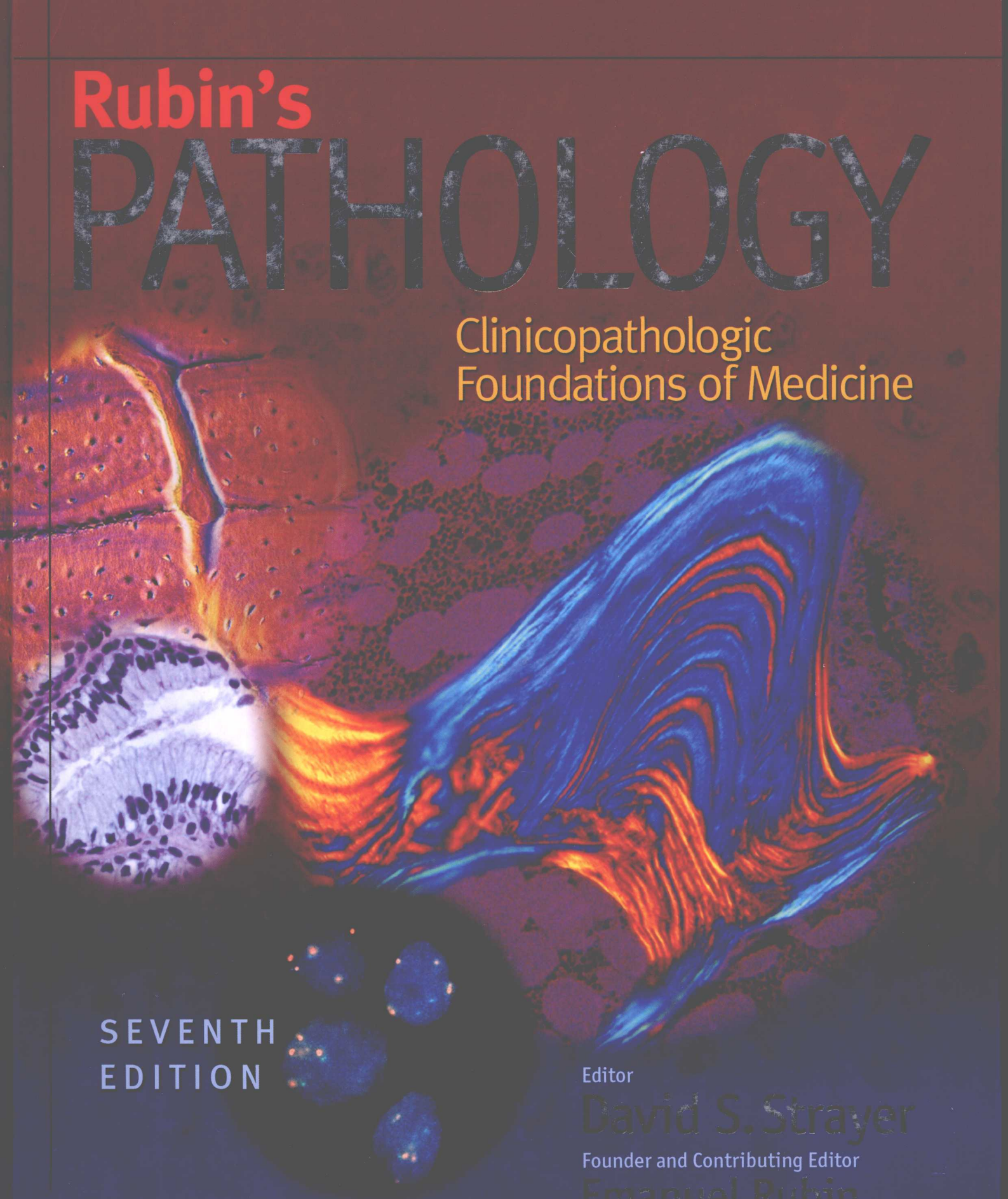
Rubin's PATHOLOGY

Clinicopathologic Foundations of Medicine



SEVENTH EDITION

Editor
David S. Strayer
Founder and Contributing Editor
Emanuel Rubin

Wolters Kluwer

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EDITOR

David S. Strayer, MD, PhD

Professor of Pathology
Department of Pathology and Cell Biology
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

FOUNDER AND CONTRIBUTING EDITOR

Emanuel Rubin, MD

Gonzalo Aponte Distinguished Professor of Pathology
Chairman Emeritus of the Department of Pathology and Cell Biology
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

ASSOCIATE EDITORS

Jeffrey E. Saffitz, MD, PhD

Mallinckrodt Professor of Medicine
Harvard Medical School
Chairman, Department of Pathology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Alan L. Schiller, MD

Professor and Chairman
Department of Pathology
John A. Burns School of Medicine
University of Hawaii
Honolulu, Hawaii

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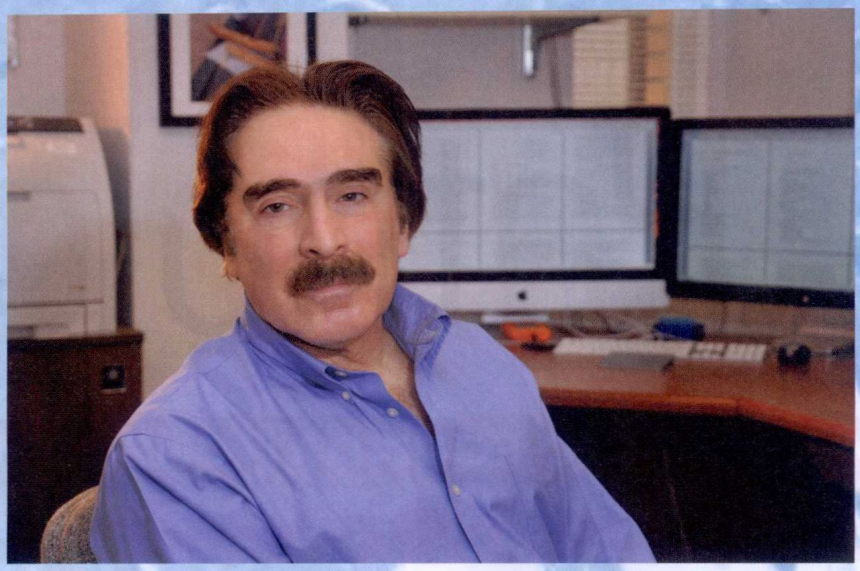

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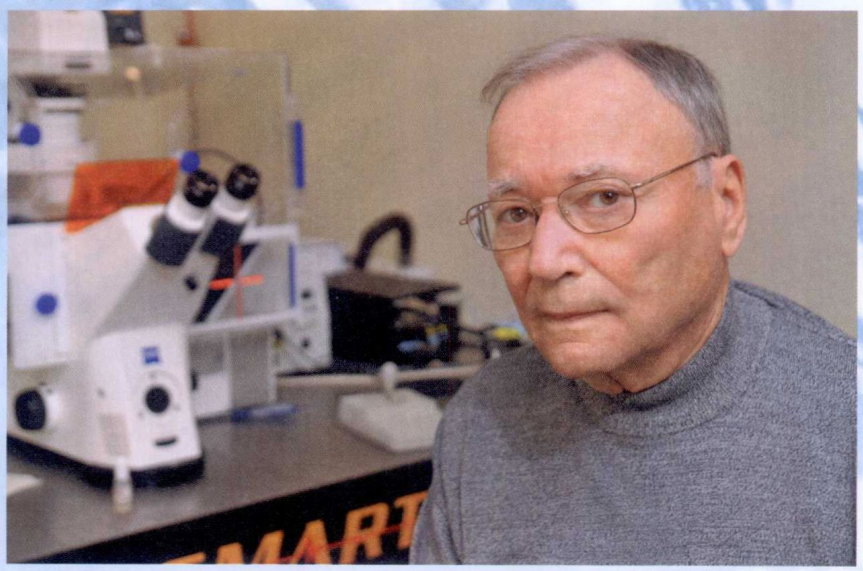

Founder and Contributing Editor Emanuel Rubin, MD

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.

CONTRIBUTORS

Ronnie Abraham, MD
Department of Pathology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Michael F. Allard, MD
Professor of Pathology and Laboratory Medicine
University of British Columbia
Cardiovascular Pathologist
Department of Pathology and Laboratory Medicine
The iCAPTURE Centre
St. Paul's Hospital
Vancouver, British Columbia, Canada

Mary Beth Beasley, MD
Associate Professor of Pathology
Mount Sinai Medical Center
New York, New York

Thomas W. Bouldin, MD
Professor of Pathology and Laboratory Medicine
Chair for Faculty and Trainee Development
University of North Carolina at Chapel Hill
Director of Neuropathology
McLendon Clinical Laboratories
University of North Carolina Hospitals
Chapel Hill, North Carolina

Linda A. Cannizzaro, PhD
Professor of Pathology
Albert Einstein College of Medicine
Director of Cytogenetics
Montefiore Medical Center
Bronx, New York

Diane L. Carlson, MD
Assistant Attending
Department of Pathology
Memorial Sloan-Kettering Cancer Center
New York, New York

Emily Y. Chu, MD, PhD
Department of Dermatology
Hospital of the University of Pennsylvania
Perelman Center for Advanced Medicine
Philadelphia, Pennsylvania

Philip L. Cohen, MD
Professor of Medicine
Temple University School of Medicine
Chief, Section of Rheumatology
Temple University Hospital
Philadelphia, Pennsylvania

Ivan Damjanov, MD, PhD
Professor of Pathology
The University of Kansas School of Medicine
Pathologist
Department of Pathology
University of Kansas Medical Center
Kansas City, Kansas

Jeffrey M. Davidson, PhD
Professor of Pathology
Vanderbilt University School of Medicine
Senior Research Career Scientist
Medical Research Service
Veterans Affairs Tennessee Valley Healthcare System
Nashville, Tennessee

Elizabeth G. Demicco, MD, PhD
Assistant Professor of Pathology
Icahn School of Medicine at Mount Sinai
Pathologist
Mount Sinai Hospital
New York, New York

Alina Dulau Florea, MD
Assistant Professor of Pathology
Thomas Jefferson University
Philadelphia, Pennsylvania

David E. Elder, MD, ChB, FRCPA
Professor of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Director of Anatomic Pathology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Gregory N. Fuller, MD, PhD
Professor of Pathology
Chief of Neuropathology
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Roberto A. Garcia, MD
Assistant Professor of Pathology
Mount Sinai School of Medicine
Chief of Orthopaedic and Soft Tissue Pathology
Mount Sinai Hospital
New York, New York

J. Clay Goodman, MD
Professor of Pathology and Neurology
Walter Henrick Moursund Chair in Neuropathology
Associate Dean of Undergraduate Medical Education
Baylor College of Medicine
Houston, Texas

Avrum I. Gotlieb, MD, CM, FRCP
Professor of Laboratory Medicine and Pathology
University of Toronto
Staff Pathologist
Laboratory Medicine Program
University Health Network
Toronto, Ontario, Canada

Leana A. Guerin, MD
Assistant Professor of Pathology
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Philip N. Hawkins, PhD, FRCP, FRCPath, FMedSci
Professor of Medicine
Centre for Amyloidosis and Acute Phase Proteins
University College London Medical School
Head, National Amyloidosis Centre
Royal Free Hospital
London, England, United Kingdom

Kendra Iskander, MD
Department of Surgery
Boston Medical Center
Boston, Massachusetts

J. Charles Jennette, MD
Brinkhous Distinguished Professor and Chair of Pathology and Laboratory Medicine
University of North Carolina, School of Medicine
Chief of Service
Department of Pathology and Laboratory Medicine
University of North Carolina Hospitals
Chapel Hill, North Carolina

Sergio A. Jimenez, MD
Professor and Co-Director
Jefferson Institute of Molecular Medicine
Director of Connective Tissue Diseases
Director of Scleroderma Center
Department of Dermatology and Cutaneous Biology
Thomas Jefferson University
Philadelphia, Pennsylvania

Lawrence C. Kenyon, MD, PhD
Associate Professor of Pathology, Anatomy and Cell Biology
Thomas Jefferson University
Pathologist and Neuropathologist
Department of Pathology, Anatomy and Cell Biology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Michael J. Klein, MD
Professor of Pathology and Laboratory Medicine
Weill Medical College of Cornell University
Pathologist-in-Chief and Director of Pathology and Laboratory Medicine
Hospital for Special Surgery
New York, New York

David S. Klimstra, MD
Chief of Surgical Pathology
Department of Pathology
Memorial Sloan-Kettering Cancer Center
New York, New York

Gordon K. Klintworth, MD, PhD
Professor of Pathology
Joseph A.C. Wadsworth Research Professor of Ophthalmology
Duke University
Durham, North Carolina

Shauying Li, MD
Assistant Professor
Department of Pathology, Microbiology and Immunology
Vanderbilt University Medical Center
Nashville, Tennessee

Amber Chang Liu, MSc
Harvard Medical School
Resident Physician
Department of Anesthesiology, Critical Care and Pain Medicine
Massachusetts General Hospital
Boston, Massachusetts

David Benner Lombard, MD, PhD
Assistant Professor of Pathology
Department of Pathology and Institute of Gerontology
Staff Pathologist
Department of Pathology
University of Michigan
Ann Arbor, Michigan

Peter A. McCue, MD
Professor of Pathology
Thomas Jefferson University
Director of Anatomic Pathology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Bruce McManus, MD, PhD, FRSC
Professor of Pathology and Laboratory Medicine
University of British Columbia
Director, Providence Heart and Lung Institute
St. Paul's Hospital
Vancouver, British Columbia, Canada

Maria J. Merino, MD
Chief of Translational Pathology
Department of Pathology
National Cancer Institute
Bethesda, Maryland

Marc S. Micozzi, MD, PhD
Private Practice, Forensic Medicine
Policy Institute for Integrative Medicine
Bethesda, Maryland

Frank Mitros, MD
Frederic W. Stamler Professor
Department of Pathology
University of Iowa
Iowa City, Iowa

Anna Marie Mulligan, MB, MSc, FRCPath
Assistant Professor of Laboratory Medicine and Pathobiology
University of Toronto
Anatomic Pathologist
Department of Laboratory Medicine
St. Michael's Hospital
Toronto, Ontario, Canada

Hedwig S. Murphy, MD, PhD
Associate Professor of Pathology
University of Michigan
Staff Pathologist
Department of Pathology and Laboratory Medicine
Veterans Affairs Ann Arbor Health System
Ann Arbor, Michigan

George L. Mutter, MD
Associate Professor of Pathology
Harvard Medical School
Pathologist
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Frances P. O'Malley, MB, FRCPC
Professor of Laboratory Medicine and Pathobiology
University of Toronto
Staff Pathologist
Department of Pathology and Laboratory Medicine
Mount Sinai Hospital
Toronto, Ontario, Canada

Jaime Prat, MD, PhD, FRCPath
Professor of Pathology
Director of Pathology
Autonomous University of Barcelona
Director of Pathology
Hospital de la Santa Creu i Sant Pau
Barcelona, Spain

Daniel G. Remick, MD
Chair and Professor, Department of Pathology and Laboratory Medicine
Boston University School of Medicine
Chief of Pathology, Department of Pathology and Laboratory Medicine
Boston Medical Center
Boston, Massachusetts

Emanuel Rubin, MD
Gonzalo Aponte Distinguished Professor of Pathology
Chairman Emeritus of the Department of Pathology and Cell Biology
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

Jeffrey E. Saffitz, MD, PhD
Mallinckrodt Professor of Medicine
Harvard Medical School
Chairman, Department of Pathology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Alan L. Schiller, MD
Professor and Chairman
Department of Pathology
John A. Burns School of Medicine
University of Hawaii
Honolulu, Hawaii

David A. Schwartz, MD, MSHyg, FCAP
Pathologist
Atlanta, Georgia

Gregory C. Sephel, PhD
Associate Professor of Pathology
Vanderbilt University School of Medicine
Nashville, Tennessee

Elias S. Siraj, MD
Associate Professor of Medicine
Section of Endocrinology
Temple University School of Medicine
Program Director, Endocrinology Fellowship
Temple University Hospital
Philadelphia, Pennsylvania

Edward B. Stelow, MD
Associate Professor of Pathology
University of Virginia
Charlottesville, Virginia

Arief A. Suriawinata, MD
Associate Professor of Pathology
Geisel School of Medicine at Dartmouth
Hanover, New Hampshire
Section Chief of Anatomic Pathology
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Swan N. Thung, MD
Professor of Pathology
Mount Sinai School of Medicine
Director, Division of Liver Pathology
Mount Sinai Medical Center
New York, New York

William D. Travis, MD
Professor of Pathology
Weill Medical College of Cornell University
Attending Thoracic Pathologist
Memorial Sloan Kettering Cancer Center
New York, New York

Riccardo Valdez, MD
Assistant Professor of Pathology
Section Head, Hematopathology
Department of Laboratory Medicine and Pathology
Mayo Clinic
Scottsdale, Arizona

Jeffrey S. Warren, MD
Aldred S. Warthin Endowed Professor of Pathology
Director, Division of Clinical Pathology
University of Michigan Medical School
University of Michigan Hospitals
Ann Arbor, Michigan

Kevin Jon Williams, MD
Professor of Medicine
Chief, Section of Endocrinology, Diabetes and Metabolism
Temple University School of Medicine
Philadelphia, Pennsylvania

Robert Yanagawa, MD, PhD
Division of Cardiac Surgery
University of Toronto, Faculty of Medicine
Toronto, Ontario, Canada

Mary M. Zutter, MD
Professor of Pathology and Cancer Biology
Vanderbilt University
Director of Hematopathology
Vanderbilt University Medical Center
Nashville, Tennessee

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.

Stuart A. Aaronson
Mohammad Alomari
Adam Bagg
Karoly Balogh
Sue Bartow
Douglas P. Bennett
Marluce Bibbo
Hugh Bonner
Patrick J. Buckley
Stephen W. Chensue
Daniel H. Connor
Jeffrey Cossman
John E. Craighead
Mary Cunnane
Giulia DeFalco
Hormuz Ehya
Joseph C. Fantone
John L. Farber
Kevin Furlong
Antonio Giordano
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Anthony A. Killeen
Robert Kisilevsky
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Victor J. Navarro
Adebeye O. Osunkoya
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Stephen Peiper
Robert O. Peterson
Roger J. Pomerantz
Martha Quezado
Timothy R. Quinn
Stanley J. Robboy
Brian Schapiro
Roland Schwarting
Stephen M. Schwartz
Benjamin H. Spargo
Charles Steenbergen, Jr.
Craig A. Storm
Steven L. Teitelbaum
Ann D. Thor
John Q. Trojanowski
Benjamin F. Trump
Beverly Y. Wang
Jianzhou Wang
Bruce M. Wenig

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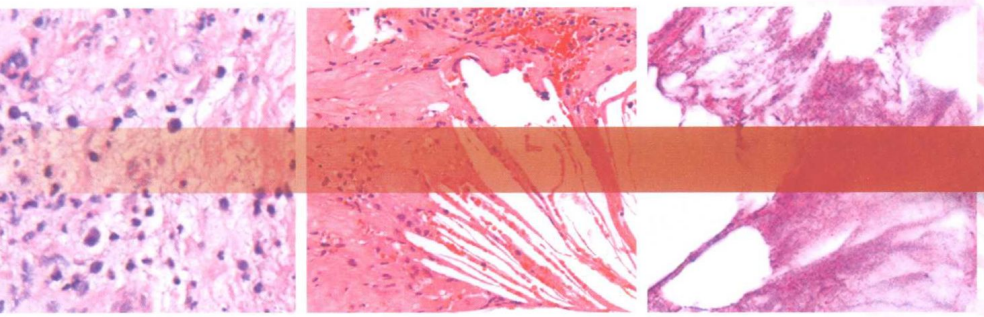
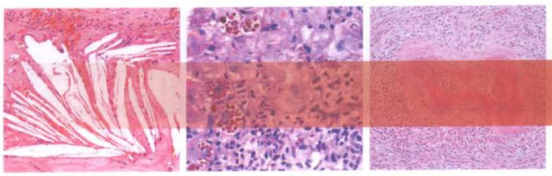


SECTION I

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.