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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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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 subspecialties 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 exciting, 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 sheaf 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
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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Mechanisms of Disease
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. 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...
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...
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 1-3.** 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).

**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.
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 (O₂) has a major role as the terminal electron acceptor in mitochondria. It is reduced from O₂ to H₂O, and resultant energy is harnessed as an electrochemical potential across the mitochondrial inner membrane.

Conversion of O₂ to H₂O entails transfer of four electrons. Three partially reduced species, representing transfers of varying numbers of electrons, are intermediate between O₂ and H₂O (Fig. 1-7). These are O₂⁻, superoxide (one electron); H₂O₂, 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 (O₂⁻) 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 O₂ to yield O₂⁻. In phagocytic inflammatory cells, activation of a plasma membrane oxidase produces O₂⁻, which is then converted to H₂O₂ and eventually to other ROS (Fig. 1-8). These ROS...
CELL ADAPTATION, INJURY AND DEATH

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 O₂ is converted to O₂⁻ in the cytosol. O₂⁻ is reduced to H₂O₂ by cytosolic superoxide dismutase (Cu/Zn SOD), and finally to water. 2. O₂ enters the mitochondria, where inefficiencies in electron transport result in conversion of O₂ to O₂⁻. This superoxide is rendered less reactive by further reduction to H₂O₂ via mitochondrial SOD (MnSOD). This H₂O₂ is then converted to H₂O by cytosolic superoxide dismutase (Cu/Zn SOD), and finally to water. 3. Cytosolic H₂O₂ enters peroxisomes where it is detoxified to hydrogen peroxide; GPX.

Hydrogen Peroxide

O₂⁻ anions are converted by superoxide dismutase (SOD) to H₂O₂. Hydrogen peroxide is also produced directly by a number of oxidases in cytoplasmic peroxisomes (Fig. 1-7). By itself, H₂O₂ is not particularly injurious, and it is largely metabolized to H₂O by catalase. However, when produced in excess, it is converted to highly reactive OH•. In neutrophils, myeloperoxidase transforms H₂O₂ to a potent radical, hypochlorite (OCI⁻), which is lethal for microorganisms and, if released extracellularly, can kill cells.

Most cells have efficient mechanisms for removing H₂O₂. Two different enzymes reduce H₂O₂ 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, H₂O₂ generated in mitochondria affects the oxidant balance, not only in mitochondria but also in other cellular compartments.

**Hydroxy radical (OH•)**

- Generated from H₂O₂ by Fe²⁺-catalyzed Fenton reaction
- The intracellular radical most responsible for attack on macromolecules

**Hypochlorous acid (HOCl)**

- Produced by macrophages and neutrophils during lipid peroxidation
- Dissociates to yield hypochlorite radical (OCI⁻)

### Table 1-1

<table>
<thead>
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<th>Molecule</th>
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<tr>
<td>Hydrogen peroxide (H₂O₂)</td>
<td>Forms free radicals via Fe²⁺-catalyzed Fenton reaction; Diffuses widely within the cell</td>
</tr>
<tr>
<td>Superoxide anion (O₂⁻)</td>
<td>Generated by leaks in the electron transport chain and some cytosolic reactions; Produces other ROS; Does not readily diffuse far from its origin</td>
</tr>
<tr>
<td>Hydroxyl radical (OH•)</td>
<td>Generated from H₂O₂ by Fe²⁺-catalyzed Fenton reaction; The intracellular radical most responsible for attack on macromolecules</td>
</tr>
<tr>
<td>Peroxynitrite (ONOO⁻)</td>
<td>Formed from the reaction of nitric oxide (NO) with O₂⁻; Damages macromolecules</td>
</tr>
<tr>
<td>Lipid peroxide radicals (RCO0•)</td>
<td>Organic radicals produced during lipid peroxidation</td>
</tr>
<tr>
<td>Hypochlorous acid (HOCI)</td>
<td>Produced by macrophages and neutrophils during respiratory burst that accompanies phagocytosis</td>
</tr>
</tbody>
</table>

Fe²⁺ = ferrous iron.