



SIXTH EDITION

PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults and Children

Kathryn L. McCance

Sue E. Huether

Valentina L. Brashers

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The Biologic Basis for Disease in Adults and Children

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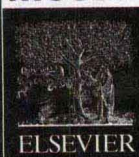
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PREFACE

Pathophysiology incorporates basic, translational, and clinical research to advance understandings of disease and dysfunction. The study of pathophysiology involves many biomedical sciences and a wide range of research activities. Multiple aspects of cellular physiology are progressing rapidly, generating vast amounts of data to understand molecular, cellular, and tissue level interactions. The information expansion involves a greater understanding of the behavior of individual cells, their neighboring microenvironment, and of the molecules that not only make up those cells but also communicate with their surroundings. Fascinating is the idea that the cell is at once a crowded structural and chemical space and surrounded by a fragile “soft” space subjected to molecular and physical forces that create structural rearrangements and pathologic states. These new findings are creating the need for an integrative approach among numerous sciences to the study of pathophysiology.

Although these advancements have created an ever-increasing state of excitement, they have also created the problem of how students, teachers, and clinicians can cope with the expanding new information. Compressing these data into simplified discussions for students and clinicians is challenging. Our approach in this book has been to emphasize this emergence by explaining new concepts in greater detail than perhaps is usual and by giving extra emphasis to important but difficult content. The primary focus is on pathophysiology, and there is less emphasis on the evaluation and treatment that is found in clinical management textbooks. In this edition are some major new chapters and several extensively rewritten previous chapters with new art.

As in previous editions, our specific goals for the textbook are to:

- Draw attention to differences in etiology, epidemiology, and pathophysiology, according to gender and age
- Include major difference in clinical manifestations and treatment by gender and age
- Pay careful attention to presentations of emerging new data on controversial topics
- Integrate health promotion and disease prevention by updating risk factors, explaining certain relationships between nutrition and disease, and noting screening recommendations and other therapeutic approaches

ORGANIZATION AND CONTENT: WHAT'S NEW IN THE SIXTH EDITION

The book is organized into two parts. The application of the principles and concepts in Part One determines the learner's ability to grasp the cellular and tissue responses to the most

common diseases presented in Part Two. All content has been reviewed with extensive new references.

Part One: Central Concepts of Pathophysiology: Cells and Tissues

Part One begins with an in-depth study of the cell and progresses to cover the underlying processes of disease. Concepts covered include cell signaling and cell communication processes; genes and common genetic diseases; fluid electrolyte and acid-base balance; inflammation, cytokines and their biologic functions, normal and altered immunity; infection, stress, coping, and immunity; tumor biology, and epidemiology of cancer. Particularly important revisions and additions to Part One include the following:

- Updated content on cellular organelles, cell signaling, and communication (Chapter 1)
- Updated content on oxidative stress, types of cell death, apoptosis, and aging (Chapter 2)
- Updated content on normal innate and adaptive immunity (Chapters 6 and 7)
- Updated content on alterations of immunity and inflammation (Chapter 8)
- Extensively revised chapter on infection (Chapter 9)
- Reorganization and updated content on stress and disease (Chapter 10)
- Extensive revisions and reorganization of tumor biology and invasion and metastases (Chapter 11)
- Extensive revisions and reorganization of epidemiology of cancer (Chapter 12)

Part Two: Pathophysiologic Alterations: Organs and Systems

Part Two is a systematic survey of diseases within body systems. Each unit focuses on a specific body system and begins with an anatomy and physiology chapter to provide a basis of comparison for understanding the alterations brought about by disease. A brief summary of normal aging is included at the end of the section on anatomy and physiology. The discussion of each disease in the alterations chapters is developed in a logical manner that begins with an introductory paragraph on etiology and epidemiology, followed by pathophysiology, clinical manifestations, and evaluation and treatment. Separate chapters are dedicated to pediatric pathophysiology, and sensitivity is paid to gender and age. Especially significant revisions and additions to Part Two include the following:

- New information on pain modulation, chronic pain syndromes, and classification of sleep disorders (Chapter 15)

- Updated content on concepts of altered cognition and coma, seizures, mechanisms of dementia, and alterations in motor function (Chapter 16)
- Rewritten content on secondary and tertiary responses to brain injury and chronic neurologic disorders including immune mechanisms associated with multiple sclerosis (Chapter 17)
- Updated content on schizophrenia, mood disorders, and anxiety (Chapter 18)
- Updates on genes and brain defects in children, brain infection, and brain tumors (Chapter 19)
- New content on neuroregulation of hormone responses and hormonal immune system interaction (Chapter 20)
- Extensive updates on the genetics of hormone disorders, pituitary and thyroid disorders, immune mechanisms of diabetes mellitus, the pathophysiology of insulin resistance, gestational diabetes, and the chronic complications of diabetes (Chapter 21)
- Extensively rewritten material on reproductive disorders, benign breast diseases, breast cancer, and prostate cancer (Chapter 23)
- Reorganized and updated content on normal blood cells, hemostasis, platelet function, and coagulation (Chapter 25)
- Extensively revised and updated content on alterations of leukocyte, lymphoid, and hemostatic function (Chapter 27)
- Reorganized and updated content on the anatomy and physiology of the cardiovascular system (Chapter 29)
- Extensively updated coverage of atherosclerosis, endothelial injury and dysfunction, coronary artery disease, myocardial infarction, and heart failure (Chapter 30)
- Major revisions of the signs and symptoms of respiratory disease and disorders of the chest wall. Updates in gene-environment interaction and the role of cytokines in the pathophysiology of asthma; pulmonary hypertension, pulmonary embolism, and lung cancers (Chapters 33)
- Major revisions in upper airway disorders in children, childhood obstructive sleep apnea syndrome, respiratory distress syndrome, lung infections, and asthma (Chapter 34)
- Major reorganization and updates on urinary tract and renal disorders including obstructive uropathies, glomerulopathies, and chronic renal failure (Chapter 36)
- New information for inherited disorders of renal function, infection and urinary tract disease, and renal failure in children (Chapter 37)
- Major revisions and new content on peptic ulcer disease, irritable bowel syndrome, inflammatory bowel disease, intestinal obstruction, obesity, and liver disease (Chapter 39)
- New information on esophageal reflux and esophagitis, necrotizing enterocolitis, and infections of the intestine in children (Chapter 40)
- Updated content on alterations of musculoskeletal system (Chapter 42)

- Updated content on allergic and autoimmune diseases of the skin, skin infections, and skin cancer (Chapter 44)
- Updated content on atopic dermatitis and immune reactions to skin infections and drug treatment in children (Chapter 45)
- Updated content on septic shock, multiple organ dysfunction syndrome, and burns for adults and children (Chapters 46 and 47)

FEATURES TO PROMOTE LEARNING

Ease of learning has been enhanced by designing a number of features that guide and support understanding, including:

- Each chapter opener notes the corresponding module in the Online Review Course. The course is available as a separate purchase.
- *Chapter Outlines* for each chapter
- *Special Headings* to underscore the consistent treatment of each disease—Pathophysiology, Clinical Manifestations, and Evaluation and Treatment
- More than 80 *What's New?* boxes review the most current research and clinical developments
- *Nutrition & Disease* boxes to emphasize nutrition as a health promotion strategy that may alter disease risk or pathogenesis
- End-of-chapter *Summary Review* sections summarize the content in each chapter and serve as built-in content review guides
- Boldface *Key Terms* with end-of-chapter term lists and page numbers for rapid access
- A comprehensive *Glossary* of more than 1000 terms on **Evolve** helps students with the often-difficult terminology related to pathophysiology; a brief version is included at the back of this book



ART PROGRAM

The art program was carefully crafted. More than 300 new full-color illustrations and photographs were created and strategically placed throughout the textbook. The art program received as much attention as the narrative. Also included are many new high-quality, full-color photographs of clinical manifestations, pathologic specimens, and clinical imaging techniques. The combination of illustrations, algorithms, photographs, and use of color for tables and boxes allows clarification for complex concepts and the emergence of easily recognized essential information.

ANCILLARIES

For Students

On **Evolve**, students may register for **free** access to 775 review questions, a comprehensive glossary, an audio glossary, 25 animations to help students master the text content, downloadable audio chapter Key Points, and updated WebLinks, which are carefully chosen Internet sites related to each chapter in the text.

The **Study Guide** includes learning objectives, special *Memory Check!* boxes, concise summaries of key concepts, and a practice examination for each chapter. Each of the disease chapters also includes a case study with a critical thinking question. Answers are found in the back.

For Instructors

The **Evolve Instructor Resources** for this textbook provide the following teaching aids:

- Teaching Difficult Concepts tool for each chapter
- Audience Response Questions (iClicker) for each chapter (141 total)
- Critical Thinking Exercises for each chapter (231 total)
- Test Bank in ExamView and Word with more than 2300 questions (in true/false, multiple choice, matching, and completion formats) with answers and textbook page references

- Image Collection with approximately 1100 key figures from the text
- Lecture Slides on PowerPoint for every chapter
- Chapter Summaries

Evolve is an Internet-based learning environment that works in coordination with the text. This resource enables you to publish your class syllabus, outline, and lecture notes; set up “virtual office hours” and e-mail communication; share important dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards. Free with qualified adoption. Contact your sales representative or visit <http://evolve.elsevier.com> for more information about integrating **Evolve** into your curriculum.

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The enormous task of keeping this book current and readable greatly depends on our contributors. We thank them for their knowledge and tremendous labor of reviewing relevant literature, synthesizing it, and writing and revising chapters to make them highly readable for others. Several chapters were completely rewritten for this edition. We have a special appreciation for Dr. Neal Rote and Dr. Tina Brashers, section editors, for their tireless editing, writing, and development of new art. Dr. Rote managed the immunity, infection, and hematology chapters. His ability to integrate, simplify, and illustrate this complex content is exceptional. Always motivated to *really* help students and clinicians—Neal, we thank you. Dr. Brashers managed the endocrine, pulmonary, and cardiovascular chapters. Tina has unsurpassed energy. She contributes major effort and tedious detail—all with an amazing sense of humor and support to contributing authors. Thank you, Tina. In addition, Dr. Brashers, Susanna Cunningham, Annette Rivera, Marie O’ Toole, Linda Turchin, and Diane Young developed modules for the Online Review Course. There were also many faculty and clinicians who provided reviews for content revision and we are grateful for their insight and recommendations.

We are also grateful to those who contributed to the book supplements. Textbook contributor Beth Forshee also wrote the glossary. Dr. Linda Edelman wrote the review questions for the Student Evolve website. Drs. Nancy Blasdel, Diane Young, Margaret Clayton, and Beth Forshee updated and developed new material for the Evolve Instructor Resources including the critical thinking exercises, teaching difficult concepts, PowerPoint lecture slides, and Test Bank. Susan Frazier created the audience response questions. We would also like to acknowledge Dr. Kraig Chugg for his previous contributions to the instructor material and PowerPoint slides and Dr. Susan Wilson for her previous work on the test bank. Thank you all for your help.

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Our developmental editor at Elsevier is Charlene Ketchum. This job is key. Charlene is organized, practical, and kept this project on target. Easy to work with and unflappable, even at times with remarkable restraint, she managed this project with a reassuring and professional style. Thank you Charlene. Senior

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INTRODUCTION TO PATHOPHYSIOLOGY

The word root “patho” is derived from the Greek word *pathos*, which means suffering. The Greek word root “logos” means discourse or more commonly, system of formal study, and “physio” pertains to functions of organisms. Generally, pathophysiology is the systematic study of the functional changes in cells, tissues, and organs altered by disease and/or injury. Important, however, is the inextricable component of suffering.

Knowledge of cellular biology as well as anatomy and physiology and the various organ systems of the body is an essential foundation for the study of pathophysiology. To understand pathophysiology the student must also use principles, concepts, and basic knowledge from other fields of study, including pathology, genetics, immunology, and epidemiology. A number of terms are used to focus the discussion of pathophysiology; they may be used interchangeably at times, but that does not necessarily indicate that they have the same meaning. These terms are reviewed in Table I-1.

Pathophysiology is one of the most important bridging sciences between preclinical and clinical courses for students in the health sciences and it requires in-depth study at an early stage in the curriculum. The definitions or conceptual models of pathophysiology that we carry in our minds influence what we do with our observations and what rationale we provide for our actions. Therefore, the clinician must understand that although pathophysiology is a science, it also designates suffering in people; the clinician should never lose sight of this aspect of its definition.

As students study clinically related sciences, they learn to recognize and categorize disease. From the formulation of a differential diagnosis one understands the different *clinical manifestations*, the signs, and the symptoms of certain

pathologies. These understandings structure further investigations, treatment plans, and evaluation. The interaction of these activities determines clinical outcomes and treatment success. Still, the concept of disease can be inherently ambiguous and elusive; many pathologies remain hidden and resist easy classification. One should appreciate that the naming and diagnosing of diseases involve evaluative judgments as well as scientific fact, and that the process is as much a social endeavor as it is a scientific one. Some diseases, such as tuberculosis, identify a highly specific causative or etiologic agent or process. Others, such as Alzheimer disease or arthritis, indicate pathologic changes of unclear cause. In addition, syndromes and functional disorders simply describe multiple symptoms and signs that frequently occur together. Does commonality exist in all of these labels?

The answer is yes and no and depends on our conception of health and disease. In the strictest sense, objective scientific facts help us know if an individual is healthy or suffering from disease. However, the individual's conception of disease is based on personal beliefs and histories, professional and lay healers who interact with that individual, and society at large. Each idea or construct has the power to influence other ideas and constructs, and each relationship has the ability to shape the way disease is understood and experienced.¹ In short, defining and understanding disease is tremendously ambiguous. Perhaps the most important and desirable trait for the new student of pathophysiology is an open and tolerant mind. To believe that science alone can overcome ignorance and that clinical training and technology can overcome ineptitude only encourages arrogance and undermines the scientific purpose.

Table I-1 Terms and Definitions Related to Pathophysiology

Pathology	Study of structural alterations in cells, tissues and organs that help to identify the cause of disease
Pathogenesis	Pattern of tissue changes associated with the development of disease
Etiology	Study of the cause(s) of disease and/or injury
Idiopathic	Diseases with no identifiable cause
Iatrogenic	Diseases and/or injury as a result of medical intervention
Clinical manifestations	Signs and symptoms
Nosocomial	Diseases acquired as a consequence of being in a hospital environment
Diagnosis	Naming or identification of disease
Prognosis	Expected outcome of a disease
Acute disease	Sudden appearance of signs and symptoms lasting a short time
Chronic disease	Develops more slowly lasting a long time or a lifetime
Remissions	Periods when clinical manifestations disappear or diminish significantly
Exacerbations	Periods when clinical manifestations become worse or more severe
Sequelae	Any abnormal conditions that follow and are the result of a disease, treatment, or injury

Pathophysiology has had great success in explaining the mechanisms and clinical manifestations associated with infectious diseases. Syndromes of unclear etiology such as headache and fibromyalgia have proven to be troublesome. Even more difficult are multifactorial conditions, such as atherosclerosis or type 2 diabetes mellitus, in which several interacting factors contribute to the etiology. Learning how interacting factors relate to one another to increase morbidity or actually cause disease contributes to an appreciation of how emerging concepts revolutionize current understandings. For example, for many years the bacterial forms seen in gastric biopsies were interpreted as contaminants. It took several decades to understand the bacterial origin of gastritis, peptic ulcer disease, and even gastric carcinoma. Such findings are a major revolution in thought. One revolution in thought that has driven intensive research is that low levels of chronic inflammation cause or contribute to many diseases.

The language that clinicians use to discuss diseases and their manifestations is powerful. Lives are altered by a few

words uttered by a clinician in a white coat or uniform. “AIDS,” “cancer,” and “heart attack” have become culturally ingrained symbols that portend an individual’s future. Although some futures are determined by scientific evidence, others are determined by subjective experience.² For example, a person diagnosed with a familial disease may ask, “Will I suffer like my mother did?” This questioning influences individuals’ suffering.

In conclusion, pathophysiology—the understanding of disease—requires descriptive evidence as well as an evaluative component regarding suffering and the language we use to describe it. Combining objective and subjective perspectives requires new conceptual models that take into account the complex interactions among the body, mind, environment, and spirit.

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