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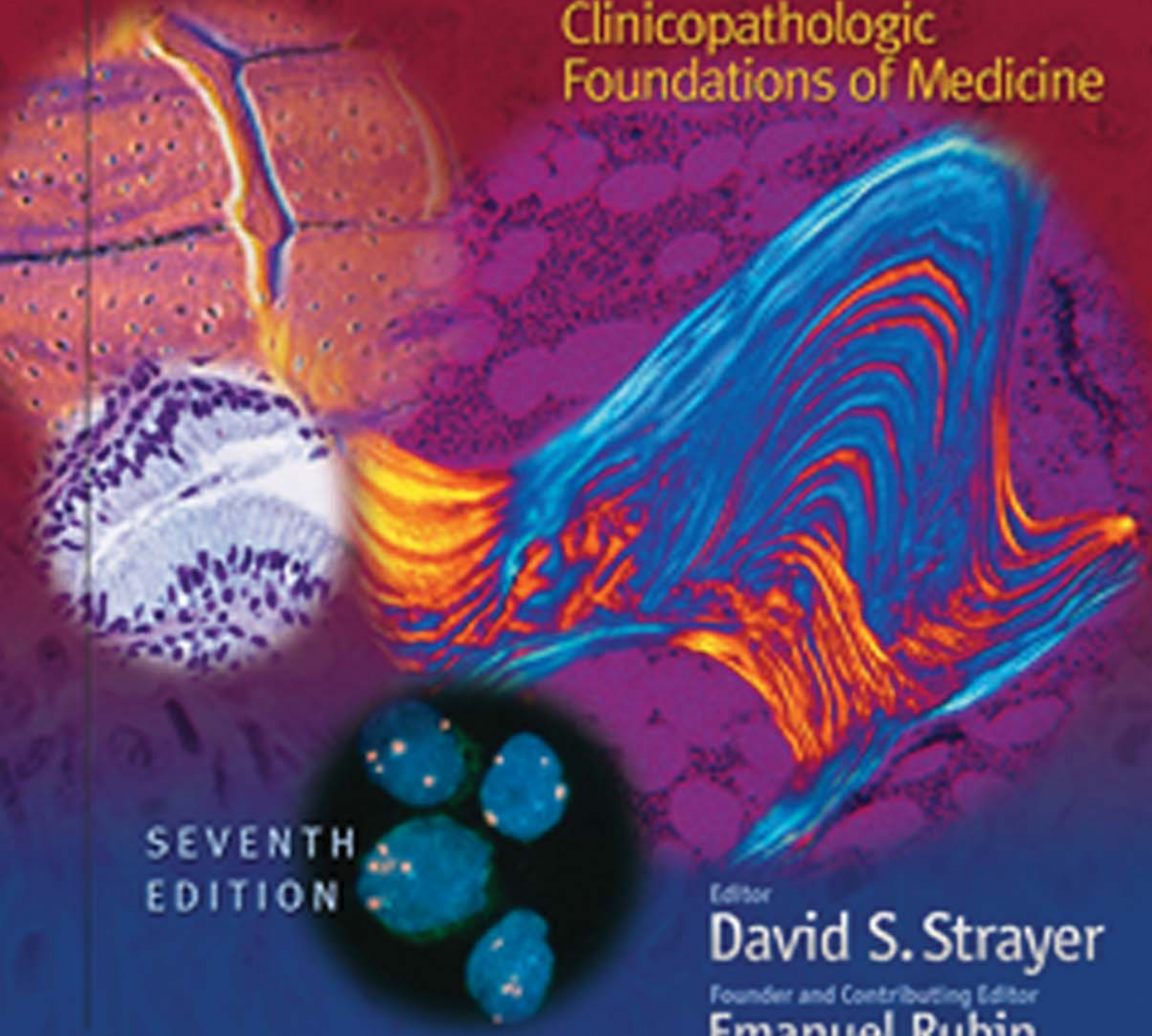
Clinicopathologic Foundations of Medicine



SEVENTH EDITION

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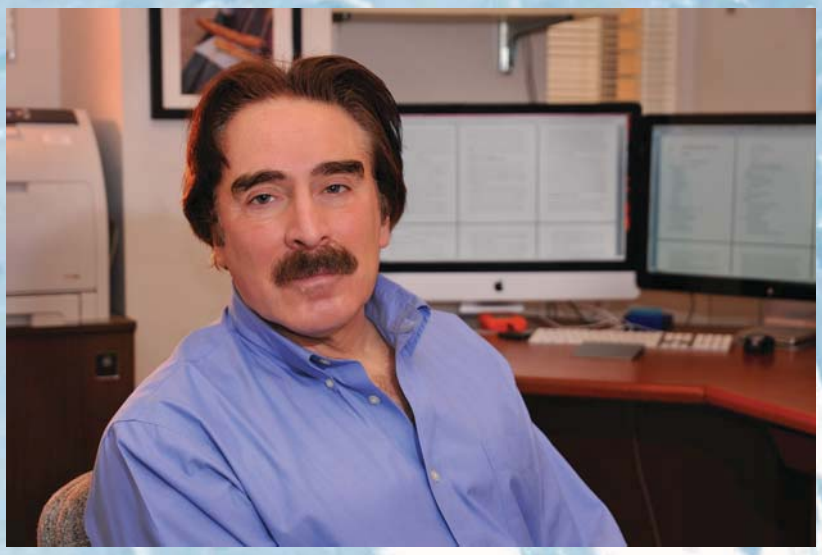

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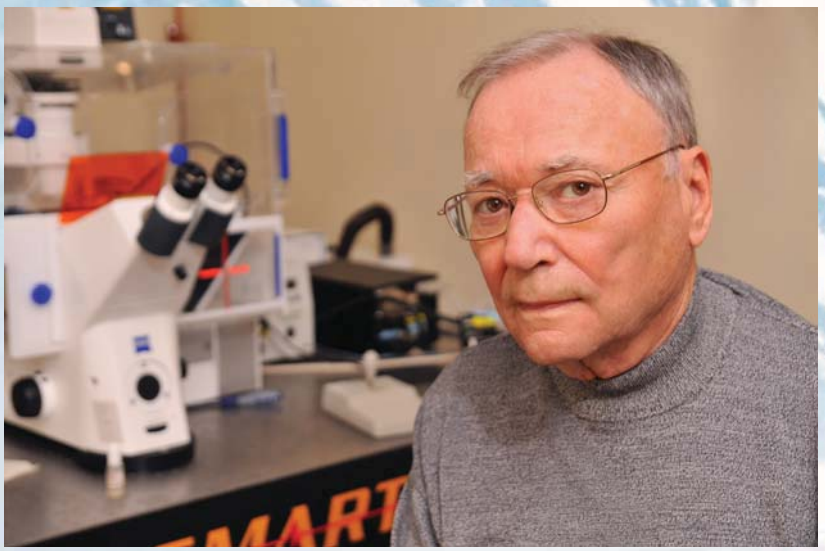

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DEDICATION

We dedicate this book to our wives and families, whose tolerance, love and support sustained us throughout this endeavor; to our colleagues, from whom we have learned so much; to our chapter authors, who have given so much of themselves to produce this new edition; and to students everywhere, upon whose curiosity and energy the future of medical science depends.

This 7th edition is also specially dedicated to the memory of Raphael Rubin, MD, who was associate editor of the 4th edition and who co-edited the 5th and 6th editions. There are no words to express either our happiness that he was part of our lives, or our feelings of loss at his untimely death. We are grateful to him for his courage and grace in the face of terrible disease and for his essential goodness, which permeated everything he did.

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PREFACE

Students and instructors have complementary roles and needs as participants in the educational process. This book is intended to help modern medical students learn—and to help instructors teach—pathology as a foundation of clinical medicine.

So much has happened to change what and how medical students are taught. Medicine is rapidly being transformed, in part by the pace of scientific advance, and in part by the world around us. These forces reshape the subject matter and how it is presented. They also require that we consider carefully what we expect students of medicine to master.

Thus, this book's purpose is to teach pathology and disease pathogenesis to medical students. It is not geared to residents or fellows in pathology, nor to bench scientists. ***Our goal is to prepare future medical practitioners—cardiologists, pediatricians, gerontologists and so forth—for their specialties, not for ours.*** We do this by helping them to understand how diseases happen and how they appear. We provide a foundation on which future clinicians of all specialties can build and, we hope, a sense of excitement for medical advances yet to come.

Perhaps the hardest—and at the same time the most important—challenge facing us in preparing this textbook is determining what should not be stressed, that is, what is better left for more specialized texts in biochemistry, molecular biology, pathology subspecialities and so on. Even as we try to avoid such superfluities as unproven hypotheses, abstruse discussions, medical minutiae and details of scientific experiments that fill some other textbooks, the amount of information remains overwhelming. We therefore applied a filter throughout this book, a question we asked both in writing our own chapters (Chapters 1, 5 and 8) and in editing the work of our superb contributors: what do students of medicine *need* to know in order to be good doctors, to prepare them for a lifetime of professional learning and to understand how advances in the medical sciences will affect their patients?

We stress the interrelatedness of the many medical disciplines. Traditional pathology texts have a section of basic principles, followed by a section covering each of the several organs in turn. This is no longer enough. Many processes and diseases affect multiple organ systems and are best understood and taught as such. It does not suffice, for example, only to describe aging as a series of separate effects on cells in culture or on the brain or on the cardiovascular system. As we can attest from personal experience, aging—apart from the very dubious wisdom that some people believe accompanies it—affects almost everything an individual does and can do. Its impact on one organ system is inextricably linked to its effects on others. It, and similar processes that affect multiple organ systems, is thus best approached against the background of the whole person, not just individual organs.

Accordingly, we have added a new section on systemic conditions: processes that affect whole human beings, not just their kidneys, lungs or joints. These include new chapters on aging (Chapter 10), autoimmune diseases (Chapter 11), sepsis (Chapter 12) and pregnancy (Chapter 14), plus amyloidosis (Chapter 15) and obesity, diabetes and metabolic syndrome (Chapter 13), which appeared in past editions. These are among the most important processes that doctors will have to understand in approaching patients. These integrated presentations should greatly facilitate how these topics are taught and, hopefully, understood. Organ-specific chapters still cover respective manifestations of these processes.

Understanding systemic processes is thus fundamental to this book and our approach to presenting pathology. Pathology is not just a compilation of burdensome, isolated facts or abstruse and arcane pathways to be memorized and promptly forgotten. It is the drama of human frailty and mortality, which we present as concepts to understand and principles to apply.

We also include a new chapter, which we feel adds excitement to the study of pathology: pathology in forensic investigation. This addition illustrates the relevance and sophistication of pathology as it interfaces with patient care and relates to the world outside of medicine.

Education in general is changing. Traditional, printed textbooks are being replaced by texts viewed on portable devices such as tablet computers. These versatile devices offer many more opportunities for interactive learning, including self-quizzing, animated illustrations, virtual microscopy, networking and many more. Many such ancillaries are part of the instructional package that begins with this textbook. Because students have become increasingly sophisticated and exacting, our presentations encompass the full range of instructional aids and are based on the principle that pathology and pathogenesis are inseparable and are fundamental to all clinical medicine.

These teaching adjuncts underscore the fact that ***the real challenge is to identify what students should understand, and then decide how best to aid that understanding***—not to apply the maximum number of electronic (or other) embellishments, or to use these tools to add yet more facts to the mountains of information that already burden students. Appreciating what a good doctor must understand, and the limits of students' time and energy, we have not tried to be comprehensive, preferring instead to be useful.

Consequently, this new edition is much different from its predecessors. The reorganization of this textbook, described above, is an attempt to help students learn about complex issues in modern medicine in a more unified way. Many chapters are rewritten or extensively revised. New authors in Chapters 6, 10, 11, 12, 14, 19, 20, 26, 28 and 34 join the outstanding authors whose continuing contributions are so valuable, and exemplify this goal. The diligent and selfless work of all these authors is the backbone of this textbook.

We emphasize what is understood but also describe the limits of our current knowledge. Hopefully, inquisitive minds will find in this textbook a springboard to further exploration, and students and colleagues will share the excitement of discovery that we have been privileged to experience in our education and careers.

What is the role of a textbook in an era when most medical school courses prepare their own syllabi, when online information and other resources are abundantly available to students and when many faculty may feel their time and energy are more profitably invested in other pursuits? This volume was designed to gather experts from around the world, to have them present to students a thorough but digestible understanding of how diseases occur and to provide for faculty an educational program that facilitates instruction. *Rubin's Pathology* is characterized by its stylistic uniformity and readability, its strikingly visual presentation, its focus on clinical relevance in all material presented, the dedication of its authors to maintaining the currency of the material and the desire of the entire production team to providing textual material and instructional ancillaries that help students to learn and that help teachers to teach. The determination to achieve these goals is, we believe, an important contribution to medical education that can only be provided in this format.

This is the 25th anniversary of the first edition of this textbook, and the occasion lends itself to recounting one of the most amusing anecdotes from editions past. Thus, we recall that one chapter author for the first edition had prepared elaborate hand-drawn figures ready to be sent for rendering by the illustrator. One night, he fell asleep on the couch, with his precious illustrations scattered on the surrounding floor. It just so happened that he was paper-training a new puppy at the time. Unaware of the significance of the papers, and not appreciating their contents, the puppy dutifully used the papers as it had been trained. The author, when he awoke, wiped the results of the dog's training from the sheets of paper and sent them to us. Picture our perplexity when we received a sheath of papers decorated with brown smears of some unknown type!! We only found out the reason later.

Finally, we remember with humility and deep enduring affection Raphael Rubin, a previous coeditor of *Rubin's Pathology*. His death in September 2011, at age 55, was an incalculable professional and personal loss for us both. We have tried to memorialize Raph in our dedication of this 7th edition. He is with us in our hearts, and we trust that this new edition would have made him proud.

David S. Strayer, MD, PhD
Emanuel Rubin, MD
Philadelphia, 2014

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Many dedicated people, too numerous to list, provided insight that made this 7th edition of *Rubin's Pathology* possible. The editors would like especially to thank the managing and editorial staff at Lippincott Williams & Wilkins and in particular Sirkka Howes and Stacey Sebring whose encouragement and support throughout all phases of this endeavor have not only touched us greatly personally but also been a key to the successful publication of this text and its ancillaries.

The editors also acknowledge contributions made by our colleagues who participated in writing previous editions and those who offered suggestions and ideas for the current edition.

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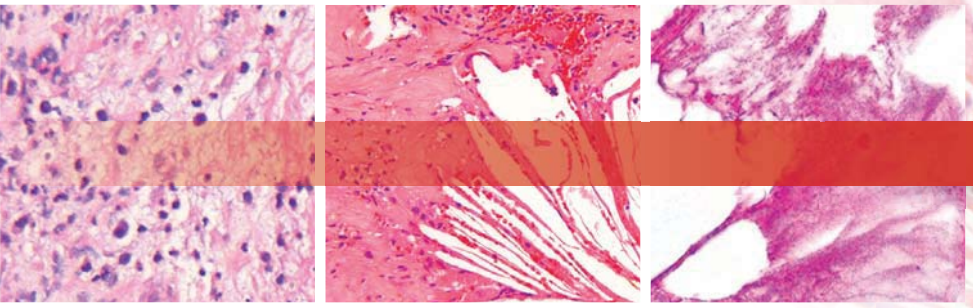
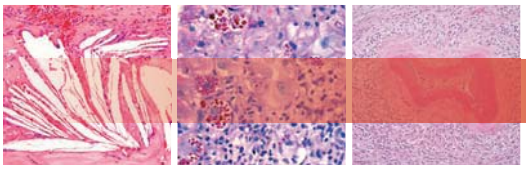


SECTION I

Mechanisms of Disease



1

Cell Adaptation, Injury and Death

David S. Strayer ■ Emanuel Rubin

Pathology ***is the study of structural and functional abnormalities that manifest as diseases of organs and systems.*** Classic theories attributed disease to imbalances or noxious effects of "humors." In the 19th century, Rudolf Virchow, often called the father of modern pathology, proposed that injury to cells, the smallest living units in the body, is the basis of all disease. To this day, this concept underlies all of pathology.

To understand cell injury, it is useful to consider how cells sustain themselves in a hostile environment.[1] To remain viable, the cell must generate energy. This process requires it to establish a structural and functional barrier between its internal milieu and the outside. The **plasma membrane** does this in several ways:

- It maintains a constant internal ionic composition against very large chemical gradients between interior and exterior compartments.
- It selectively admits some molecules while excluding or extruding others.
- It provides a structural envelope to contain the cell's informational, synthetic and catabolic constituents. Thus, it creates an environment to house signal transduction molecules that communicate between each other and between the external and internal milieus.

Cells must also be able to adapt to fluctuating environmental conditions, such as changes in temperature, solute concentrations, oxygen supply, noxious agents and so on. The evolution of multicellular organisms eased the precarious lot of individual cells by establishing a controlled extracellular environment, in which temperature, oxygen availability, ionic content and nutrient supply remain

[1]Facts can only be established by observation (i.e., without imposing an external logical framework suggesting that certain functions or abilities evolved in order to achieve a particular goal). However, teleology—the study of design or purpose in nature—can be a useful tool to help in framing questions, even though it is not accepted as a legitimate part of scientific investigation.

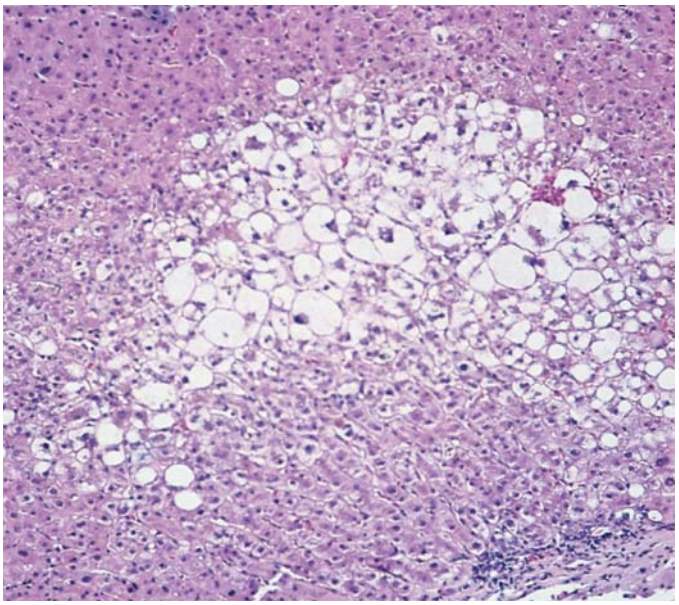


FIGURE 1-1. Hydropic swelling. The liver of a patient with toxic hepatic injury shows severe hydropic swelling in the centrilobular zone. Affected hepatocytes exhibit central nuclei and cytoplasm distended by excess fluid.

relatively constant. It also permitted the luxury of cell differentiation for such diverse functions as energy storage (glycogen in hepatocytes, lipids in adipocytes), communication (neurons), contractile activity (heart muscle), protein synthesis for export (pancreas, endocrine cells), absorption (intestine) and defenses from foreign invaders (immune system).

These adaptations notwithstanding, changes in an organism's internal and external environments strain the tranquility of its constituent cells. ***Patterns of response to such stresses make up the cellular basis of disease.*** If an injury exceeds a cell's adaptive capacity, that cell dies. A cell exposed to persistent sublethal injury has limited available responses, expression of which we interpret as cell injury. ***Thus, pathology is the study of injury to cells and organs and of their capacity to adapt to such injury.*** The science of disease (pathology) is thus an application of normal biological principles.

Mechanisms and Morphology of Cell Injury

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. When environmental changes exceed the cell's capacity to maintain normal homeostasis, we recognize acute cell injury. If the stress is removed in time or if the cell can withstand the assault, the damage is reversible, and complete structural and functional integrity is restored. For example, when circulation to the heart is interrupted for less than 30 minutes, all structural and functional alterations prove to be reversible. 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. Cells have time to adapt to reversible injury in a number of ways, each of which has a morphologic counterpart. On the other hand, if the stress is sufficiently severe, irreversible injury leads to cell death. The moment when reversible injury becomes irreversible injury, the "point of no return," is not known at present.

Hydropic Swelling Is a Reversible Increase in Cell Volume

Hydropic swelling is characterized by a large, pale cytoplasm and a normally located nucleus (Fig. 1-1). The greater volume is caused by increased water content and reflects acute, reversible cell injury. It may result from such varied causes as chemical and biological toxins, viral or bacterial infections, ischemia, excessive heat or cold and so on.

By electron microscopy, the number of organelles is unchanged, although they appear dispersed in a larger volume. The excess fluid accumulates preferentially in cisternae of the endoplasmic reticulum, which are conspicuously dilated, presumably because of ionic shifts into this compartment (Fig. 1-2).

Hydropic swelling results from impairment of cellular volume regulation, a process that controls ionic concentrations in the cytoplasm. This regulation, particularly for sodium, involves three components: (1) the plasma

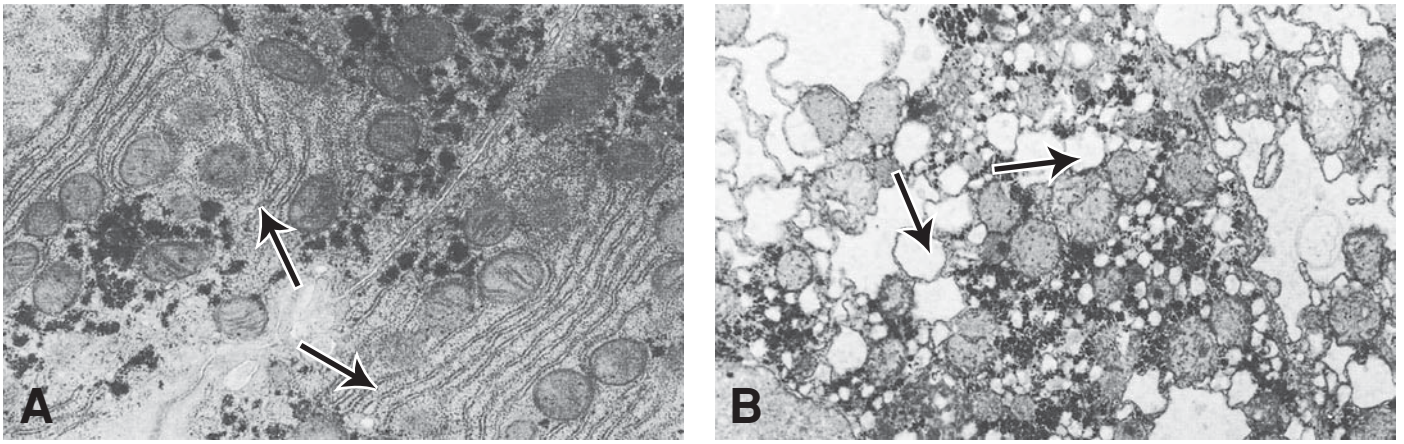


FIGURE 1-2. Ultrastructure of hydropic swelling. A. Two apposed normal hepatocytes contain tightly organized, parallel arrays of rough endoplasmic reticulum (*arrows*). **B.** Swollen hepatocytes show dilations of the cisternae of the endoplasmic reticulum by excess fluid (*arrows*).

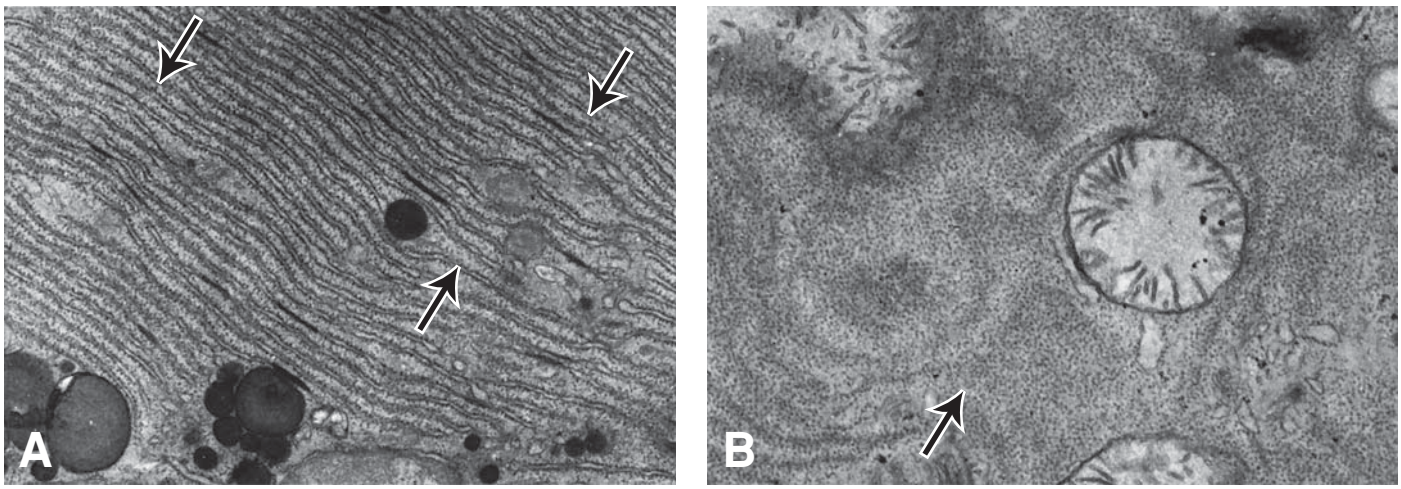


FIGURE 1-3. Disaggregation of membrane-bound ribosomes in acute, reversible liver injury. A. The profiles of endoplasmic reticulum (*arrows*) in a normal hepatocyte are studded with ribosomes. **B.** An injured hepatocyte shows detachment of ribosomes from the membranes of the endoplasmic reticulum and accumulation of free ribosomes in the cytoplasm (*arrow*).

membrane, (2) the plasma membrane sodium (Na^+) pump and (3) adenosine triphosphate (ATP). The plasma membrane prevents two gradient-driven ion flows: the flow of Na^+ from the extracellular fluid into the cell, and the flow of potassium (K^+) out of the cell. The barrier to sodium is imperfect and its relative leakiness permits some 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 ATP, extrudes sodium from the cell. Noxious agents may interfere with this membrane-regulated process by (1) increasing plasma membrane permeability to Na^+, thereby exceeding the capacity of the pump to extrude the ion; (2) damaging the pump directly; or (3) interfering with ATP synthesis, and so depriving the pump of its fuel. In any event, accumulation of sodium in the cell leads to increased intracellular water to maintain isosmotic conditions. The cell then swells.

Subcellular Changes in Reversibly Injured Cells

- **Endoplasmic reticulum (ER):** The cisternae of the ER are distended by fluid in hydropic swelling (Fig. 1-2). Membrane-bound polysomes may disaggregate and detach from the surface of the rough endoplasmic reticulum (Fig. 1-3).
- **Mitochondria:** In some forms of acute injury, particularly ischemia (lack of adequate blood flow; see below), mitochondria swell (Fig. 1-4). This enlargement is due to dissipation of the mitochondrial energy gradient (membrane potential), impairing volume control.

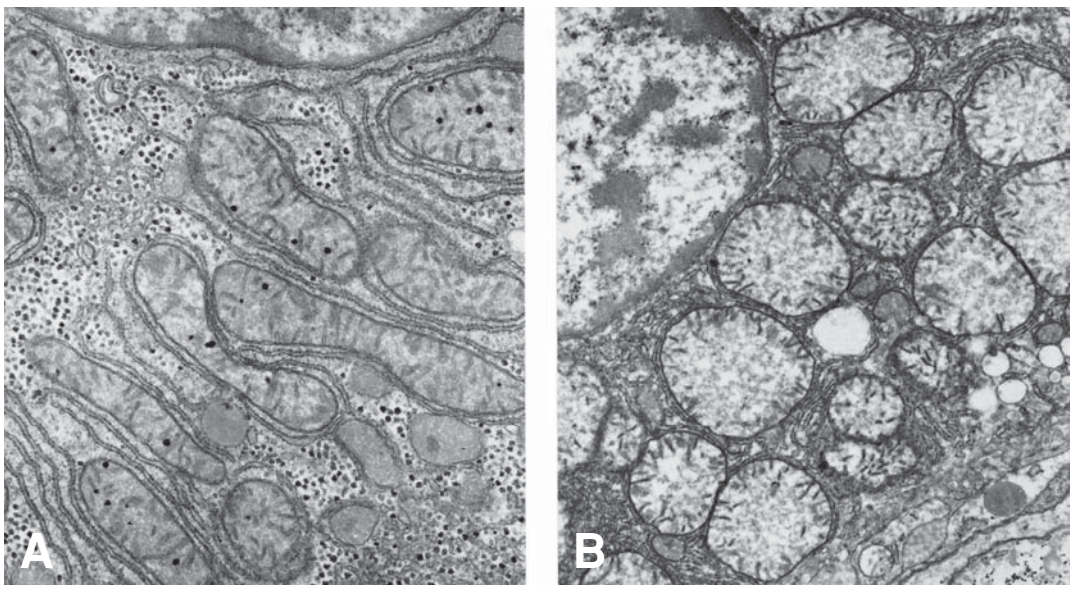


FIGURE 1-4. Mitochondrial swelling in acute ischemic cell injury. A. Normal hepatocyte mitochondria are elongated and display prominent cristae, which traverse the mitochondrial matrix. **B.** Mitochondria from an ischemic cell are swollen and round and exhibit a decreased matrix density. The cristae are less prominent than in the normal organelle.

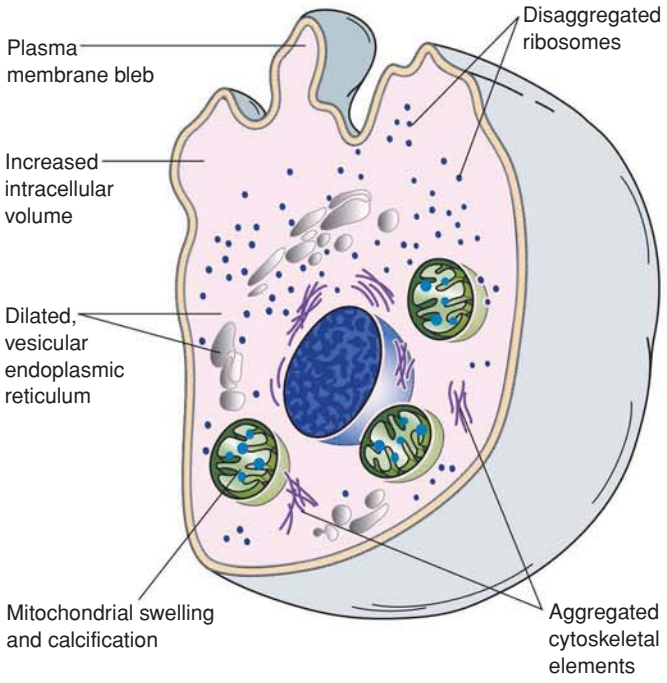


FIGURE 1-5. Ultrastructural features of reversible cell injury.

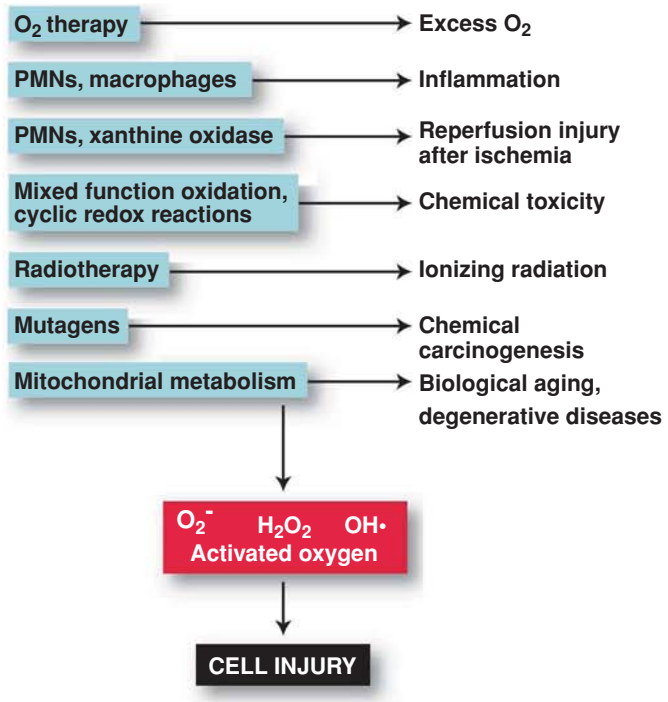


FIGURE 1-6. The role of activated oxygen species in cell injury. *H_2O_2* = hydrogen peroxide; *O_2* = oxygen; *O_2^-* = superoxide; *OH•* = hydroxyl radical; *PMNs* = polymorphonuclear neutrophils.

Amorphous densities rich in phospholipid may appear in the mitochondria, but these effects are fully reversible on recovery.

- **Plasma membrane:** Blebs of plasma membrane—that is, focal extrusions of the cytoplasm—are occasionally noted. These can detach from the membrane into the external environment without loss of cell viability.
- **Nucleus:** Reversible injury of the nucleus is reflected mainly by segregation of the fibrillar and granular components of the nucleolus. Alternatively, the granular component may be diminished, leaving only a fibrillar core.

These changes in cell organelles (Fig. 1-5) are reflected in functional derangements (e.g., reduced protein synthesis, impaired energy production). ***After withdrawal of the stress that caused the reversible cell injury, by definition, the cell returns to its normal state.***

Ischemic Cell Injury Results from Obstruction to the Flow of Blood

When tissues are deprived of oxygen, ATP cannot be produced by aerobic metabolism and is instead made inefficiently by anaerobic metabolism. Ischemia initiates a series of chemical and pH imbalances, which are accompanied by increased generation of injurious free radical species. The damage produced by short periods of ischemia tends to be reversible if circulation is restored. However, long periods of ischemia lead to irreversible cell injury and death. The mechanisms of cell damage are discussed below.

Oxidative Stress Is a Key Trigger for Cell and Tissue Injury and Adaptive Responses

For human life, oxygen is both a blessing and a curse. Without it, life is impossible, but some of its derivatives are partially reduced oxygen species that can react with, and damage, virtually any molecule they reach.

Reactive Oxygen Species

Reactive oxygen species (ROS) are the likely causes of cell and tissue injury in many settings (Fig. 1-6). Oxygen (O_2) has a major role as the terminal electron acceptor in mitochondria. It is reduced from O_2 to H_2O, and resultant energy is harnessed as an electrochemical potential across the mitochondrial inner membrane.

Conversion of O_2 to H_2O entails transfer of four electrons. Three partially reduced species, representing transfers of varying numbers of electrons, are intermediate between O_2 and H_2O (Fig. 1-7). These are O_2^-, superoxide (one electron); H_2O_2, hydrogen peroxide (two electrons); and OH•, the hydroxyl radical (three electrons). Under physiologic conditions these ROS come from several sources, including leaks in mitochondrial electron transport and mixed-function oxygenases (P450). In addition, ROS are important cellular signaling intermediates. The major forms of ROS are listed in Table 1-1. Importantly, excessive ROS levels both cause and aggravate many disorders (Fig. 1-6).

Superoxide

The superoxide anion (O_2^-) is produced mainly by leaks in mitochondrial electron transport or as part of inflammatory responses. In the first case, the promiscuity of coenzyme Q (CoQ) and other imperfections in the electron transport chain allow transfer of electrons to O_2 to yield O_2^-. In phagocytic inflammatory cells, activation of a plasma membrane oxidase produces O_2^-, which is then converted to H_2O_2 and eventually to other ROS (Fig. 1-8). These ROS

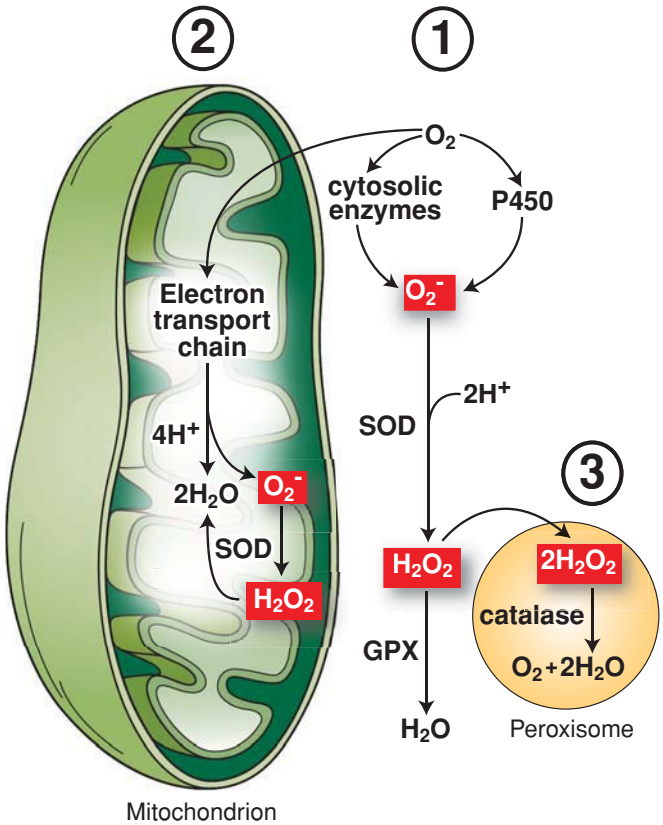


FIGURE 1-7. Mechanisms by which reactive oxygen radicals are generated from molecular oxygen and then detoxified by cellular enzymes. Circulating oxygen delivered to the cell may follow one of three paths: **1.** Molecular O_2 is converted to O_2^- in the cytosol. O_2^- is reduced to H_2O_2 by cytosolic superoxide dismutase (Cu/Zn SOD), and finally to water. **2.** O_2 enters the mitochondria, where inefficiencies in electron transport result in conversion of O_2 to O_2^-. This superoxide is rendered less reactive by further reduction to H_2O_2, via mitochondrial SOD (MnSOD). This H_2O_2 is then converted to H_2O by GPX. **3.** Cytosolic H_2O_2 enters peroxisomes where it is detoxified to H_2O by catalase. *CoQ* = coenzyme Q; *GPX* = glutathione peroxidase; H^+ = hydrogen ion; H_2O = water; H_2O_2 = hydrogen peroxide; O_2 = oxygen; O_2^- = superoxide; *SOD* = superoxide dismutase.

have generally been viewed as key effectors of cellular defenses that destroy pathogens, fragments of necrotic cells or other phagocytosed material (see Chapter 2). ROS acting as signaling intermediates elicit the release of proteolytic and other degradative enzymes, which are critical effectors of neutrophil-mediated destruction of bacteria and other foreign materials.

Hydrogen Peroxide

O_2^- anions are converted by superoxide dismutase (SOD) to H_2O_2. Hydrogen peroxide is also produced directly by a number of oxidases in cytoplasmic peroxisomes (Fig. 1-7). By itself, H_2O_2 is not particularly injurious, and it is largely metabolized to H_2O by catalase. However, when produced in excess, it is converted to highly reactive OH•. In neutrophils, myeloperoxidase transforms H_2O_2 to a potent radical, hypochlorite (OCl^-), which is lethal for microorganisms and, if released extracellularly, can kill cells.

Most cells have efficient mechanisms for removing H_2O_2. Two different enzymes reduce H_2O_2 to water: (1) catalase within peroxisomes and (2) glutathione peroxidase (GPX) in both the cytosol and mitochondria (Fig. 1-7). GPX uses reduced glutathione (GSH) as a cofactor in a reaction yielding oxidized glutathione (GSSG). Because it is membrane permeable, H_2O_2 generated in mitochondria affects the oxidant balance, not only in mitochondria but also in other cellular compartments.

TABLE 1-1
REACTIVE OXYGEN SPECIES (ROS)

Molecule	Attributes
Hydrogen peroxide (H_2O_2)	Forms free radicals via Fe^{2+}-catalyzed Fenton reaction Diffuses widely within the cell
Superoxide anion (O_2^-)	Generated by leaks in the electron transport chain and some cytosolic reactions Produces other ROS Does not readily diffuse far from its origin
Hydroxyl radical (OH•)	Generated from H_2O_2 by Fe^{2+}-catalyzed Fenton reaction The intracellular radical most responsible for attack on macromolecules
Peroxynitrite (ONOO•)	Formed from the reaction of nitric oxide (NO) with O_2^- Damages macromolecules
Lipid peroxide radicals (RCOO•)	Organic radicals produced during lipid peroxidation
Hypochlorous acid (HOCl)	Produced by macrophages and neutrophils during respiratory burst that accompanies phagocytosis Dissociates to yield hypochlorite radical (OCl^-)

Fe^{2+} = ferrous iron.

Hydroxyl Radical

Hydroxyl radicals (OH•) are formed by (1) radiolysis of water, (2) reaction of H_2O_2 with ferrous iron (Fe^{2+}) or cuprous copper (Cu^{1+}) (Fenton reaction) and (3) conversion of O_2^- with H_2O_2 (Haber-Weiss reaction) (Fig. 1-9). *The hydroxyl radical is the most reactive ROS*, and there are several mechanisms by which it can damage macromolecules.

Iron is often an active participant in oxidative damage to cells (see below) by virtue of the Fenton reaction. In a number of different cell types, H_2O_2 stimulates iron uptake and so increases production of hydroxyl radicals.

- **Lipid peroxidation:** The hydroxyl radical removes a hydrogen atom from unsaturated fatty acids in membrane phospholipids, a process that forms a free lipid radical (Fig. 1-10). The lipid radical then reacts with molecular oxygen to generate a lipid peroxide radical. Subsequently, lipid peroxides act as initiators, removing a hydrogen atom from a second unsaturated fatty acid, to yield a lipid peroxide and a new lipid radical, initiating

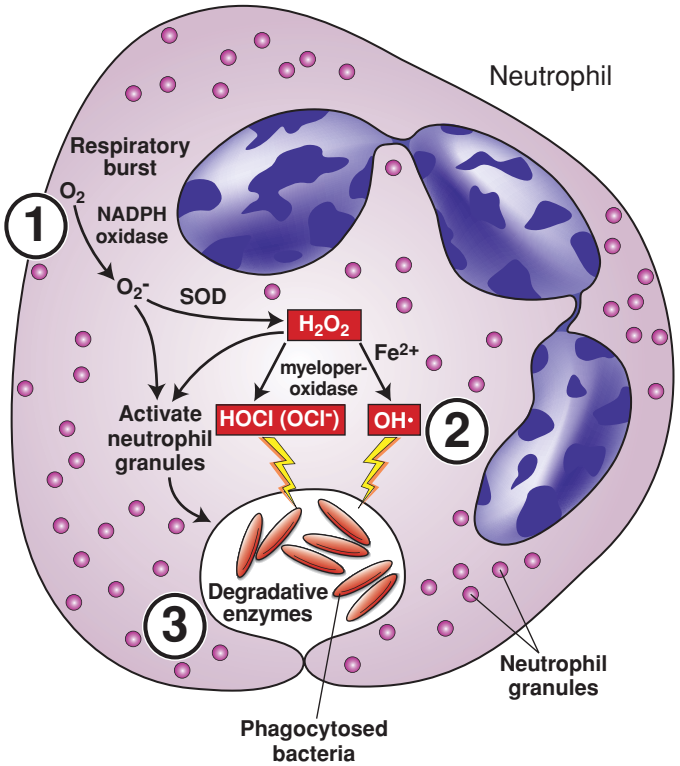


FIGURE 1-8. Generation of reactive oxygen species in neutrophils as a result of phagocytosis of bacteria. 1. The respiratory burst in neutrophils begins with reduction of O_2 to O_2^- by NADPH oxidase. In turn, O_2^- is converted to H_2O_2 by SOD. **2.** Reactive oxygen species (ROS) (HOCl, OH•) are produced from H_2O_2 by myeloperoxidase. Concurrently, O_2^- and H_2O_2 activate neutrophil granules to release degradative enzymes. **3.** Bacteria are engulfed by neutrophils, where they are destroyed by ROS and degradative enzymes. *Fe^{2+}* = ferrous iron; *H_2O_2* = hydrogen peroxide; *HOCl* = hypochlorous acid; *NADPH* = reduced nicotinamide adenine dinucleotide phosphate; *OCl^-* = hypochlorite radical; *OH•* = hydroxyl radical; *SOD* = superoxide dismutase.

a chain reaction. Lipid peroxides are unstable and break down into smaller molecules. Destruction of unsaturated fatty acids of phospholipids results in a loss of membrane integrity.

- **Protein interactions:** Hydroxyl radicals may also attack proteins. The sulfur-containing amino acids cysteine and methionine, as well as the nitrogen-containing moieties arginine, histidine and proline, are especially vulnerable to attack by OH•. As a result of oxidative damage, proteins undergo fragmentation, cross-linking, aggregation and eventually degradation (see below).
- **Sugars:** OH• can attack a variety of sugars and other carbohydrates to generate reactive intermediates that modify proteins to form injurious compounds, called advanced glycation end-products (AGEs).
- **DNA damage:** The hydroxyl radical causes diverse structural alterations in DNA, including strand breaks, modified bases and cross-links between strands. The integrity of the genome can usually be reconstituted by the various DNA repair pathways. However, if oxidative damage to DNA is sufficiently extensive, permanent DNA mutations or cell death may result.

Fig. 1-11 summarizes the mechanisms of cell injury by ROS.

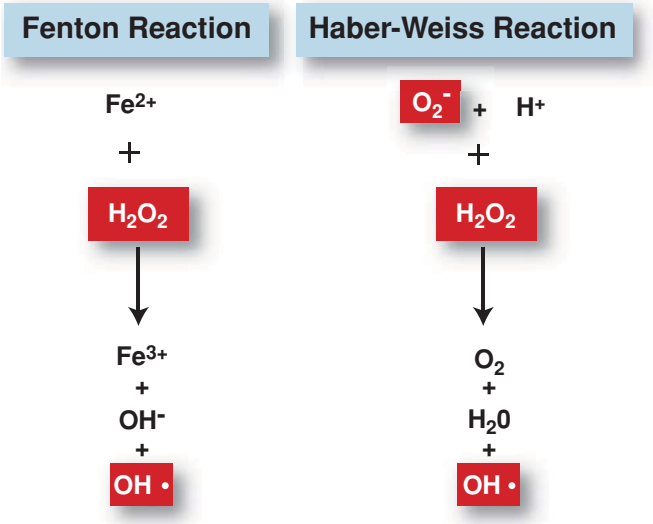


FIGURE 1-9. Fenton and Haber-Weiss reactions generate the highly reactive hydroxyl radical. Reactive species are in red. *Fe^{2+}* = ferrous iron; *Fe^{3+}* = ferric iron; *H^+* = hydrogen ion; *H_2O_2* = hydrogen peroxide; *OH^-* = hydroxide; *OH•* = hydroxyl radical.

Nitric Oxide and Peroxynitrite

Nitric oxide (NO) is a reactive nitrogen molecule that is found in many cells and has a half-life measured in seconds. It is the product of nitric oxide synthase (NOS), a ubiquitous enzyme that comes in two flavors: inducible NOS (iNOS) and constitutive NOSs that are found in several tissues. NO has diverse signaling properties and may be harmful or protective to cells, depending on the circumstances. As a free radical, NO reacts with many molecular targets and activates or inhibits numerous cell functions.

When NO and oxygen interact, production of other free radicals results. These secondary radicals may nitrosate amines or modify other available groups, such as sulfurs on some amino acids. In addition, NO can react with

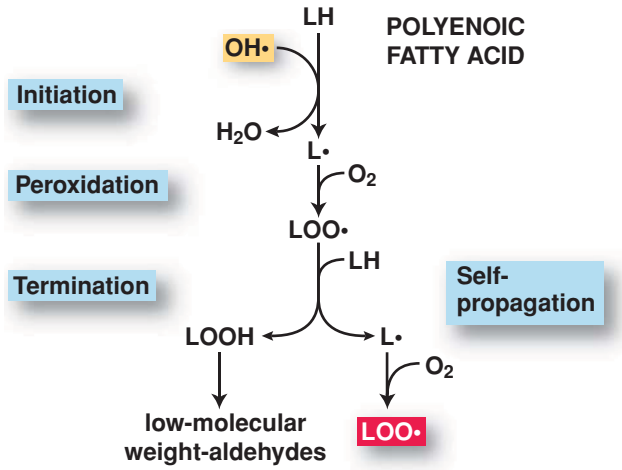


FIGURE 1-10. Lipid peroxidation initiated by the hydroxyl radical (OH•). Unsaturated fatty acids are converted to lipid radicals by OH•, which in turn reacts with molecular oxygen to form lipid peroxides. *H_2O* = water; *O_2* = oxygen; *L•* = lipid radical; *LOO•* = lipid peroxy radical; *LOOH* = lipid peroxide.

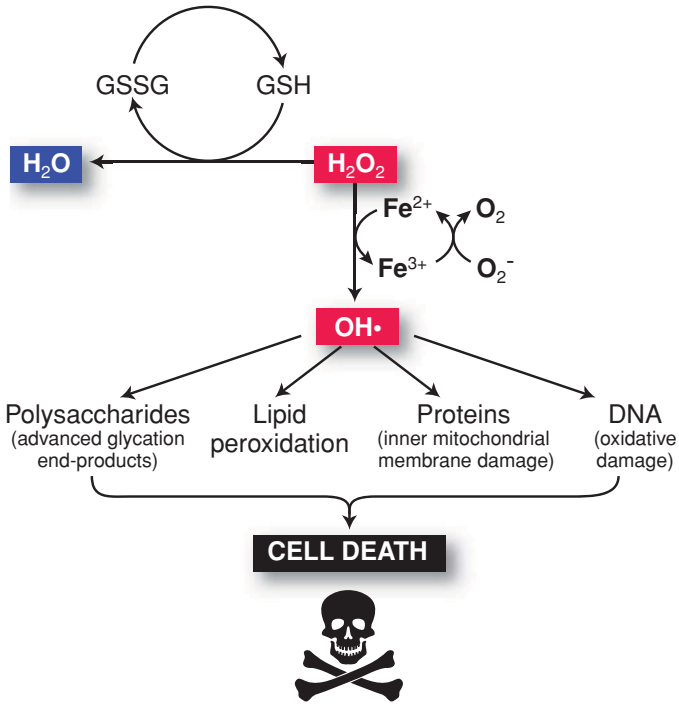


FIGURE 1-11. Mechanisms of cell injury by activated oxygen species. Fe^{2+} = ferrous iron; Fe^{3+} = ferric iron; *GSH* = glutathione; *GSSG* = oxidized glutathione; H_2O_2 = hydrogen peroxide; O_2 = oxygen; O_2^- = superoxide anion; *OH•* = hydroxyl radical.

superoxide to form another free radical, namely, peroxynitrite ($ONOO^-$):

$$NO\bullet + O_2^- \rightarrow ONOO^-.$$

Peroxynitrite attacks many important cellular molecules, including lipids, proteins and DNA. Its actions may be beneficial or harmful, depending on the context.

Miscellaneous ROS

Recent data suggest that other ROS, particularly singlet oxygen (O•) and carbonyl radical ($CO_3^-\bullet$), may play important roles in oxidative stress.

The Effectiveness of Cellular Defenses May Determine the Outcome of ROS-Mediated Injury

Cells possess potent antioxidant defenses, including detoxifying enzymes and exogenous free radical scavengers (e.g., vitamins). The major enzymes that convert ROS to less reactive molecules are SOD, catalase and GPX.

Detoxifying Enzymes

- **SOD** is the first line of defense against O_2^-, converting it to H_2O_2 and O_2 ($2O_2^- + 2H^+O_2 + H_2O_2$).
- **Catalase,** mainly located in peroxisomes, is one of two enzymes that complete the detoxification of O_2^- by converting H_2O_2 to water, thereby, preventing its conversion to OH• ($2H_2O_2 \rightarrow 2H_2O + O_2$).
- **GPX** catalyzes the reduction of H_2O_2 and lipid peroxides in mitochondria and the cytosol ($H_2O_2 + 2GSH \rightarrow 2H_2O +$ GSSG).

Scavengers of ROS

- **Vitamin E (α-tocopherol)** is a terminal electron acceptor that aborts free radical chain reactions. As it is fat soluble, α-tocopherol protects membranes from lipid peroxidation.
- **Vitamin C (ascorbate)** is water soluble and reacts directly with O_2, OH• and some products of lipid peroxidation. It also serves to regenerate the reduced form of vitamin E.
- **Retinoids,** the precursors of vitamin A, are lipid soluble and act as chain-breaking antioxidants.
- **NO•** may scavenge ROS, principally by chelation of iron and combination with other free radicals.

Extracellular Oxidants and Antioxidants

Many intracellular processes generate ROS that diffuse or are transported outside cells, where they then may act as precursors of further oxidants. Such molecules include H_2O_2, lipid hydroperoxides, halogenated species such as hypochlorous acid (HOCl) derived from myeloperoxidase and related enzymes, as well as other compounds. Extracellular molecules that act as antioxidants include albumin, glutathione, ascorbate (vitamin C), α-tocopherol (vitamin E) and an extracellular form of SOD.

Although the consequences of oxidative stress in the extracellular matrix (ECM) are not well understood, matrix proteins such as collagen, elastin, fibronectin and laminin are damaged. Nonprotein ECM constituents (glycosaminoglycans, chondroitin sulfate, hyaluronan, etc.) may also be altered. Damage to these ECM molecules may lead to functional impairments in skin, bone and cartilage. Basement membranes throughout the body are also affected, particularly in the kidney and lungs.

p53 May Enhance or Inhibit Oxidative Damage

p53 is a versatile actor that plays diverse roles in the drama of cell survival and death (see later and Chapter 5). On the one hand, p53 helps to prevent and repair DNA damage, thereby rescuing cells from injury due to many endogenous and exogenous sources. On the other hand, if DNA damage is irreparable, p53 activates cell death programs (see below). In addition to these activities, p53 orchestrates cellular metabolic activity in response to levels of oxidative stress.

Under normal conditions with low oxidant stress and normal levels of metabolic activity, this protein maintains expression of many antioxidant genes, thus promoting cell survival. In the face of severe oxidant stress, p53 performs an about-face and activates a different suite of target genes that impair oxidant defenses, allow cellular damage to accumulate and eventuate in cell death. In addition to these effects on gene transcription, p53 directs metabolic pathways that reinforce its transcriptional activity.

Intracellular Storage Is Retention of Materials within the Cell

Substances that accumulate within cells may be normal or abnormal, endogenous or exogenous, harmful or innocuous.

- **Nutrients,** such as fat, glycogen, vitamins and minerals, are stored for later use.
- **Degraded phospholipids,** from the turnover of endogenous membranes, are engulfed in lysosomes and may be recycled.

- **Substances that are not metabolized** accumulate in cells. These include (1) endogenous substrates that are not further processed because a key enzyme is missing (hereditary storage diseases), (2) insoluble endogenous pigments (e.g., lipofuscin, melanin), (3) aggregates of normal or abnormal proteins and (4) foreign particulates, such as inhaled silica or carbon or injected tattoo pigments.
- **Overload of normal body constituents,** including iron, copper and cholesterol, injures a variety of cells.
- **Abnormal forms of proteins** may be toxic if they are retained within cells (e.g., Lewy bodies in Parkinson disease and mutant α_1-antitrypsin; see below).

Fat

Bacteria and other unicellular organisms continuously ingest nutrients. By contrast, mammals do not need to eat continuously. They eat periodically and can survive a prolonged fast because they store nutrients in specialized cells for later use—fat in adipocytes and glycogen in the liver, heart and muscle.

Abnormal accumulation of fat is most conspicuous in the liver (see Chapter 20). Briefly, hepatocytes always contain some fat, because they take up free fatty acids released from adipose tissue and convert them to triglycerides. Most such newly synthesized triglycerides are secreted by the liver as lipoproteins. If delivery of free fatty acids to the liver increases, as in diabetes, or intrahepatic lipid metabolism is disturbed, as in alcoholism, triglycerides accumulate in liver cells. Fatty liver is visualized as lipid globules in the cytoplasm. Other organs, including the heart, kidney and skeletal muscle, also store fat. ***Fat storage is always reversible and there is no evidence that excess fat in the cytoplasm per se interferes with cell function.***

Glycogen

Glycogen is a long-chain polymer of glucose, formed and largely stored in the liver and to a lesser extent in muscles. It is depolymerized to glucose and liberated as needed. Glycogen is degraded in steps by a series of enzymes, each of which may be deficient because of an inborn error of metabolism. Regardless of the specific enzyme deficiency, the result is a glycogen storage disease (see Chapter 6). These inherited disorders affect the liver, heart and skeletal muscle and range from mild and asymptomatic conditions to inexorably progressive and fatal diseases (see Chapters 11, 20 and 31).

Glycogen storage in cells is normally regulated by blood glucose concentration, and hyperglycemic states are associated with increased glycogen stores. Thus, in uncontrolled diabetes, hepatocytes and epithelial cells of the renal proximal tubules are enlarged by excess glycogen.

Inherited Lysosomal Storage Diseases

As with glycogen, catabolism of certain complex lipids and mucopolysaccharides (glycosaminoglycans) takes place by a sequence of enzymatic steps. Since these enzymes are located in the lysosomes, their absence results in lysosomal storage of incompletely degraded lipids, such as cerebrosides (Gaucher disease) and gangliosides (Tay-Sachs disease) or products of mucopolysaccharide catabolism (Hurler and Hunter syndromes). Although these disorders are all progressive, their manifestations vary from asymptomatic organomegaly to rapidly fatal brain disease (see Chapter 6 for the metabolic bases of these disorders and Chapters 30 and 32 for specific organ pathology).

Cholesterol

The human body has a love–hate relationship with cholesterol. On the one hand, it is a critical component of all plasma membranes. On the other hand, when stored in excess, it is closely associated with atherosclerosis and cardiovascular disease, which is the leading cause of death in the Western world (see Chapter 16).

Briefly, the initial lesion of atherosclerosis (fatty streak) reflects accumulation of cholesterol and cholesterol esters in macrophages within the arterial intima. As the disease progresses, smooth muscle cells also store cholesterol. Advanced lesions of atherosclerosis are characterized by extracellular deposition of cholesterol (Fig. 1-12A).

In some disorders characterized by elevated blood levels of cholesterol (e.g., familial hypercholesterolemia), macrophages store cholesterol. If clusters of these cells in subcutaneous tissues are grossly visible, they are called **xanthomas** (Fig. 1-12B).

Lipofuscin

Lipofuscin is a mixture of lipids and proteins that appears as a golden-brown pigment and has been termed "wear and tear" pigment. **It tends to accumulate by accretion of peroxidized unsaturated lipids and oxidized, cross-linked proteins. It is indigestible** and has been compared to production of linoleum by oxidation of linseed oil. This process causes the unsaturated lipids in the oil progressively to solidify, turn brown and become less soluble. Lipofuscin accumulates mainly in postmitotic cells (e.g., neurons, cardiac myocytes) or in cells that cycle infrequently (e.g., hepatocytes) (Fig. 1-12C) and increases with age. In fact, measurement of lipofuscin in optic neurons has been used by fisheries to estimate age in lobsters and other crustaceans. It is often more conspicuous in conditions associated with atrophy of an organ.

Although it was previously thought to be benign, there is increasing evidence that lipofuscin may be both a result and a cause of increasing oxidant stress in cells. It may impair both proteasomal function and lysosomal degradation of senescent or poorly functioning organelles, and so promote cellular oxidant injury. Inefficient or misfunctioning mitochondria may accumulate, make more ROS and continue the cycle.

Melanin

Melanin is an insoluble, brown-black pigment found principally in epidermal cells of the skin, but also in the eye and other organs (Fig. 1-12D). It is located in intracellular organelles known as melanosomes and results from polymerization of certain oxidation products of tyrosine. The amount of melanin is responsible for the differences in skin color among the various races, as well as the color of the eyes. It serves a protective function owing to its ability to absorb ultraviolet light. In white persons, exposure to sunlight increases melanin formation (tanning). The hereditary inability to produce melanin is known as **albinism**. The presence of melanin is also a marker of cancers that arise from melanocytes (melanoma). Melanin is discussed in detail in Chapter 28.

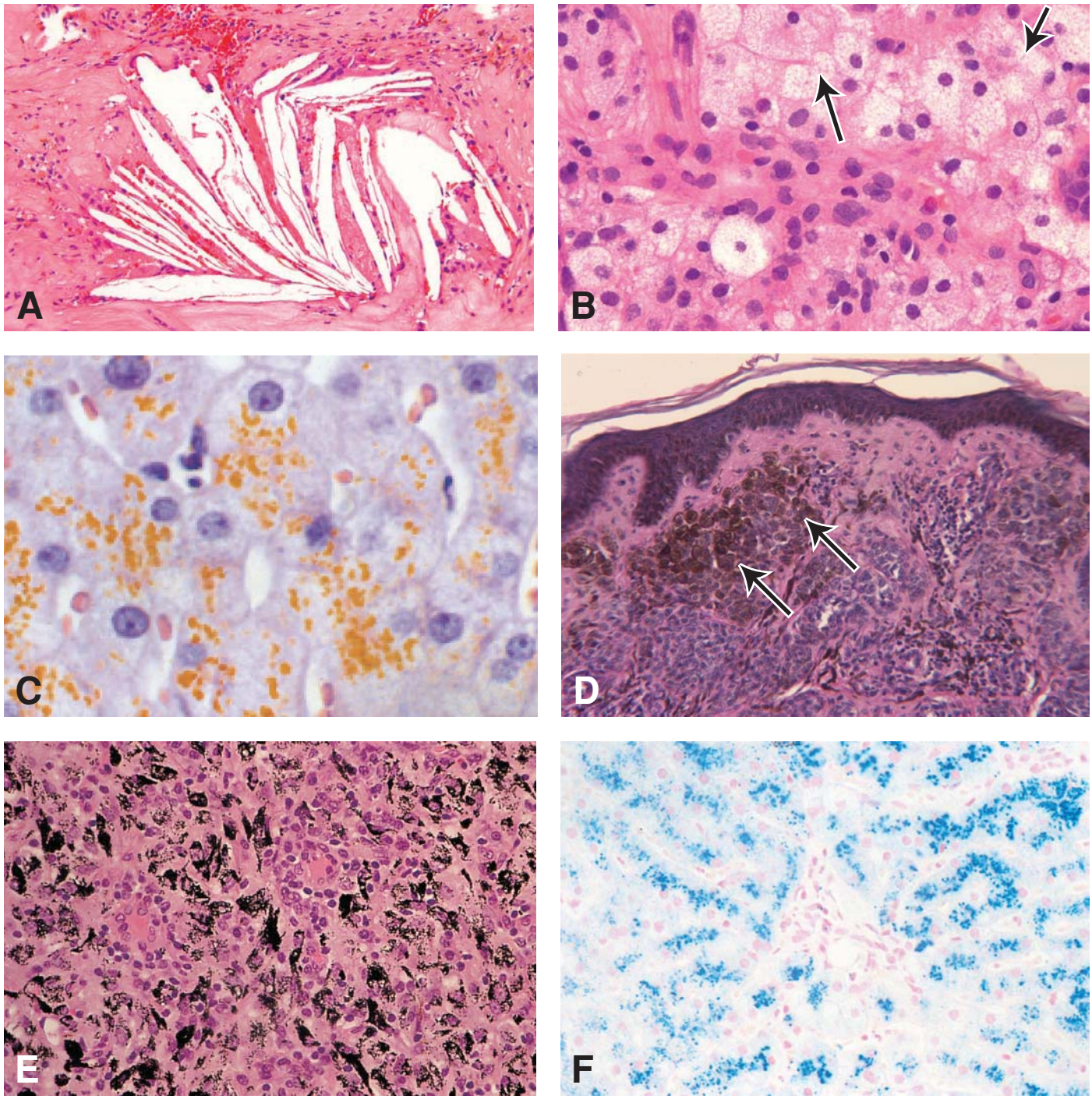


FIGURE 1-12. Abnormal intracellular storage. A. Abnormal cholesterol accumulation is characterized by transparent clefts, shown here in an atherosclerotic plaque. **B.** Lipid is stored in macrophages (*arrows*) in a cutaneous xanthoma. **C.** Lipofuscin in the liver from an 80-year-old man appears as golden cytoplasmic granules in lysosomes. **D.** Melanin (*arrows*) is stored in the cells of an intradermal nevus. **E.** Carbon pigment storage. A mediastinal lymph node, which drains the lungs, exhibits numerous macrophages that contain black anthracotic (carbon) pigment. This material was inhaled and originally deposited in the lungs. **F.** Iron storage in hereditary hemochromatosis. Prussian blue stain of the liver reveals large deposits of iron within hepatocellular lysosomes.

Exogenous Pigments

Anthracosis refers to storage of carbon particles in the lung and regional lymph nodes (Fig. 1-12E). Virtually all urban dwellers inhale particulates of organic carbon generated by the burning of fossil fuels. These particles accumulate in alveolar macrophages and are also transported to hilar and mediastinal lymph nodes, where the indigestible material is stored indefinitely within macrophages. Although the gross appearance of the lungs of persons with anthracosis may be alarming, the condition is innocuous.

Tattoos (from the Samoan, "tatou") reflect the introduction of insoluble metallic and vegetable pigments into the skin,

where they are principally engulfed by dermal macrophages and persist for a lifetime.

Iron and Other Metals

Iron

About 25% of the body's total iron content is in an intracellular storage pool composed of the iron-storage proteins **ferritin** and **hemosiderin**. The liver and bone marrow are particularly rich in ferritin, although it is present in virtually all cells. Hemosiderin is a partially denatured form of ferritin that aggregates easily and is recognized microscopically as yellow-brown granules in the cytoplasm. Normally, hemosiderin is found mainly in the spleen, bone marrow and Kupffer cells of the liver.

Total body iron may be increased by enhanced intestinal iron absorption, as in some anemias, or by repeated blood transfusions, which include iron-containing erythrocytes. In either case, the excess iron is stored intracellularly as ferritin and hemosiderin. Increasing the body's total iron content leads to progressive accumulation of hemosiderin, which is called **hemosiderosis**. In this case, iron is present throughout the body, including the skin, pancreas, heart, kidneys and endocrine organs. However, by definition, intracellular accumulation of iron in hemosiderosis does not injure cells.

If, contrariwise, the increase in total body iron is extreme, it damages vital organs—the heart, liver, testes and pancreas. Iron overload can result from a genetic abnormality in iron absorption, namely, **hereditary hemochromatosis (HH)** (Fig. 1-12F). Tissue injury in HH most likely reflects iron-generated oxidative stress, as described above. In HH, mutations occur in one of the several genes responsible for iron transport and regulation of iron absorption.

Excessive iron storage in some organs is also associated with an increased risk of cancer. Metal polishers with pulmonary siderosis developed lung cancer with greater than normal frequency. Hemochromatosis increases the risk of liver cancer.

Other Metals

Excess accumulation of lead, particularly in children, causes mental retardation and anemia (see Chapter 8). The storage of other metals also presents dangers. In Wilson disease (Chapter 20), a hereditary disorder of copper metabolism, storage of excess copper in the liver and brain leads to severe chronic disease of those organs.

Calcification May Reflect Normal Development or an Abnormal Process

The deposition of mineral salts of calcium is, of course, a normal part of the formation of bone from cartilage. Calcium enters dead or dying cells because such cells cannot maintain a steep calcium gradient (see below). This cellular calcification is not ordinarily visible except as inclusions within mitochondria.

In "dystrophic" calcification macroscopic calcium salt deposits occur in injured tissues. This process does not simply represent accumulation of calcium derived from the bodies of dead cells but rather is caused by extracellular deposition of calcium from the circulation or interstitial fluid. Dystrophic calcification apparently requires the persistence of necrotic tissue; it is often visible to the naked eye and ranges from gritty, sand-like grains to firm, rock-hard material. Often, as in the lung or lymph nodes with tuberculous caseous necrosis, calcification has no functional consequences. However, dystrophic calcification that occurs in crucial locations, such as the mitral or aortic valves (Fig. 1-13), leads to obstruction of blood flow by making valve leaflets rigid and narrowing valve orifices (mitral and aortic stenosis). Dystrophic calcification in atherosclerotic coronary arteries contributes to narrowing of those vessels. Although molecules that participate in physiologic calcium deposition in bone (e.g., osteopontin, osteonectin and osteocalcin) are reported in association with dystrophic calcification, the mechanisms underlying this process remain obscure.

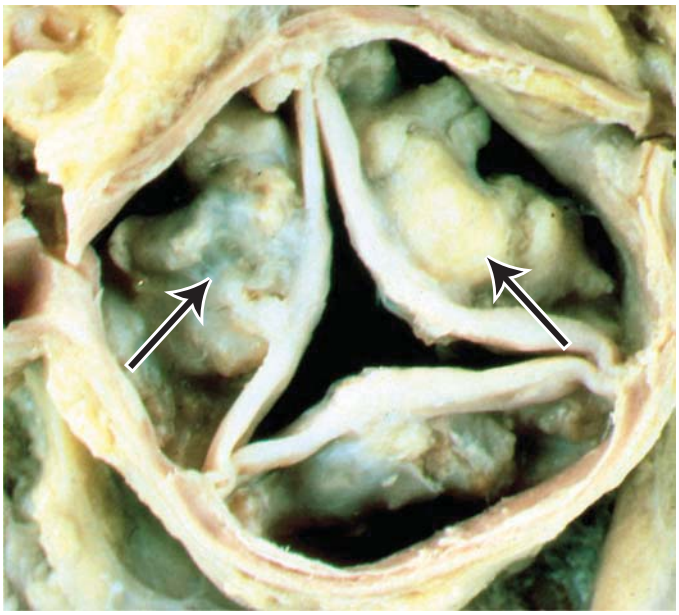


FIGURE 1-13. Calcific aortic stenosis. Deposits of solid calcium salts (*arrows*) are seen in the cusps and the free margins of the thickened aortic valve, viewed from above.

Dystrophic calcification also plays a role in diagnostic radiography. For example, mammography is based largely on the detection of small calcifications in breast cancers; congenital toxoplasmosis, an infection involving the central nervous system, is suggested when calcification is visualized in an infant's brain.

Unlike dystrophic calcification, which has its origin in cell injury, "metastatic" calcification reflects deranged calcium metabolism and is associated with increased serum calcium concentrations **(hypercalcemia)**. In general, almost any disorder that increases blood calcium levels can lead to calcification in such inappropriate locations as pulmonary alveolar septa, renal tubules and blood vessels. Metastatic calcification is seen in various disorders, including chronic renal failure, vitamin D intoxication and hyperparathyroidism.

The formation of calcium-containing stones in sites such as the gallbladder, renal pelvis, bladder and pancreatic duct is another form of pathologic calcification. Under certain circumstances, the mineral salts precipitate from solution and crystallize about foci of organic material. Those who have suffered the agony of gallbladder or renal colic will attest to the unpleasant consequences of this type of calcification.

Hyaline Refers to Any Reddish, Homogeneous Material That Stains with Eosin

The term **hyaline** was used in classic descriptions of diverse and unrelated lesions, such as hyaline arteriolosclerosis, alcoholic hyaline in the liver, hyaline membranes in the lung and hyaline droplets in various cells. The various lesions called hyaline have nothing in common. Alcoholic hyaline is composed of cytoskeletal filaments; the hyaline found in arterioles of the kidney is derived from basement membranes; and hyaline membranes in the lung consist of plasma proteins deposited in alveoli. The term is anachronistic but is still used as a morphologic descriptor.

Hyperplasia Is an Increase in Cell Numbers in an Organ or Tissue

Stimuli that induce hyperplasia and the mechanisms by which they act vary greatly from one tissue and cell type to the next. An agent that elicits hyperplastic responses in one tissue either may not do so in another or may do so via mechanisms that are totally distinct. In response to such stimuli, cells divide to generate an organ or tissue that contains more than its usual complement of those cells (hypercellular). The dividing cells may derive from cells that are already cycling or from resting progenitors. This process may occur as a response to an altered endocrine milieu, increased functional demand or chronic injury. Hypertrophy (an increase in organ and/or cell size; see below) may occur simultaneously with hyperplasia.

Hormonal Stimulation

Changes in hormone concentrations can elicit proliferation of responsive cells. These changes may reflect developmental, pharmacologic or pathologic influences. For example, the normal increase in estrogens at puberty or early in the menstrual cycle leads to increased numbers of endometrial and uterine stromal cells. Estrogen administration to postmenopausal women has the same effect. Enlargement of the male breast, called gynecomastia, may occur in men with excess estrogens (e.g., following estrogen therapy for prostate cancer or when the liver's inability to metabolize endogenous estrogens leads to their accumulation, as in liver failure). Ectopic hormone production may be a tumor's first presenting symptom (e.g., erythropoietin secretion by renal tumors leads to hyperplasia of erythrocytes in the bone marrow).

Increased Functional Demand

Increased physiologic requirements may result in hyperplasia. For example, at high altitudes, low atmospheric oxygen tension causes compensatory hyperplasia of erythroid precursors in the bone marrow and increased blood erythrocytes (secondary polycythemia) (Fig. 1-14). In this fashion, increased numbers of cells compensate for the decreased oxygen carried by each erythrocyte. The number of red blood cells promptly falls to normal on return to sea level. Similarly, chronic blood loss, as in excessive menstrual bleeding, also causes hyperplasia of erythrocytic elements.

Immune responsiveness to many antigens may lead to lymphoid hyperplasia (e.g., the enlarged tonsils and swollen lymph nodes that occur with streptococcal pharyngitis). The hypocalcemia that occurs in chronic renal failure produces increased demand for parathyroid hormone in order to augment blood calcium. The result is hyperplasia of the parathyroid glands.

Chronic Injury

Persistent injury may result in hyperplasia. Long-standing inflammation or chronic physical or chemical injury is often accompanied by a hyperplastic response. For instance, pressure from ill-fitting shoes causes hyperplasia of the skin of the foot, so-called corns or calluses. Resultant thickening of the skin protects it from the continued pressure. Chronic inflammation of the bladder (chronic cystitis) often causes hyperplasia of the bladder epithelium, visible as white plaques on the bladder lining.

Inappropriate hyperplasia can itself be harmful—witness the unpleasant consequences of psoriasis, which is characterized by conspicuous hyperplasia of the skin (Fig. 1-14D). Excessive estrogen stimulation, whether from endogenous sources or from medication, may eventuate in endometrial hyperplasia.

The variety of cellular and molecular mechanisms responsible for the increased mitotic activity that characterizes hyperplastic responses clearly relates to altered control of cell proliferation. These topics are discussed in Chapters 3 and 5.

Metaplasia Is Conversion of One Differentiated Cell Type to Another

Metaplasia is usually an adaptive response to persistent injury. That is, a tissue will assume a phenotype that protects it best from the insult. Most often, glandular epithelium is replaced by squamous epithelium. Columnar or cuboidal lining cells that are committed to mucus production may not be adequately resistant to the effects of chronic irritation or a pernicious chemical. For example, prolonged exposure of bronchial epithelium to tobacco smoke leads to squamous metaplasia. A similar response is associated with chronic infection in the endocervix (Fig. 1-15). Whether metaplasia results from altered differentiation of maturing cells or a change in the commitment of tissue stem cells to one lineage rather than another remains unknown.

The process is not restricted to squamous differentiation. When highly acidic gastric contents reflux chronically into the lower esophagus, the squamous epithelium of the esophagus may be replaced by glandular mucosa **(Barrett esophagus)**. This effect can be thought of as an adaptation to protect the esophagus from injury by gastric acid and pepsin, to which the glandular mucosa is more resistant.

Metaplasia may also consist of replacement of one glandular epithelium by another. In chronic gastritis, chronic inflammation causes atrophic stomach glands to be replaced by cells resembling those of the small intestine. The adaptive value of such intestinal metaplasia is not clear. Metaplasia of transitional epithelium to glandular epithelium occurs when the bladder is chronically inflamed (cystitis glandularis).

Although metaplasia may be thought of as adaptive, it is not necessarily innocuous. For example, squamous metaplasia may protect a bronchus from tobacco smoke, but it also impairs mucus production and ciliary clearance. Cancers

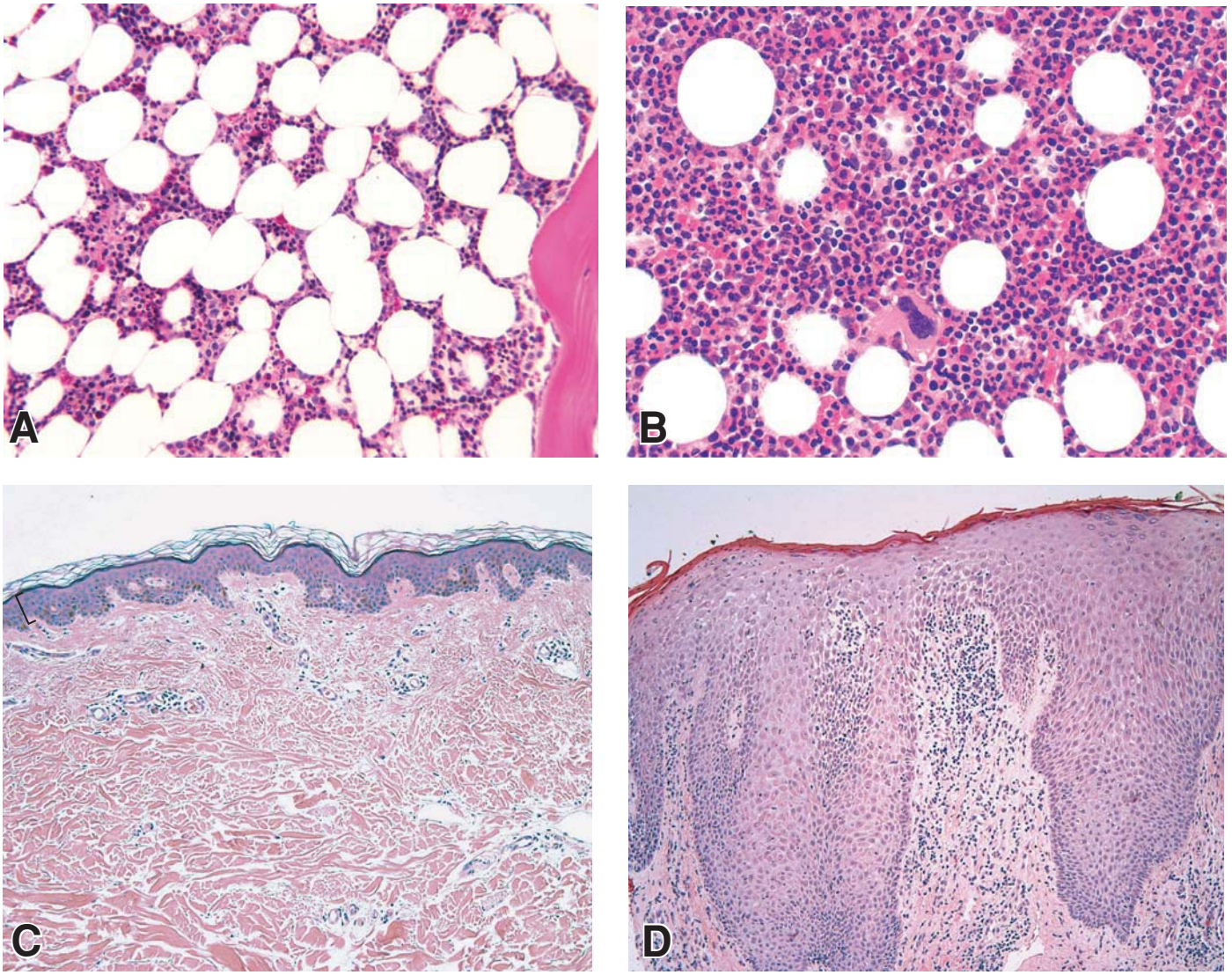


FIGURE 1-14. Hyperplasia. A. Normal adult bone marrow. Normocellular bone marrow shows the usual ratio of fat to hematopoietic cells. **B. Hyperplasia** of the bone marrow. Cellularity is increased; fat is relatively decreased. **C. Normal epidermis.** Epidermal thickness is modest (*bracket*) compared to the dermis (below). **D. Epidermal hyperplasia** in psoriasis is shown at the same magnification as in C. The epidermis is thickened owing to an increase in the number of squamous cells.

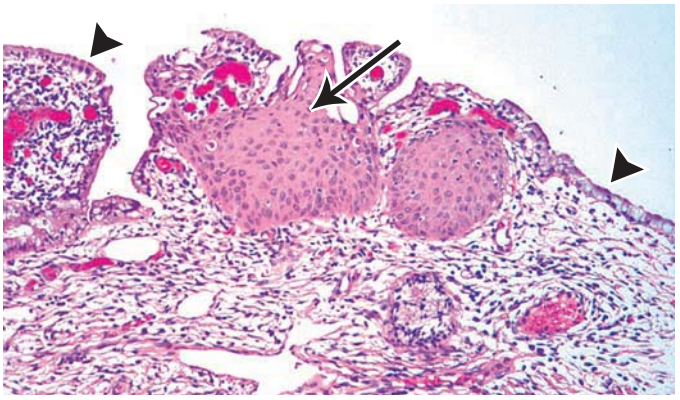


FIGURE 1-15. Squamous metaplasia. A section of endocervix shows the normal columnar epithelium at both margins (*arrowheads*) and a focus of squamous metaplasia in the center (*arrow*).

may develop in metaplastic epithelium; malignancies of the lung, cervix, stomach and bladder often arise in such areas. However, if the chronic injury ceases, there is little stimulus for cells to proliferate, and the epithelium does not become cancerous.

Metaplasia is usually fully reversible. If the noxious stimulus is removed (e.g., when one stops smoking), the metaplastic epithelium eventually returns to normal.

Dysplasia Is Disordered Cellular Growth and Maturation

The cells that compose an epithelium normally exhibit uniformity of size, shape and nuclei. Moreover, they are arranged in a regular fashion; for example, a squamous epithelium progresses from plump basal cells to flat superficial cells. In dysplasia, this pattern is disturbed by (1) variation