors may be encoded by viral genes or by the genes of the infected host cells.

An important point is that in all of these situations, *the hyperplastic process remains controlled; if the signals that initiate it abate, the hyperplasia disappears.* It is this responsiveness to normal regulatory control mechanisms that distinguishes pathologic hyperplasias from cancer, in which the growth control mechanisms become dysregulated or ineffective (Chapter 5). Nevertheless, in many cases, pathologic hyperplasia constitutes a fertile soil in which cancers may eventually arise. For example, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer (Chapter 18).

Atrophy

Shrinkage in the size of the cell by the loss of cell substance is known as atrophy. When a sufficient number of cells are involved, the entire tissue or organ diminishes in size, becoming atrophic (Fig. 1–4). Although atrophic cells may have diminished function, they are not dead.

Causes of atrophy include a decreased workload (e.g., immobilization of a limb to permit healing of a fracture),

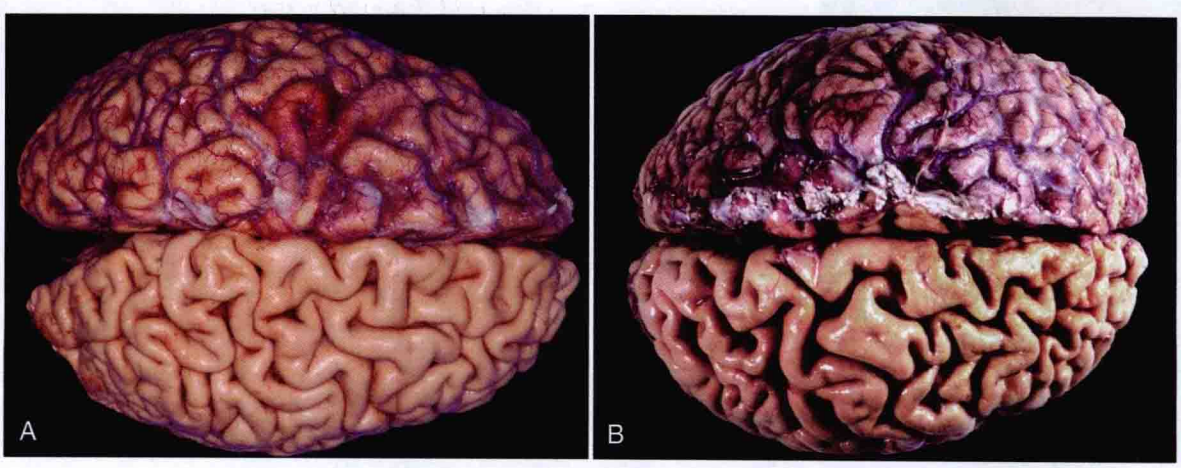

Figure 1–4 Atrophy as seen in the brain. **A,** Normal brain of a young adult. **B,** Atrophy of the brain in an 82-year-old man with atherosclerotic disease. Atrophy of the brain is due to aging and reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the bottom half of each specimen to reveal the surface of the brain.

loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging (senile atrophy). Although some of these stimuli are physiologic (e.g., the loss of hormone stimulation in menopause) and others pathologic (e.g., denervation), the fundamental cellular changes are identical. They represent a retreat by the cell to a smaller size at which survival is still possible; a new equilibrium is achieved between cell size and diminished blood supply, nutrition, or trophic stimulation.

The mechanisms of atrophy consist of a combination of decreased protein synthesis and increased protein degradation in cells.

- Protein synthesis decreases because of reduced metabolic activity.
- The degradation of cellular proteins occurs mainly by the *ubiquitin-proteasome pathway.* Nutrient deficiency and disuse may activate ubiquitin ligases, which attach multiple copies of the small peptide ubiquitin to cellular proteins and target them for degradation in proteasomes. This pathway is also thought to be responsible for the accelerated proteolysis seen in a variety of catabolic conditions, including the cachexia associated with cancer.
- In many situations, atrophy is also accompanied by increased *autophagy,* with resulting increases in the number of *autophagic vacuoles.* Autophagy ("self-eating") is the process in which the starved cell eats its own components in an attempt to survive. We describe this process later in the chapter.

Metaplasia

Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. In this type of cellular adaptation, a cell type sensitive to a particular stress is replaced by another cell type better able to withstand the adverse environment. Metaplasia is thought to arise by reprogramming of stem cells to differentiate along a new pathway rather than a phenotypic change (transdifferentiation) of already differentiated cells.

Epithelial metaplasia is exemplified by the squamous change that occurs in the respiratory epithelium of habitual cigarette smokers (Fig. 1–5). The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelial cells. The rugged stratified squamous epithelium may be able to survive the noxious chemicals in cigarette smoke that the more fragile specialized epithelium would not tolerate. *Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost,* such as mucus secretion and ciliary clearance of particulate matter. Epithelial metaplasia is therefore a double-edged sword. Moreover, *the influences that induce metaplastic change, if persistent, may predispose to malignant transformation of the epithelium.* In fact, squamous metaplasia of the respiratory epithelium often coexists with lung cancers composed of malignant squamous cells. It is thought that cigarette smoking initially causes squamous metaplasia, and cancers arise later in some of these altered foci. Since vitamin A is essential for normal epithelial differentiation, its deficiency may also induce squamous metaplasia in the respiratory epithelium. Metaplasia need not always occur in the direction of columnar to squamous epithelium; in chronic gastric reflux, the normal stratified squamous epithelium of the lower esophagus may undergo metaplastic transformation to gastric or intestinal-type columnar epithelium. Metaplasia may also occur in mesenchymal cells but in these situations it is generally a reaction to some pathologic alteration and not an adaptive response to stress. For example, bone is occasionally formed in soft tissues, particularly in foci of injury.

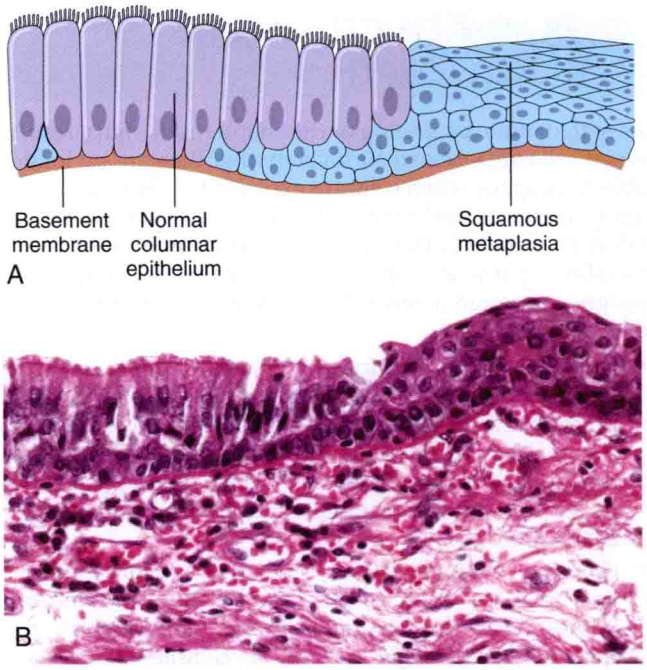

Figure 1–5 Metaplasia of normal columnar (*left*) to squamous epithelium (*right*) in a bronchus, shown schematically (**A**) and histologically (**B**).

SUMMARY

Cellular Adaptations to Stress

- *Hypertrophy:* increased cell and organ size, often in response to increased workload; induced by growth factors produced in response to mechanical stress or other stimuli; occurs in tissues incapable of cell division
- *Hyperplasia:* increased cell numbers in response to hormones and other growth factors; occurs in tissues whose cells are able to divide or contain abundant tissue stem cells
- *Atrophy:* decreased cell and organ size, as a result of decreased nutrient supply or disuse; associated with decreased synthesis of cellular building blocks and increased breakdown of cellular organelles
- *Metaplasia:* change in phenotype of differentiated cells, often in response to chronic irritation, that makes cells better able to withstand the stress; usually induced by altered differentiation pathway of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation

OVERVIEW OF CELL INJURY AND CELL DEATH

As stated at the beginning of the chapter, cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities (e.g., in DNA or proteins). Different injurious stimuli affect many metabolic pathways and cellular organelles. Injury may progress through a reversible stage and culminate in cell death (Fig. 1–1).

- *Reversible cell injury.* In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution.
- *Cell death.* With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. *There are two types of cell death – necrosis and apoptosis – which differ in their mechanisms, morphology, and roles in disease and physiology* (Fig. 1–6 and Table 1–1). When damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell, resulting in *necrosis.* Cellular contents also leak through the damaged plasma membrane into the extracellular space, where they elicit a host reaction (inflammation). Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma. When a cell is deprived of growth factors, or the cell's DNA or proteins are damaged beyond repair, typically the cell kills itself by another type of death, called *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 pathologic cell injury. Furthermore, in keeping with its role in certain physiologic processes, apoptosis does not elicit an inflammatory response.* The morphologic features, mechanisms, and significance of these two death pathways are discussed in more detail later in the chapter.

CAUSES OF CELL INJURY

The causes of cell injury range from the gross physical trauma of a motor vehicle accident to the single gene defect that results in a nonfunctional enzyme underlying a

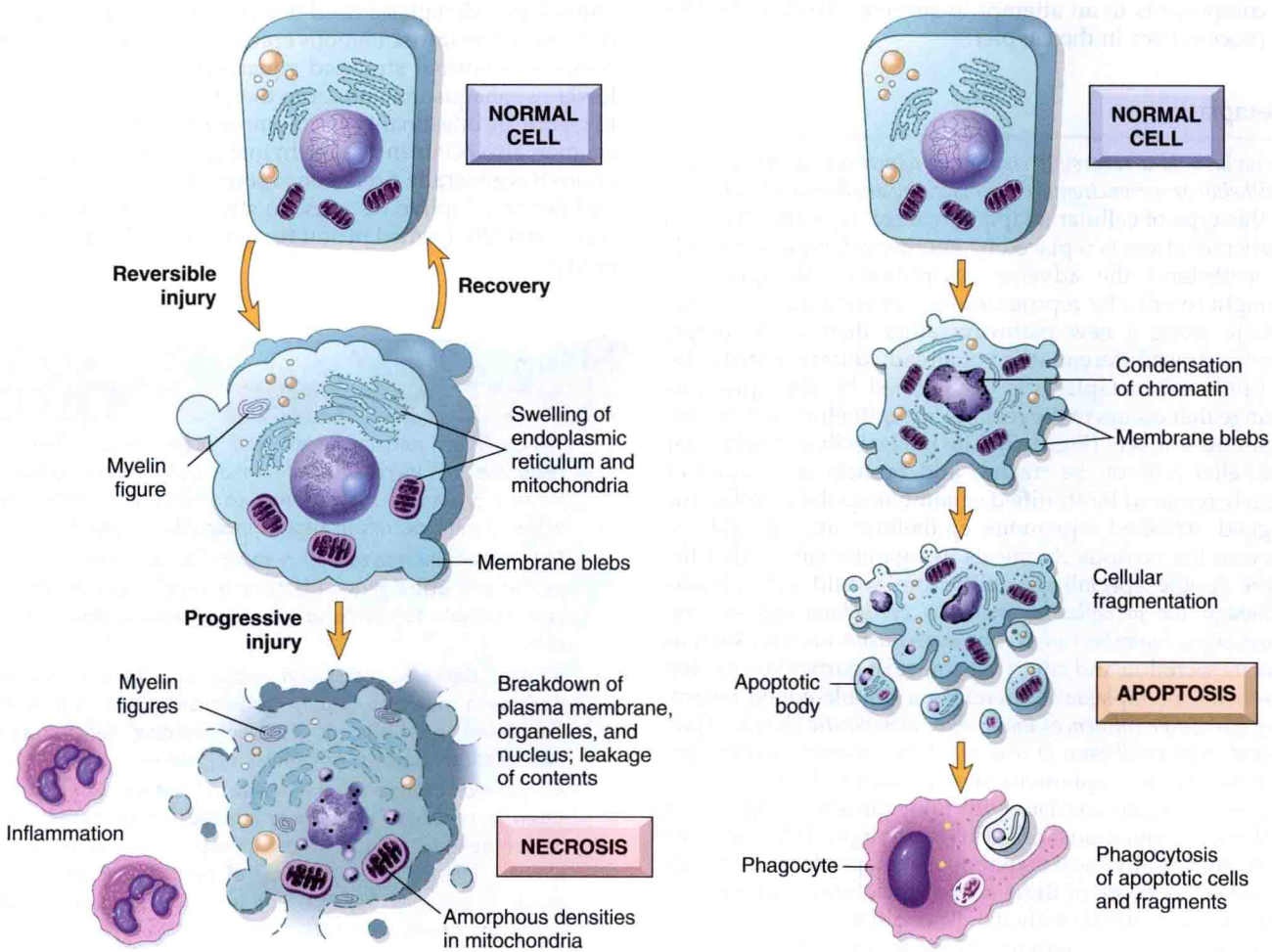

Figure 1–6 Cellular features of necrosis (*left*) and apoptosis (*right*).