



Rubin's

# PATHOLOGY

Clinicopathologic  
Foundations of Medicine

SEVENTH  
EDITION

Editor

David S. Strayer

Founder and Contributing Editor

Emanuel Rubin



Wolters Kluwer



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CLINICOPATHOLOGIC FOUNDATIONS OF MEDICINE

SEVENTH EDITION

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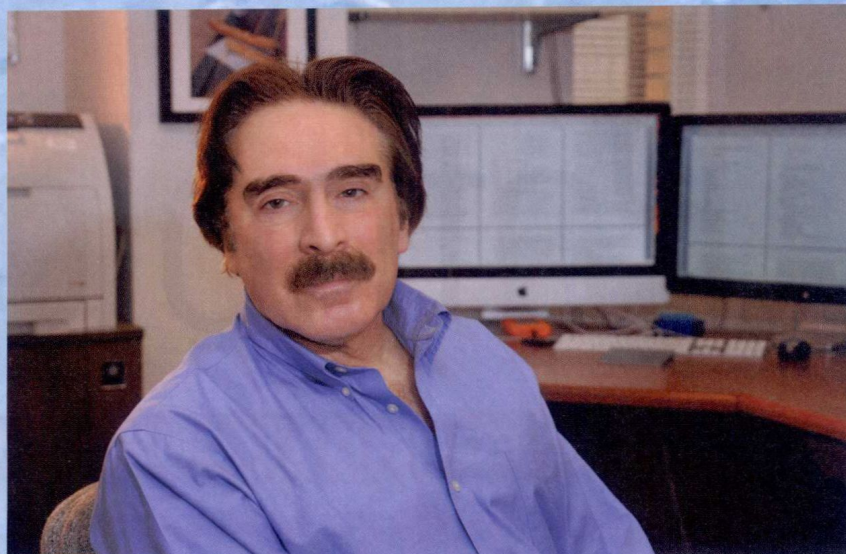
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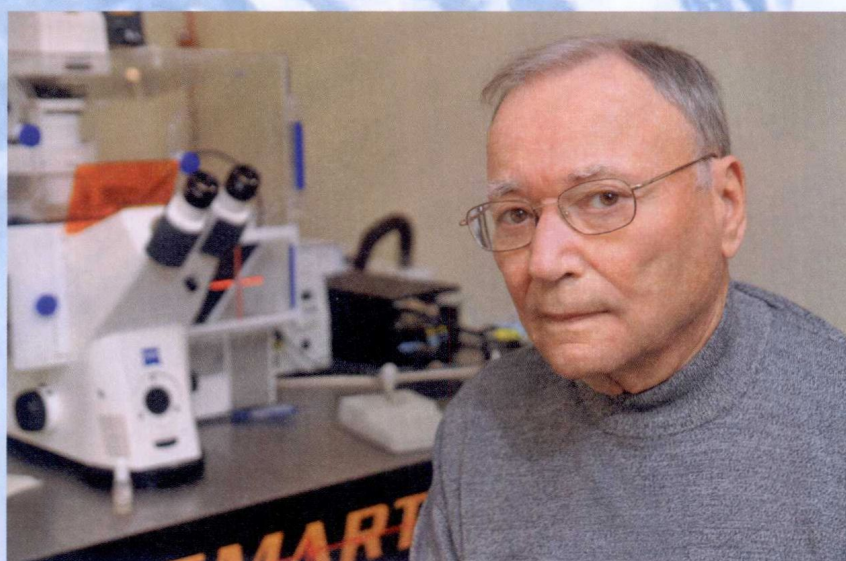
SEVENTH EDITION

Founding and Contributing Editor Emanuel Rubin, MD





**Editor David S. Strayer, MD, PhD**



**Founder and Contributing Editor Emanuel Rubin, MD**



*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 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  
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Philadelphia, 2014



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#### **Figure Acknowledgments 1533**

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The background of the slide is a composite of histological images. A large, faint image of a blood vessel with a thick, irregular wall is visible in the upper right. A horizontal red banner spans the width of the slide, partially obscuring the background images. To the left of the banner, there are three smaller, more distinct histological images: one showing a dense cellular area, another showing a structure with a central lumen, and a third showing elongated, fibrous structures.

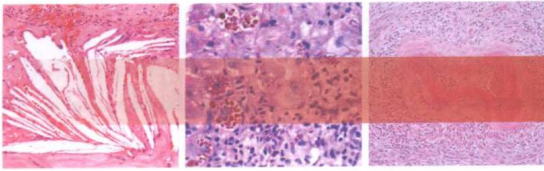
SECTION I

# **Mechanisms of Disease**









# Cell Adaptation, Injury and Death

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## MECHANISMS AND MORPHOLOGY OF CELL INJURY

Hydropic Swelling  
Ischemic Cell Injury  
Oxidative Stress  
Antioxidant Defenses  
Role of p53 in Oxidative Injury  
Intracellular Storage  
Calcification  
Hyaline  
Hyperplasia  
Metaplasia  
Dysplasia

## Reactions to Persistent Stress and Cell Injury

Atrophy and Hypertrophy  
Normal Homeostasis  
Atrophy and Hypertrophy as Inverses  
Signaling in Atrophy and Hypertrophy

Loss of Muscle Mass  
Turnover of Postmitotic Cells

## Ubiquitin and Ubiquitin-Proteasome System

Ubiquitin and Ubiquitination  
Proteasomes and Cell Homeostasis  
UPS and Pathogens  
UPS and Disease  
Autophagy  
Molecular Chaperones and Chaperonopathies  
Nonlethal Mutations That Impair Cell Function

## CELL DEATH

### Morphology of Cell Death

Pathology of Necrotic Cell Death  
Pathology of Apoptotic Cell Death  
Active Cell Death

### Necrosis

Ischemic Injury and Reperfusion

## Programmed Cell Death

Apoptosis

### Mechanisms of Apoptosis

Apoptosis Signaling Pathways  
Extrinsic Pathway of Apoptosis  
Intrinsic Pathway of Apoptosis  
Endoplasmic Reticulum  $Ca^{2+}$  Release and Apoptosis  
Role of Mitochondrial Proteins in Apoptosis  
Apoptosis in Disease

### Other Forms of Programmed Cell Death

Autophagy and Cell Death  
Necroptosis  
Anoikis  
Granzymes and Apoptosis  
Pyroptosis  
NETosis  
Entosis

**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.<sup>1</sup> 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

<sup>1</sup>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.