Pathology

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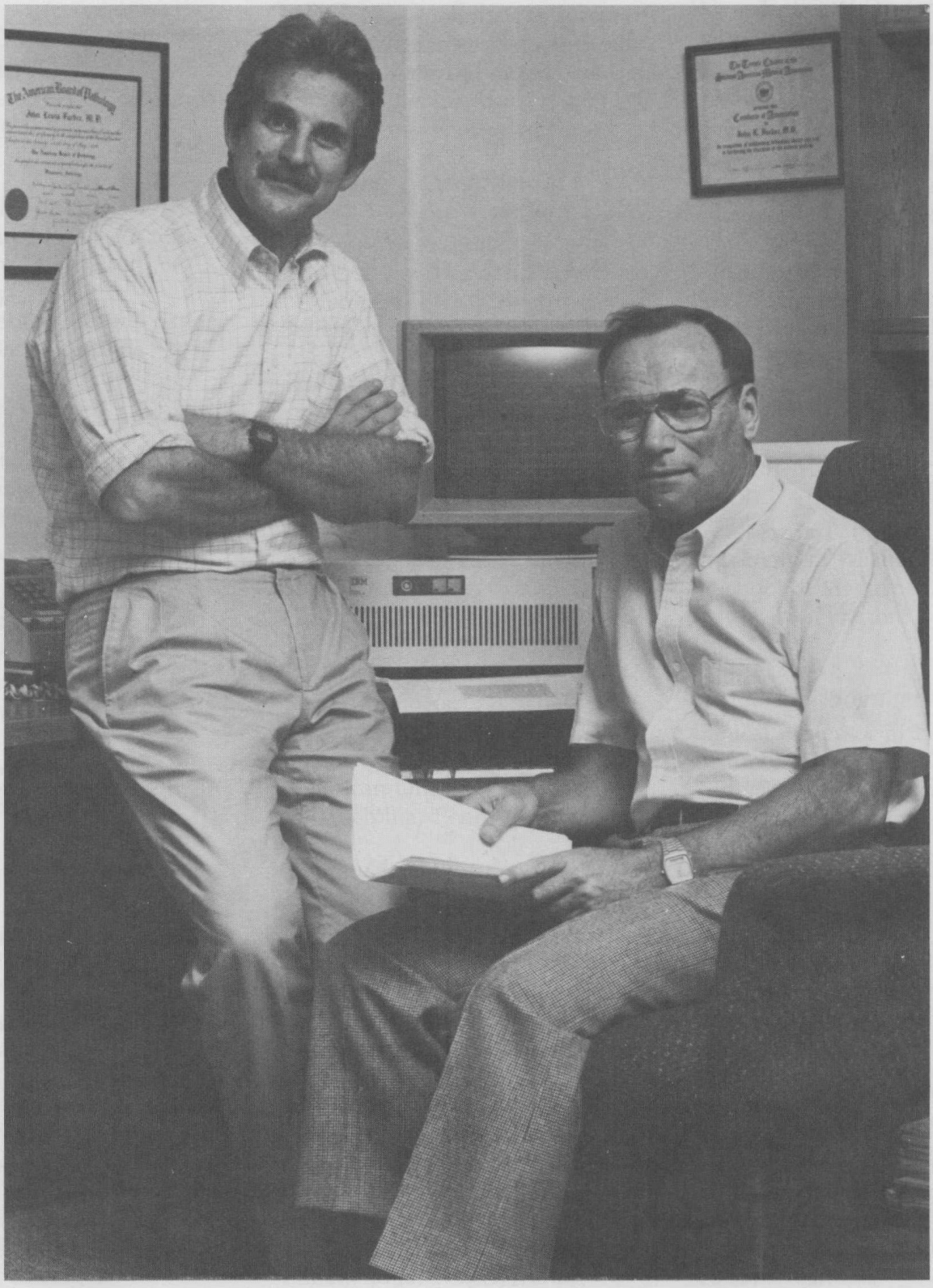

Preface

Pathology has been defined as the medical science that deals with all aspects of disease, but with special reference to the essential nature, the causes, and the development of abnormal conditions. In this sense, literacy in pathology is the bedrock of practice and research for the student of medical science. This book provides such a foundation by presenting classical general pathology and systemic pathologic anatomy in the context of modern biology.

To aid the reader in understanding and retaining complex and detailed information, we have devoted much space to graphic representations of the pathogenesis of disease, the complications of various disorders, and sequences of pathologic alterations. Because graphic images take advantage of pattern recognition, one of the most fundamental characteristics of the human brain, they powerfully communicate abstract and complex material, as any lecturer who has presented a graph will attest. At the same time, we have been guided by Einstein's admonition that "everything should be made as simple as possible, but not simpler." Whereas photomicrographs invariably include some distracting details and artifacts, graphics concentrate only on the essential features. They provide a direct route to the important principles—a "road map" to the basic concepts of pathology. Furthermore, graphics avoid semantic ambiguities and serve as effective summaries of the material presented in the text.

Every photograph included in this work had to pass two tests. It had to illustrate an important morphologic entity by supplementing its description in the text as well as serving as an example of a disease process. We further required that each photograph be sufficiently representative, technically precise, and devoid of artifact as to be clearly interpretable independent of its description in the text.

The scope of contemporary pathology can only be encompassed in a work such as this one through the participation of recognized authorities who are also experienced teachers. Yet we realized that a consistent literary style—beyond that usually found in multi-authored works—coupled with a constant graphic approach was essential for a coherent presentation. This goal required an unusually close working collaboration between the editors, the contributors, and the artist, Dimitri Karetnikov.

In the preparation of this book, we were mindful of the unparalleled advances in biology that have occurred over the past half century. The towering achievements in the study of ultrastructure, biochemistry, immunology, and molecular genetics have had a profound effect on current thinking about the pathogenesis of disease. At the same time, we remained dedicated to Virchow's original concept that ". . . the cell is really the ultimate morphological element in which there is any manifestation of life, and . . . we must not transfer the seat of real action to any point beyond the cell." The marriage of classical morphologic descriptions of disease and contemporary scientific concepts in this book serves to join traditional pathology with the modern revolution in biology.

Emanuel Rubin
John L. Farber

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1 Cell Injury

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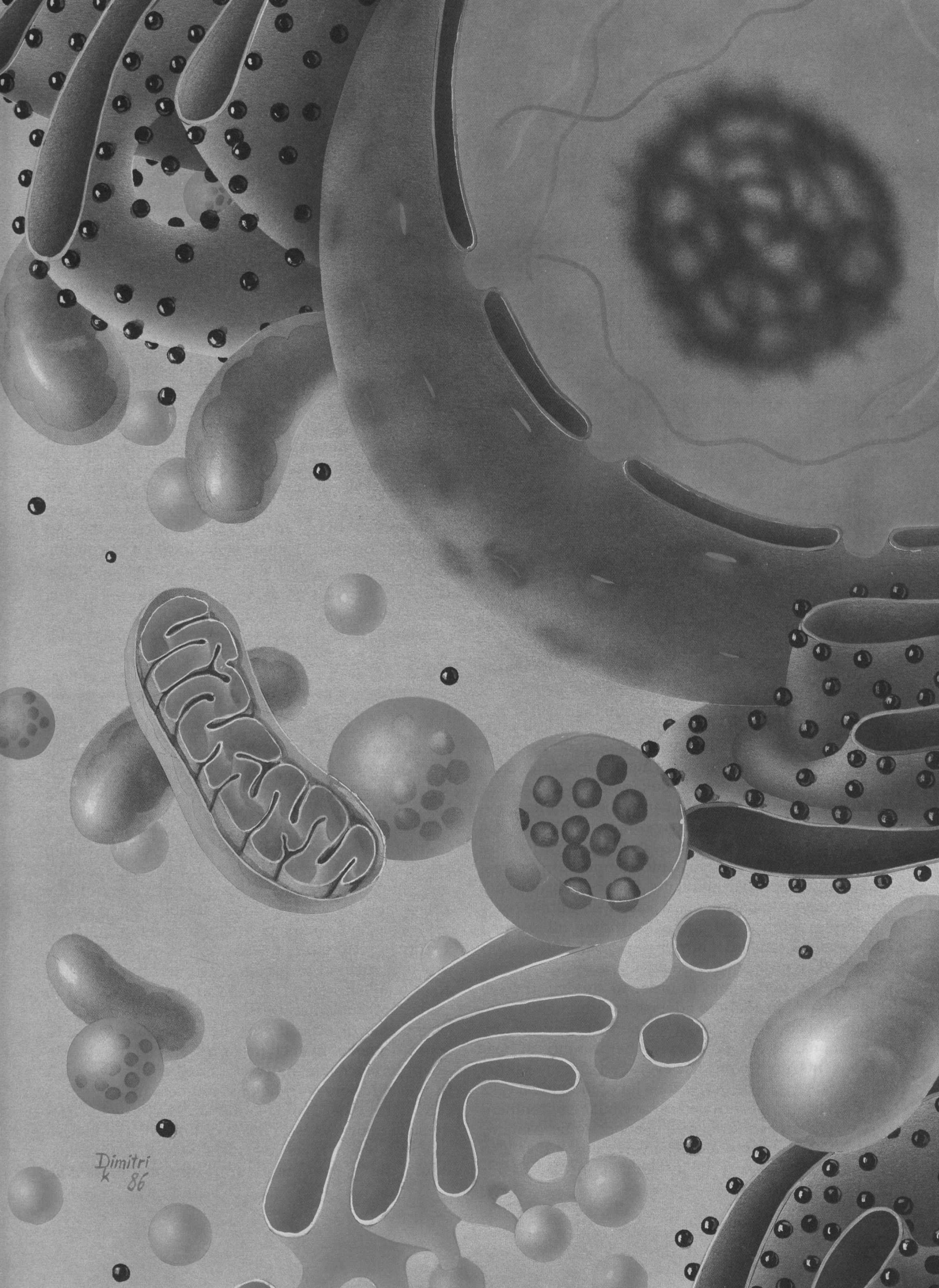
Figure 1-1. Interior of an idealized cell.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Pathology in its simplest sense is the study of structural and functional abnormalities that are expressed as diseases of organs and systems. Classical theories of disease attributed all disorders to systemic imbalances or to noxious effects of humors on specific organs. In the 19th century, Rudolf Virchow, often referred to as the father of modern pathology, broke sharply with such traditional concepts by proposing that the basis of all disease is injury to the smallest living unit of the body, namely the cell. More than a century later, clinical and experimental pathology remain rooted in Virchow's cellular pathology.

To appreciate the mechanisms of injury to the cell, it is useful to consider its global needs in a philosophical sense. In the reaction against mystical or vitalistic theories of biology, teleology—the study of design or purpose in nature—was discredited as a means of scientific investigation. Nevertheless, although facts can only be established by observations, teleologic thinking can be important in framing questions. As an analogy, without an understanding of the goals of chess and prior knowledge that a particular computer is programmed to play it, no analysis of the machine would be likely to uncover its method of operation. Moreover, it would be futile to search for the sources of defects in the specific program or overall operating system while lacking an appreciation of the goals of the device. In this sense, it is helpful to understand the problems with which the cell is confronted and the strategies that have evolved to cope with them.

If one accepts the premise that a living cell must maintain an organization capable of producing energy, then the most pressing need for a free living cell, whether prokaryotic or eukaryotic, is to establish a structural and functional barrier between its internal milieu and a hostile environment. The plasma membrane serves this purpose in three ways: it maintains a constant internal ionic composition against very large chemical gradients between the interior and exterior compartments; it selectively admits some molecules while excluding or extruding others; and it provides a structural envelope to contain the informational, synthetic, and catabolic constituents of the cell. At the same time, in order to survive, the cell must be able to adapt to adverse environmental conditions, such as changes in temperature, solute concentrations, or oxygen supply, the presence of noxious agents, and so on. The evolution of multicellular organisms eased the hazardous lot of individual cells by establishing a controlled extracellular environment in which temperature, oxygenation, ionic content, and nutrient supply are relatively constant. It also permitted the luxury of differentiation of cells for such widely divergent functions as nutrient storage (liver cell glycogen and adipocytes), communication (neurons), contractile activity (heart muscle), synthesis of proteins or peptides for export (liver, pancreas, and endocrine cells), absorption (intestine), and defense against foreign invaders (polymorphonuclear leukocytes, lymphocytes, and macrophages).

Cells encounter many stresses as a result of changes in their internal and external environments. The patterns of response to this stress constitute the cellular bases of disease. If an injury exceeds the adaptive capacity of the cell, it dies. A cell exposed to persistent sublethal injury has a limited repertoire of responses, the expression of which we interpret as evidence of cell injury. In general, the mammalian cell adapts to injury by conserving its resources; it decreases or ceases its differentiated functions and reverts to its ancestral, unicellular character, which is concerned with functions exclusively dedicated to its own survival. In this perspective, **pathology is the study of cell injury and the expression of a preexisting capacity to adapt to such injury, on the part of either injured or intact cells.** Such an orientation leaves little room for the concept of parallel—normal and pathologic—biologies.

Cellular Patterns of Response to Stress

All cells have efficient mechanisms to deal with shifts in environmental conditions. Thus, ion channels open or close, harmful chemicals are detoxified, metabolic stores such as fat or glycogen may be mobilized, and catabolic processes lead to the segregation of internal particulate materials. It is when environmental changes exceed the capacity of the cell to maintain normal homeostasis that we recognize acute cell injury. If the stress is removed in time, or if the cell is able to withstand the assault, cell injury is reversible, and complete structural and functional integrity is restored. For example, this is the situation when circulation to the heart is interrupted for less than one-half hour. The cell can also be exposed to persistent, sublethal stress, as in mechanical irritation of the skin or exposure of the bronchial mucosa to tobacco smoke. In such instances the cell has time to adapt to reversible injury in a number of ways, each of which has its morphologic counterpart.

On the other hand, if the stress is severe, irreversible injury leads to death of the cell. The precise moment when reversible gives way to irreversible injury, the "point of no return," cannot at present be

identified. **The morphologic pattern of cell death occasioned by disparate exogenous environmental stresses is coagulative necrosis.** This type of necrosis is common to almost all forms of cell death and precedes the other forms described below.

Reversible Cell Injury

Hydropic Swelling

Acute cell injury may result from such disparate causes as chemical and biologic toxins, viral or bacterial infections, ischemia, excessive heat or cold, and so on. Regardless of the cause, reversibly injured cells are often enlarged. The greater volume reflects an increased water content and is known as **hydropic swelling, a condition characterized by a large, pale cytoplasm and a normally located nucleus** (Fig. 1-2). The number of organelles is unchanged, although they appear dispersed in a larger volume. The term "cloudy swelling" refers to the gross appearance of injured tissue, but is archaic.

Hydropic swelling results from impairment of cellular volume regulation, a process which controls ionic concentrations in the cytoplasm. This regulation, particularly for sodium, operates at three levels: the plasma membrane itself, the plasma membrane sodium pump, and the supply of ATP. The plasma membrane imposes a barrier to the flow of sodium down a concentration gradient into the cell and prevents a similar efflux of potassium from the cell. The barrier to sodium is imperfect, and the relative leakiness to that ion permits the passive entry of sodium into the cell. To compensate for this intrusion, the energy-dependent plasma membrane sodium pump (Na^+, K^+-ATPase), which is fueled by adenosine triphosphate (ATP), extrudes sodium. Injurious agents may interfere with this membrane-regulated process by increasing the permeability of the plasma membrane to sodium, thereby exceeding the capacity of the pump to extrude sodium; by damaging the pump directly; or by interfering with the synthesis of ATP, thus depriving the pump of its fuel. In any event, the accumulation of sodium in the cell leads to a water increase to maintain isosmotic conditions, and the cell swells.

Ultrastructural Changes

Changes in the ultrastructure of intracellular organelles occur in reversibly injured cells.

Endoplasmic Reticulum With swelling of the cell, the cisternae of the endoplasmic reticulum become dilated, presumably because of shifts in ions and water (Fig. 1-3). Independently, membrane-bound polysomes may undergo disaggregation and detach from the surface of the rough endoplasmic reticulum (Fig. 1-4).

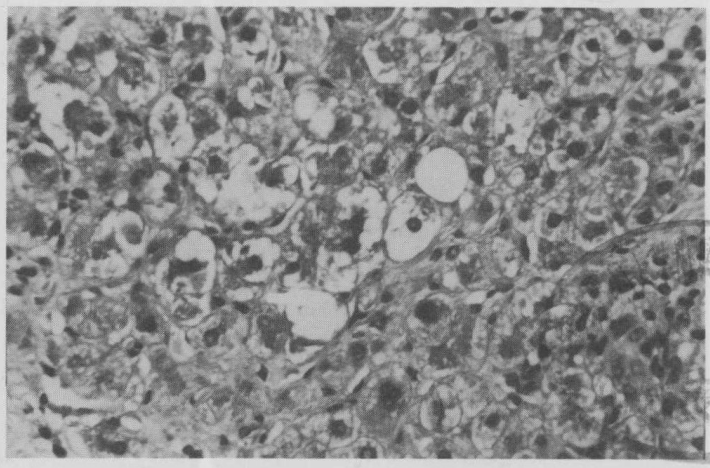


Figure 1-2. Hydropic swelling of liver cells in alcoholic liver injury. The hepatocytes in the center show central nuclei and cytoplasm distended (ballooned) by excess fluid.

Mitochondria In some forms of injury, particularly ischemia, mitochondria swell (Fig. 1-5). This enlargement is probably caused by the dissipation of the energy gradient and consequent impairment of mitochondrial volume control. Amorphous densities rich in phospholipid may appear, but these effects are fully reversible upon recovery.

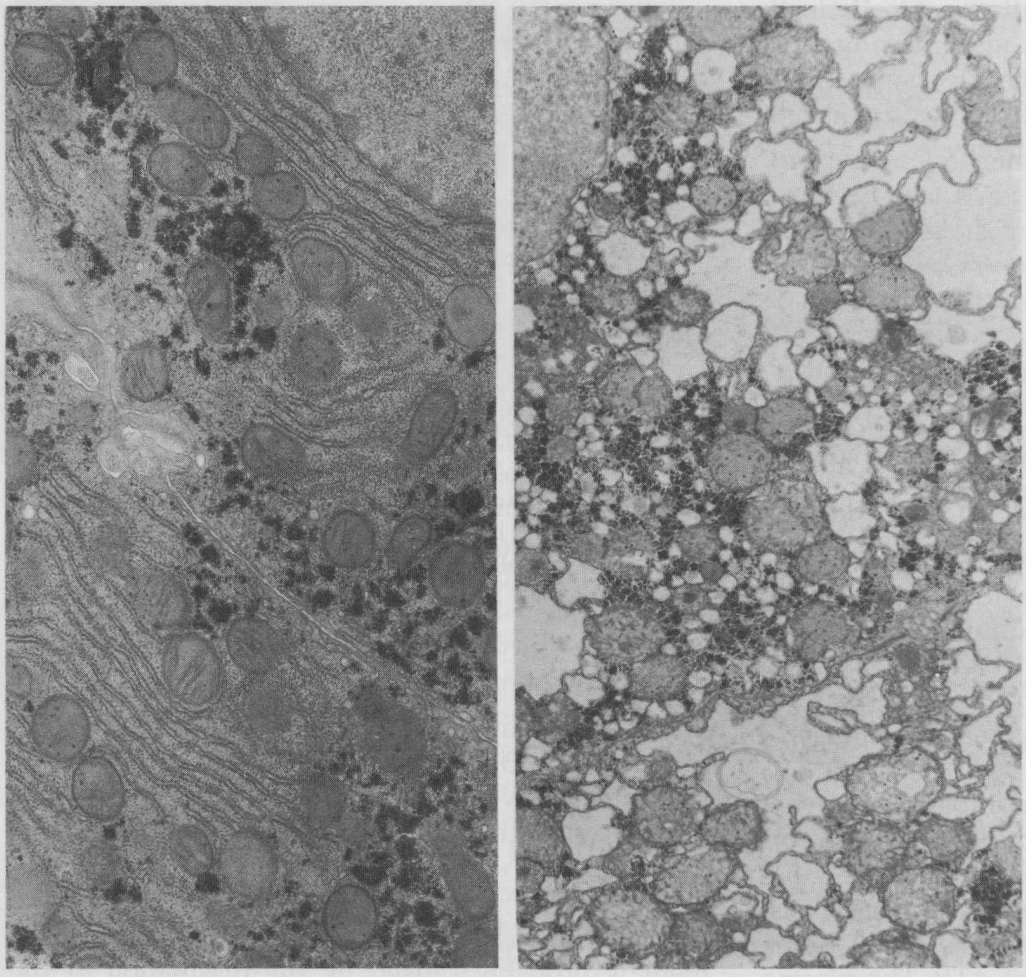
Plasma Membrane Blebs of the plasma membrane—that is, focal extrusions of the cytoplasm—are occasionally noted. These can be pinched off and released while the cell remains viable.

Nucleolus In the nucleus, reversible injury is reflected principally in changes in the nucleolus, characterized by the separation of fibrillar and granular components, or a diminution in the latter, leaving naked fibrillar cores.

It is important to recognize that after withdrawal of an acute stress that has led to reversible cell injury, by definition, the cell returns to its normal state.

Morphologic Reactions to Persistent Stress

Persistent stress is often described as leading to chronic cell injury. Yet few if any of the morphologic changes at the cellular level reflect the type of chronic



A B

Figure 1-3. Ultrastructure of hydropic swelling of a liver cell. (*A*) Two apposed normal hepatocytes with tightly organized, parallel arrays of rough endoplasmic reticulum. (*B*) Swollen hepatocyte in which the cisternae of the endoplasmic reticulum are dilated by excess fluid.

damage seen in chronically injured organs. Similar responses to insults at the cellular level can produce different gross appearances in injured organs. For example, chronic ischemia of the brain leads to permanent injury and shrinkage of that organ. Chronic liver injury produces irreversible damage in the form of a diffuse scarring, called cirrhosis. In general, **permanent organ injury** is associated with the **death of individual cells.** By contrast, the cellular response to **persistent sublethal injury,** whether chemical or physical, reflects **adaptation of the cell** to a hostile environment. Again, these changes are, for the most part, reversible upon discontinuation of the stress. In response to persistent stress, a cell dies or adapts. Cells experiencing persistent stress manifest few if any of the characteristic alterations described for acute cell injury. It is thus our view that **at the cellular level** it is more appropriate to speak of **chronic adaptation** than of **chronic injury** (Fig. 1-6). The major adaptive responses are **atrophy, hypertrophy, metaplasia, dysplasia, and intracellular storage.** According to some theories, certain forms of neoplasia may also result from adaptive responses.

Atrophy

Atrophy is a decrease in the size and function of a cell. It is often seen in areas of vascular insufficiency or chronic inflammation and may result from disuse of skeletal muscle. Atrophy may be thought of as an adaptive response to stress in which the cell shrinks in volume and shuts down its differentiated functions, thus reducing its need for energy to a minimum. Upon restoration of normal conditions, atrophic cells are fully capable of resuming their differentiated functions; size increases to normal, and specialized functions, such as protein synthesis or contractile force, return to their original levels. Atrophy occurs under a variety of conditions outlined below.

Reduced Functional Demand

The most common form of atrophy follows reduced functional demand. For example, after immobilization of a limb in a cast as treatment for a bone fracture, or after prolonged bed rest, muscle cells atrophy

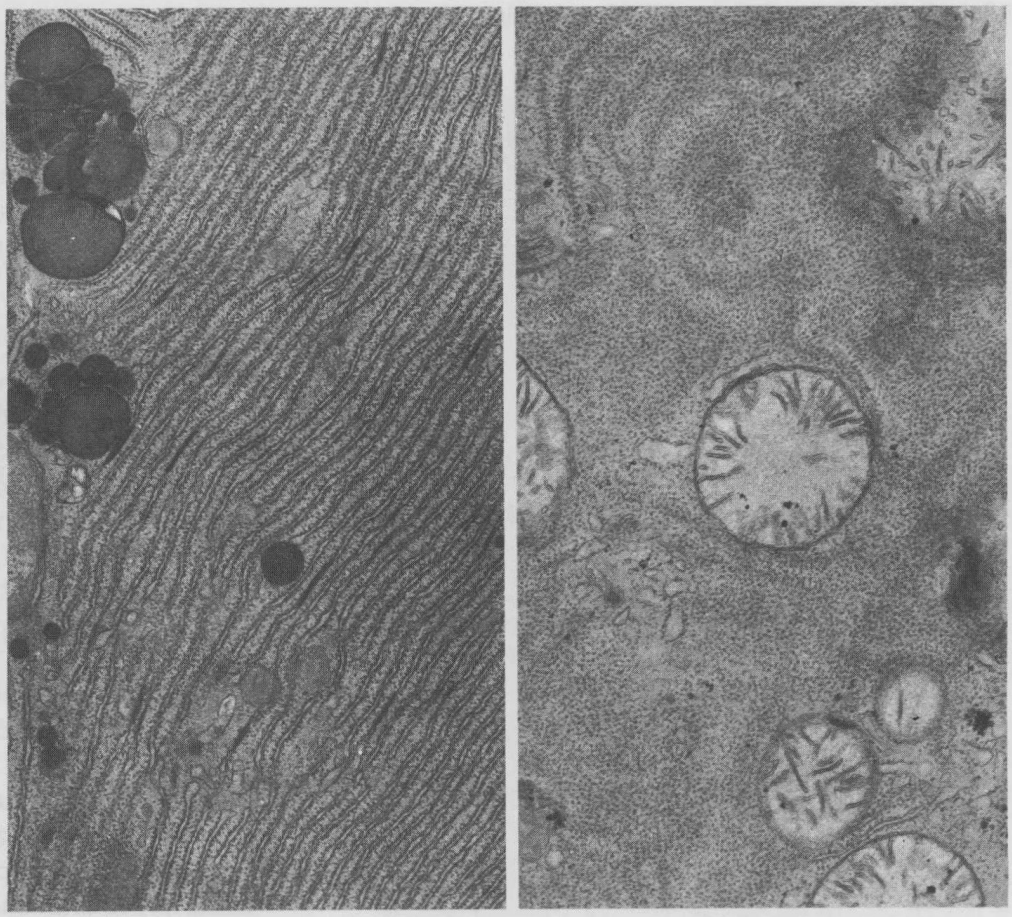


Figure 1-4. Disaggregation of membrane-bound polyribosomes in acute, reversible liver injury. (*A*) Normal hepatocyte, in which the profiles of endoplasmic reticulum are studded with ribosomes. (*B*) An injured hepatocyte, showing detachment of ribosomes from the membranes of the endoplasmic reticulum and the accumulation of free ribosomes in the cytoplasm.

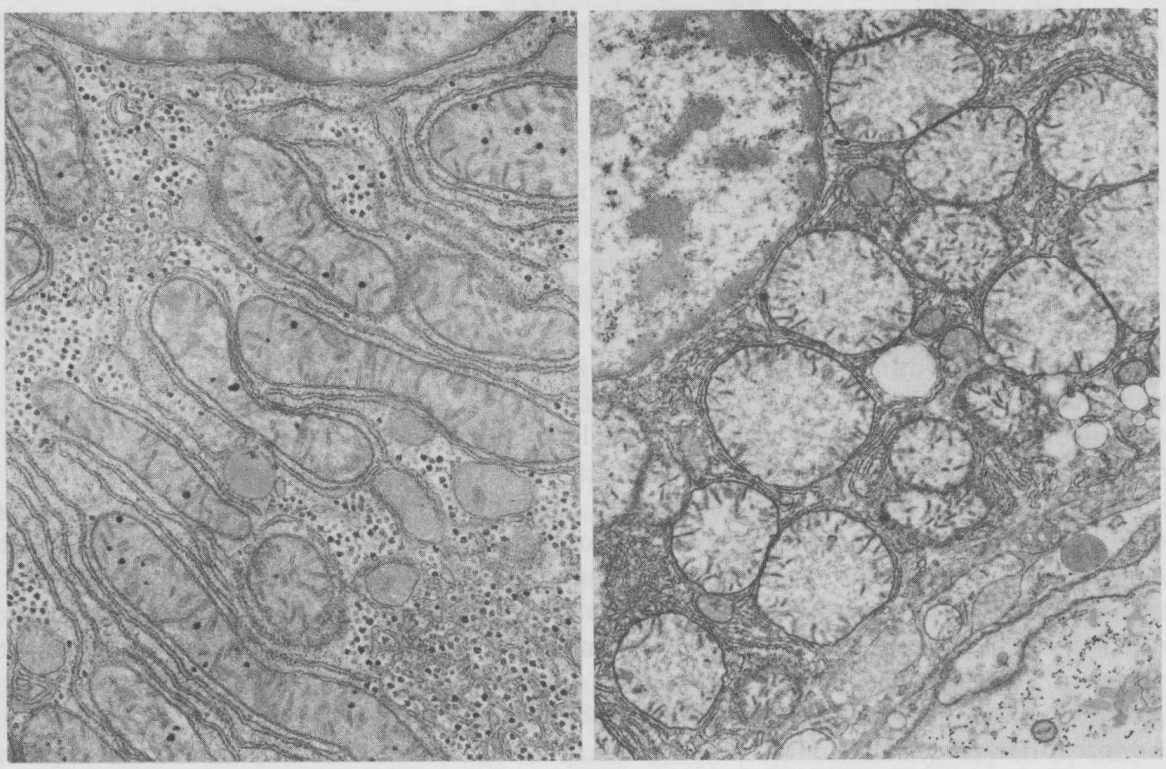


Figure 1-5. Mitochondrial swelling in acute ischemic cell injury. (*A*) Normal mitochondria are elongated and display prominent cristae, which traverse the mitochondrial matrix. (*B*) Mitochondria from an ischemic cell are swollen and round, and exhibit a decreased matrix density. The cristae are less prominent than in the normal organelle.