Specifically designed for future healthcare providers who will diagnose, manage, and prescribe. This advanced physiology and pathophysiology text is designed to address the specific learning needs of future nurse practitioners, physician assistants, and other advanced healthcare providers caring for patients across the lifespan. Focusing on practical applications of physiology, it facilitates in-depth understanding of important pathophysiological concepts as they relate to major disorders commonly seen in clinical practice and includes comprehensive pediatric and geriatric considerations. This knowledge is crucial to providing the foundation required to be an informed and confident clinical decision maker.

The author team includes experienced clinicians and educators: nurses and nurse practitioners, physician assistants, doctors of pharmacy, physicians, and basic scientists. This collaboration has produced a text that carefully details and richly illustrates the cellular structure and function of each organ system and mechanisms of associated major clinical disorders. Uniquely interweaving aspects of organ function during healthy states with disease-associated changes, the text emphasizes and extends the basic science foundation to practical clinical applications. The text promotes a deep understanding of cellular function in health and disease that provides the bedrock knowledge required to master pharmacology for prescriptive practice. Equally important, the solid foundation of applied pathophysiological mechanisms offered in this text prepares the student clinician to care for patients with a broad variety of disorders. This resource not only provides a deep dive into pathophysiology, but it also examines why patients often present with particular symptoms, the rationale for ordering specific diagnostic tests and interpretation of results, and common management strategies that proceed from the underlying pathophysiology.

Key Features:
• Designed explicitly to build a foundation for pharmacology and clinical courses that lead to successful clinical practice and prescribing
• Includes comprehensive lifespan considerations with key insights from specialists in pediatric and geriatric pathophysiology
• Provides a complete chapter on the basic principles of genetics and genomics with coverage of genetic variations, assessment, and genomics woven throughout the book
• Integrates thought questions and case studies to promote discussion and synthesis of information
• Offers a unique Bridge to Clinical Practice in each chapter to translate science to patient care
• Includes more than 500 images to illustrate complex scientific concepts
• Summarizes the contents succinctly with handy key points at the end of each chapter
• Provides access to the fully searchable ebook, including student ancillaries on Springer Publishing ConnectTM
Nancy C. Tkacs, PhD, RN, received her BSN and MSN degrees from the University of Pennsylvania School of Nursing and her PhD in physiology with a focus in neuroscience from Loyola University of Chicago Graduate School at the Stritch School of Medicine. She completed postdoctoral training in neuroendocrinology in the laboratory of Dr. William F. (Fran) Ganong at University of California San Francisco. Dr. Tkacs conducted preclinical research on neuroendocrine responses to physiological stressors in rodent models, particularly pertaining to the diabetes complication hypoglycemia unawareness. Dr. Tkacs has been teaching pathophysiology for advanced nursing practice for over 25 years, drawing on her knowledge of organ systems physiology and pathophysiology to provide a strong basic science foundation for advanced nursing practice. As a master’s-prepared nurse with a doctorate in physiology, she is able to build a bridge between physiology concepts and the pathophysiology of disease. Students learn how findings from the history and physical and diagnostic test results relate to the underlying disease process at the cell and organ level. She taught advanced pathophysiology and neuroscience courses at the University of Medicine and Dentistry of New Jersey and the New Jersey Medical School; she taught advanced pathophysiology and pathogenesis of mental health disorders courses at the University of Pennsylvania; and she directed and taught advanced pathophysiology and advanced pharmacology online courses at the University of Southern California. She also served as assistant dean for Diversity and Inclusivity at the University of Pennsylvania School of Nursing.

Linda L. Herrmann, PhD, RN, AGACNP-BC, GNP-BC, ACHPN, FAANP, is a clinical assistant professor and nurse practitioner with expertise in gerontology, neuroscience, and palliative care. Dr. Herrmann’s clinical and research interests are acute neurological injury in older adults, dementia, stroke, caregivers, palliative care of patients with neurological diseases, and transitional care of older adults. Dr. Herrmann teaches advanced pathophysiology and aging at the graduate level. Her research also explores innovative pedagogy using virtual reality and mixed reality to teach advanced pathophysiology and advanced nurse practitioner courses in acute care and aging. Dr. Herrmann earned her BSN, MSN, and PhD from the University of Pennsylvania School of Nursing under the mentoring of Neville E. Strumpf, PhD, RN. She was a John A. Hartford predoctoral scholar and is currently a Fellow of the Hartford Institute for Geriatric Nursing and a Fellow of the American Association of Nurse Practitioners. She is a nationally recognized expert in neuroscience, aging, and advanced pathophysiology; and is known internationally for expertise in patient safety in hospital and clinic settings in Africa.

Randall L. Johnson, PhD, RN, is an associate professor of nursing at the University of Tennessee Health Science Center. He is also a pediatric critical care nurse practitioner. Dr. Johnson has clinical experience in pediatric medical–surgical nursing and pediatric intensive care and trauma. His research interests are in clinical care of hospital-acquired infection reduction. Dr. Johnson has taught pathophysiology in both undergraduate and graduate degree programs. He has also taught various pediatric and pharmacology courses through the course of his academic career. Dr. Johnson earned his BSN from Cedarville University, his MSN from the University of Pennsylvania, and his PhD from the University of Central Florida. Dr. Johnson has held academic appointments since 1999 and has served in a leadership capacity in academics.
We dedicate the book to our students who have asked such great questions through the years. You inspire us to do all we can to provide detailed, yet understandable explanations of the pathophysiological phenomena underlying advanced clinical practice.
# CONTENTS

Case Studies  xxiii  
Foreword by Linda S. Costanzo, PhD  xxv  
Acknowledgments  xxvii  
Contributors  xxxix  
Case Study Contributors  xxxv  
Reviewers  xxxvii  
How to Use This Book  xxxix  
Instructor Resources  xliii

## 1. THE FOUNDATIONAL CONCEPTS OF CLINICAL PRACTICE  1

### PATHOPHYSIOLOGY AND THE PROCESS OF CLINICAL DECISION-MAKING  1

#### BUILDING FROM A BASIC SCIENCE FOUNDATION: CHAPTERS 2 TO 4  2
- Chemistry (Chapter 2)  2  
- Biochemistry (Chapter 2)  3  
- Molecular Biology and Genetics (Chapter 3)  3  
- Cell Biology (Chapter 4)  3

#### ADVANCED PHYSIOLOGY AND PATHOPHYSIOLOGY: CHAPTERS 5 to 17  3
- Infectious Disease (Chapter 5)  3  
- The Immune System and Leukocyte Function (Chapter 6)  4  
- Neoplasia (Chapter 7)  4  
- Blood and Clotting (Chapter 8)  4  
- Circulation (Chapter 9)  4  
- Heart (Chapter 10)  5  
- Lungs (Chapter 11)  5  
- Kidneys (Chapter 12)  5  
- Gastrointestinal Tract (Chapter 13)  6  
- Liver (Chapter 14)  6  
- Nervous System (Chapter 15)  6  
- Musculoskeletal System (Chapter 16)  6  
- Endocrine System (Chapter 17)  6

### CONNECTING THE DOTS  7

#### PATHOPHYSIOLOGY AND THE INDEPENDENT CLINICIAN  7
- References  8

## 2. CHEMICAL AND BIOCHEMICAL FOUNDATIONS  9

### THE CLINICAL CONTEXT  9

#### CHEMICAL FOUNDATIONS OF LIFE  9
- Atomic Structure  9  
- The Periodic Table and Families of Elements  10  
- Electron Shells and Chemical Reactivity  10  
- Ion Formation and Roles in the Body  12

#### ACIDS AND BASES  12

#### COVALENT BOND STRUCTURE AND FORMATION  14

#### CHEMICAL PATTERNS IN PHYSIOLOGY AND PATHOPHYSIOLOGY  15
- Nonpolar versus Polar Covalent Bonds  15  
- Molecular Geometry  16  
- Molecular Properties of Water  16  
- Hydrogen Bonding and Aqueous Solutions of Polar Molecules and Ions  17  
- Hydrophobicity and Hydrophilicity  17

#### ORGANIC CHEMISTRY FOUNDATIONS  18
- Carbon-Based Molecules  18  
- Major Organic Functional Groups  18  
- Major Biochemical Reaction Types  19
4. CELL PHYSIOLOGY AND PATHOPHYSIOLOGY 73

Nancy C. Tkacs, Fruzsina K. Johnson, Robert A. Johnson, and Spencer A. Rhodes

THE CLINICAL CONTEXT 73
OVERVIEW 73
CELL COMPONENTS 74
Cell Membrane 74
Cytoplasm 75
Nucleus 76
Ribosomes and Rough Endoplasmic Reticulum 76
Smooth Endoplasmic Reticulum 76
Golgi Apparatus 76
Mitochondria 76
Lysosomes 77
Peroxisomes 77
Cytoskeleton 77

MECHANISMS OF MEMBRANE TRANSPORT 77
Diffusion 77
Endocytosis and Exocytosis 79
Endocytosis 79
Exocytosis 80
Facilitated Diffusion 80
Active Transport 82
Primary Active Transport 82
Secondary Active Transport 83
Aquaporins 84
Ion Channels 84

Thought Questions 1–3 87

MECHANISMS OF CELL SIGNALING 87
Overview of Signal Transduction 87
Autonomic Nervous System and Signaling
by G Protein–Coupled Receptors 87
G Protein–Coupled Receptors Linked to Adenylyl Cyclase 88

G Protein–Coupled Receptors Linked to Phospholipase C 90
G Protein GTPase Activity Is a Timing Mechanism 91
Cell Signaling by Cyclic Guanosine Monophosphate 91
Cell Signaling by Enzyme-Linked Receptors 92
Cell Signaling by Cytoplasmic and Nuclear Receptors 95
Summary of Cell Signaling 96

Thought Questions 4–6 96

MECHANISMS OF CONTRACTILE CELLS 96
Overview of Contractile Cell Structure and Function 96
The Sarcomere of Skeletal and Cardiac Muscle 96
Mechanism of Myofibril Crossbridge Formation and Contraction 97
Comparison of Skeletal Muscle Fibers and Cardiac Muscle Cells 98
Mechanisms of Smooth Muscle Contraction 100
Summary of Muscle Cell Function 102

Thought Questions 7 and 8 102

CELL RENEWAL, STRESS, AND CELL DEATH 104
Overview of Cell Renewal, Maintenance, and Adaptation 104
Overview of Cell Injury and Death 105
Tissue Responses to Acute, Severe Ischemia—Necrotic Cell Death 105
Apoptotic Cell Death 105
Autophagy 106

Thought Questions 9 and 10 106

GERONTOLOGICAL CONSIDERATIONS 108
Lori St. John
Cellular Theories of Aging 108
Nine Hallmarks of Aging 108
Frailty 110

Thought Questions 11 and 12 110

KEY POINTS 111
References 112
Suggested Resources 112

5. INFECTIOUS DISEASE 113

Ross S. Johnson, Jennifer Bailey, and Roseann Velez

THE CLINICAL CONTEXT 113
OVERVIEW OF INFECTIOUS DISEASE PATHOPHYSIOLOGY 113
Human–Microbe Interactions 113
Mechanisms of Protection from Pathogens 115
Portals of Pathogen Entry and Targets of Colonization 115
Pathogen Virulence Factors 115
Host Response Factors 116

Thought Questions 1–3 116
6. THE IMMUNE SYSTEM AND LEUKOCYTE FUNCTION 155
Jo Kirman and Raffaela Ghittoni

THE CLINICAL CONTEXT 155

ROLE OF THE IMMUNE SYSTEM 155

INTRODUCTION TO HOST DEFENSES 156
Overview of Physical and Chemical Barriers 156
Overview of the Innate Immune Response 158
Overview of the Adaptive Immune Response 158

FUNCTIONAL ANATOMY OF THE IMMUNE SYSTEM 160
Hematopoiesis 160
Cells and Tissues of the Immune System 161
B Cells Develop in the Bone Marrow 161
T Cells Develop in the Thymus 161
B Cells and T Cells Circulate Through the Lymphatic System 165
The Spleen 165
Gut-Associated Lymphoid Tissue 165

PATHOGENESIS OF SELECTED MICROBES 126
Streptococcus pyogenes 126
Methicillin-Resistant Staphylococcus aureus 127
Mycobacterium tuberculosis 129
Chlamydia trachomatis 131
Neisseria gonorrhoeae 132
Clostridioides difficile 133
Borrelia burgdorferi 135
Influenza Virus 135
Human Immunodeficiency Virus 138
Plasmodium Species 140

INNATE IMMUNITY 166
Acute Inflammation 166
Innate Immune Cells 167
Neutrophils 167
Basophils, Mast Cells, and Eosinophils 167
Monocytes and Macrophages 170
Dendritic Cells 170
Opsonization and Phagocytosis 170
Innate Lymphoid Cells 171
Activation of the Innate Inflammatory Response 172
Recognition of Pathogens and Tissue Damage 172
Sequence of Inflammation and Inflammatory Mediators 174
Resolving an Inflammatory Response 176
The Complement Pathway 177
Innate Responses to Viral Infection 178
Chronic Inflammation 179
Trained Innate Immunity 182
Transition from Innate to Adaptive Immunity: Antigen Presentation and the Major Histocompatibility Complex 182

ADAPTIVE IMMUNITY 183
B Cells are Responsible for Humoral Immunity 184
Antibody Structure 184
Antibody Classes 184
Steps in B-Cell Activation and Maturation 188
B-Cell Memory 189
Antibody Production 189
Clinical Applications of Antibodies 190
7. NEOPLASIA 215

Thought Questions 10 and 11 191
T-Cell Functions 191
Major Histocompatibility Complex Restriction 191
CD4 T-Cell Responses 191
T-Helper Subsets 192
CD8 T-Cell Responses 193
Unconventional T Cells: γδ T Cells, Mucosal-Associated Invariant T, and Invariant Natural Killer T Cells 194
T-Cell Memory 195
Pathogen–Host Immune Evasion Mechanisms 196
Vaccination 196
Hypersensitivity 198
Type 1: Immediate Hypersensitivity 199
Type 2: Antibody-Mediated Hypersensitivity 199
Type 3: Immune Complex–Mediated Hypersensitivity 199
Type 4 (Delayed): T-Cell–Mediated Hypersensitivity 199
Autoimmunity 199
Immunodeficiency 201
Thought Questions 12–14 202
IMMUNE RESPONSES ACROSS THE LIFE SPAN 202
PEDIATRIC CONSIDERATIONS 203
Jane Tobias
Type 1 Hypersensitivity in Children and Adolescents 204
Atopic Dermatitis 205
Food Allergies 206
GERONTOLOGICAL CONSIDERATIONS 207
Nancy C. Tkacs
Immune Cellular Senescence and Disease 207
Inflammaging 208
CASE STUDY 6.1
A Patient With Allergic Rhinitis 209
Linda W. Good
BRIDGE TO CLINICAL PRACTICE 210
Ben Cocchiaro
KEY POINTS 211
References 213
Suggested Resources 213

7. NEOPLASIA 215

Kolbrun (Kolla) Kristjansdottir, Thomas M. Bodenstine, and Sandhya Noronha

THE CLINICAL CONTEXT 215
OVERVIEW OF CANCER PATHOPHYSIOLOGY 215
THE CELL CYCLE 216
Interphase 216
M-Phase (Mitotic Phase) 217
Exit and Reentry of the Cell Cycle 218
Control of the Cell Cycle 219
Checkpoints 220
Thought Questions 1 and 2 220
PROPERTIES OF NEOPLASMS 220
Tumor Terminology 220
Thought Questions 3 and 4 222
Characteristics of a Cancer Cell 222
Proto-Oncogenes, Oncogenes, and Tumor Suppressor Genes 222
Uncontrolled Proliferative Signaling 222
Evading Growth Suppressors 222
Genomic Instability 222
Enabling Replicative Immortality 223
Resisting Cell Death 223
Promotion of Angiogenesis 224
Invasive and Metastatic Ability 224
Recently Identified Cancer Cell Characteristics 224
Evasion of Immune Destruction 224
Cancer Cell Metabolic Alterations 225
Thought Questions 5–7 226
CLINICAL ASPECTS OF NEOPLASIA 226
Pathophysiology of Cancer Manifestations and Treatment Sequelae 226
Biological Aspects of Gene Mutations and Cancer Risk Factors 226
Viral Causes of Cancer 227
Thought Questions 8–10 228
GENOTYPING IN CANCER DIAGNOSIS AND TREATMENT 229
Thought Questions 11 and 12 229
PEDIATRIC CONSIDERATIONS 230
Theresa Kyle
Overview of Pediatric Cancer 230
Leukemias 230
Bone Tumors 231
Nervous System Tumors 231
GERONTOLOGICAL CONSIDERATIONS 232
Rita M. Jakubowski and Janet H. Van Cleave
Physiological Processes of Aging that May Promote Cancer Development 232
Aging and Cancer: Practice Implications 234
CASE STUDY 7.1
A Patient With Breast Cancer 235
Beth Boyer
BRIDGE TO CLINICAL PRACTICE 236
Ben Cocchiaro
KEY POINTS 237
References 238
Suggested Resources 240
8. BLOOD AND CLOTTING 241

Allison Rusgo, Megan E. Schneider, Daniela Livingston, and Patrick C. Auth

THE CLINICAL CONTEXT 241

OVERVIEW OF BLOOD AND CLOTTING  241

RED BLOOD CELLS 242

Erythropoiesis 242

Thought Questions 1 and 2 244

Hemoglobin 244

Genetic Hemoglobinopathies 245

Iron 246

Vitamin B12 and Folate 247

Thought Questions 3 and 4 247

GENERAL CONCEPTS IN ANEMIA 247

Iron-Deficiency Anemia (Microcytic Anemia) 247

Vitamin B12 Deficiency Anemia (Macrocytic Anemia) 248

Anemia of Chronic Inflammation 248

Anemia in Chronic Kidney Disease 249

Hemolytic Anemia 249

Glucose-6-Phosphate Dehydrogenase Deficiency 250

Autoimmune Hemolytic Anemia 250

Thought Questions 5 and 6 250

HEMOSTASIS 250

Platelet Structure and Function 251

Modulation of Clotting and Anticlotting by Products of Arachidonic Acid Metabolism 251

Thought Questions 7 and 8 253

COAGULATION CASCADE 253

Laboratory Assessment of Clotting 255

Control of the Clotting Process 255

Endothelial Influences on Clotting 255

Plasmin and the Fibrinolytic Process 256

Cessation of Clotting Activity 257

Modulation of Clotting Activity by Anticoagulant Drugs 257

Thought Questions 9 and 10 258

THROMBOEMBOLIC STATES 259

Specific Disorders of Hypercoagulation 260

Factor V Leiden and Other Genetic Disorders 260

Antiphospholipid Syndrome 260

STATES OF EXCESS BLEEDING 261

Thrombocytopenia 261

von Willebrand Disease 261

Coagulation Cascade–Associated Disorders 262

Hemophilia A 262

Cirrhosis-Related Coagulation Dysfunction 263

Thought Questions 11 and 12 263

PEDiATRIC CONSiDERATIONS 264

Stephanie L. Carper

Developmental Changes in Red Blood Cell Measures 264

Iron-Deficiency Anemia 265

Hyperbilirubinemia 265

Sickle Cell Disease 266

Von Willebrand Disease 267

GERONTOLOGICAL CONSiDERATIONS 268

Linda L. Herrmann

Anemia 268

Changes in Bone Marrow 268

Hypercoagulability 268

Medication Effects on Blood and Clotting 268

CASE STUDY 8.1 A Patient With Pernicious Anemia 270

Allison Rusgo

CASE STUDY 8.2 A Patient With Deep Venous Thrombosis 271

Allison Rusgo and Michelle Zappas

BRIDGE TO CLiNiCAL PRACtICE 272

Ben Cocchiaro

KEY POINTS 273

References 274

Suggested Resources 275

9. CIRCULATIoN 277

Fruzsina K. Johnson, Robert A. Johnson, and Spencer A. Rhodes

THE CLiNiCAL CONTEXT 277

OVERViEW OF CiRCULATORY STRUCTURE AND FUNCTION 277

Homeostatic Functions of the Circulatory System 277

Organizing Principles of the Circulatory System 278

The Pulmonary Circulation 278

The Systemic Circulation 278

Structure and Properties of Blood Vessels 278

General Structure of Blood Vessels 278

Comparative Structure of Blood Vessels 279

PROPERTIES AND DISORDERS OF LARGE ARTERIES 280

Overview of Large Artery Structure and Function 280

Biophysics of Vascular Wall Tension (Law of Laplace) 280

Vascular hypertrophy 281

Vascular aneurysm 281

Biophysics of Vascular Compliance 281

Biophysics of Blood Flow Velocity and Shear Stress 282
Atherosclerosis: The Most Common Disease of Large Arteries 283

Overview of Large Vessel Diseases 283
Overview of Atherosclerosis 284
Stages of Atherosclerosis Development 284
Fate of Atherosclerotic Plaques 284
Stages of plaque growth and vessel narrowing 284
Plaque growth and aneurysm formation 286
Risk Factors for Atherosclerosis 286
Endothelial Vulnerability and Risk Factors Contributing to Atherosclerotic Plaque Development 287
Endothelial vulnerability 287
Dyslipidemia: Altered blood lipoprotein levels 287
Hypertension 287
Smoking 287
Diabetes mellitus 287
Interactions among risk factors 287
Inflammation 287
Genetics of familial hypercholesterolemia 288
Risk reduction 288
Atherosclerotic Peripheral Arterial Disease 288

Thought Questions 1–3 289

PROPERTIES AND DISORDERS OF ARTERIOLES 289
Overview of Arteriole Structure and Function 289
Biophysical Determinants of Blood Pressure 289
Determinants of Vascular Resistance 290
Distribution of Vascular Resistance in the Systemic Circulation 291

Thought Questions 4 and 5 292

Regulation of Blood Pressure 292
Overview of Blood Pressure Control 292
Maintenance of Vascular Smooth Muscle Tone: Intrinsic, Neural, and Local Mechanisms 293
The cellular basis of vascular smooth muscle control 294
Vascular autoregulation 294
Extrinsic vascular regulation 294
Neural and endocrine mediators that regulate vascular smooth muscle contraction and arteriolar resistance 294
Local mechanisms of vascular smooth muscle control 297
Integration of Mediators Regulating Peripheral Resistance 299
Baroreflexes and Circulatory Control 299
Long-Term Blood Pressure Control by Hormones That Control Blood Volume and Vascular Tone 301

Thought Questions 6–8 302

Pathophysiology of Elevated Vascular Resistance: Hypertension 302
Definition and Causes of Hypertension 302
Hypertension Damages Several Organs 303
Management of Hypertension 304
Pathophysiology of Decreased Blood Pressure and Peripheral Resistance: Shock 304
Definition of Shock 304
Common Shock Progression 304
Compensated shock 304
 Decompensated shock 304
Irreversible shock and circulatory collapse 305
Forms of Shock 305
Hypovolemic shock 305
Distributive shock 305
Cardiogenic shock 306
Obstructive shock 306
Management of Shock 306

Thought Questions 9–11 306

PROPERTIES AND DISORDERS OF CAPILLARIES 306
Overview of Capillary Structure and Function 306
Principles Governing Capillary Fluid Exchange 306
Lymphatics 307
Principles Governing Capillary Fluid Movement and Edema Formation 308

Thought Question 12 308

PROPERTIES AND DISORDERS OF VEINS 308
Overview of Venous Structure and Function, and Vulnerability to Pressure Elevations 308
Venous Disorders 312
Varicose Veins 312
Deep Venous Thrombosis 312

Thought Questions 13 and 14 312

PEDIATRIC CONSIDERATIONS 313
Randall L. Johnson
Embryological Development of the Circulatory System 313

Blood Pressure and Pediatric Hypertension 313

GERONTOLOGICAL CONSIDERATIONS 314
Susan Krekun and Linda L. Herrmann
Vascular Changes with Aging 314
Aging-Associated Vascular Disorders 315

CASE STUDY 9.1
A Patient With Hypertension 318
David A. Roberts and Michelle Zappas

CASE STUDY 9.2
A Patient With Edema 319
David A. Roberts and Michelle Zappas

BRIDGE TO CLINICAL PRACTICE 319
Ben Cocchiaro

KEY POINTS 321
References 323
Suggested Resources 324
10. HEART 325

Fruzsina K. Johnson, Robert A. Johnson, and Spencer A. Rhodes

THE CLINICAL CONTEXT 325

OVERVIEW OF CARDIOVASCULAR STRUCTURE AND FUNCTION 325

Homeostatic Functions of the Heart 325
Structural Organization of the Heart 325
Cardiac Chambers and Valves 325
Membranes Protecting the Heart 327
Structure of the Heart Wall 327
Overview of Myocardial Cell Structure 327
Myocardial Oxygen Supply and Demand 329

CARDIAC ELECTROPHYSIOLOGY AND PATHOPHYSIOLOGY 329

Myocardial Cell Ion Channels and Transporters 329
Structure of the Cardiac Conduction System 329
Cardiac Cell Action Potentials 330
Refractory Periods in Contractile Cardiac Muscle Cells 331
Supranormal Period in Contractile Cardiac Muscle Cells 333
Slow-Response Action Potentials in Pacemaker Cardiac Muscle Cells 333

Thought Questions 1 and 2 333

Functional Aspects of Cardiac Action Potentials 335
Slope of Phase 4 Depolarization in the SA Node Cells Regulates Heart Rate 335
Pharmacological slowing of the heart rate by HCN inhibition 336
Cardiac Action Potentials Determine Conduction Speed in the Heart 336
AV node conduction slows action potential propagation to the ventricles 336
Alterations of fast-response action potentials can also influence action potential conduction 336
L-Type Ca²⁺ Channels Play Multiple Roles in Cardiovascular Function 337

Thought Question 3 338

The ECG: Record of Cardiac Electrical Activity 338
Disorders of Cardiac Electrical Activity (Arrhythmias or Dysrhythmias) 338
General Mechanisms of Arrhythmias 338
Altered impulse formation: Native and latent pacemakers, escape rhythms 338
Ectopic pacemakers, triggered activity, and premature beats 340
Conduction blocks and reentry 341
Bradyarrhythmias 341
Sinus bradycardia and escape rhythms 341
AV conduction blocks 342
Tachyarrhythmias 343
Supraventricular versus ventricular tachycardias 343

Atrial Fibrillation 345
Definition 345
Mechanisms of atrial fibrillation 345
Functional consequences of atrial fibrillation 345
Ventricular Arrhythmias 346
Genetic Disorders Associated With Arrhythmias 346
Brugada syndrome 346
Long QT syndromes 346

Thought Questions 4 and 5 346

CARDIAC PERFORMANCE PHYSIOLOGY 347

Cardiac Muscle 347
Histology 347
Parameters of Cardiac Function 347
Excitation–Contraction Coupling 347
Contractility, Preload, and Afterload: Determinants of Pump Function and Stroke Volume 347
Sympathetic activity increases force of contraction and rate of relaxation 347
Increase in preload increases stroke volume 348
Increased contractility augments preload effects on performance 349
Digitalis increases cardiac contractility by increasing intracellular calcium 349
Increased afterload reduces stroke volume 349
Summary: Determinants of Cardiac Output 349

Thought Questions 6-8 350

Cardiac Cycle 350
Viewing the Cardiac Cycle Using Pressure–Volume Loops 350

Thought Question 9 351

CORONARY BLOOD FLOW AND ISCHEMIC HEART DISEASE 351

Cardiac Vasculature 351
Coronary Arteries 351
Coronary Veins 355
Cardiac Oxygen Supply and Demand 355
Determinants of Cardiac Oxygen Supply 356
Determinants of Cardiac Oxygen Demand 356
Coronary Artery Disease 356
Acute Coronary Syndromes 357
Non-ST-Elevation Myocardial Infarction and Unstable Angina 357
ST-Elevation Myocardial Infarction 358
Patterns of Ischemic Heart Disease in Women 358
Sequelae Associated with Myocardial Infarctions 359

Thought Questions 10 and 11 359

HEART FAILURE 359

Left-Sided Heart Failure 359
Left Ventricular Failure With Reduced Ejection Fraction 362
Heart Failure Stimulates Neurohormonal Compensation 362
Left-Sided Heart Failure Effect on Lung Vascular Volumes and Pressures 362
Left Ventricular Failure With Preserved Ejection Fraction 363
11. LUNGS 389

Nancy C. Tkacs, Charrell S. Porter, and Nicholas A. Barker

THE CLINICAL CONTEXT 389

OVERVIEW OF LUNG STRUCTURE AND FUNCTION 389

Structures of the Respiratory System 389
Mechanisms of Respiration 390
Anatomy and Histology of Airways and Alveoli 392
Mechanisms of Lung Protection 393
Cystic Fibrosis: A Genetic Disorder that Compromises Lung Protection 393

Lung Volumes and Capacities 394
Lung–Chest Wall Interactions 394
Pleural Effusion 397

Thought Questions 1–3 397

COMPLIANCE OF THE LUNGS AND CHEST WALL IN HEALTH AND DISEASE 397
Surfactant and Lung Compliance 397
Emphysema 399
Diseases of Decreased Lung Compliance 400
Idiopathic Pulmonary Fibrosis 400
Chest Wall Compliance 400

Thought Question 4 400

AIRWAY RESISTANCE 400

Overview of Airway Resistance 400
Forced Expiratory Maneuvers are Used to Assess Airway Resistance 401
Concepts in Obstructive Lung Disease 401
Asthma 403
Chronic Obstructive Pulmonary Disease 405
Obstructive Sleep Apnea 406

Thought Questions 5–7 407

GAS EXCHANGE IN THE LUNGS 407

Overview of Gas Exchange 407
Oxygen–Hemoglobin Dissociation Curve 407
Influences on the Oxyhemoglobin Dissociation Curve 408
Effects of partial pressure of carbon dioxide and pH 408
Effect of 2,3-diphosphoglycerate 409
Effects of temperature 409
Hypoxia and Hypoxemia 409
Generalized Hypoventilation 409
Ventilation/Perfusion (V/Q) Mismatch 410
Shunt 411
Diffusion Limitation 412

Thought Questions 8 and 9 412

LUNG VASCULAR CONSIDERATIONS 413

Cardiac Consequences of Pulmonary Disease 413
Pulmonary Embolism 413
Pulmonary Edema 414
Pulmonary Hypertension 414

Thought Questions 10 and 11 415

PEDIATRIC CONSIDERATIONS 416

Randall L. Johnson

Lung Development 416
Respiratory Problems Associated with Preterm Birth 416
Lung Concerns in Infancy 417
Childhood Asthma 417

GERONTOLOGICAL CONSIDERATIONS 418

Ingrid Deming and Alison Fife

Pneumonia 419
Chronic Obstructive Pulmonary Disease (Chronic Bronchitis and Emphysema) 419
12. KIDNEYS 427

Connie B. Scanga and Nancy C. Tkacs

THE CLINICAL CONTEXT 427

OVERVIEW OF KIDNEY STRUCTURE AND FUNCTION 427
The Kidney and Homeostasis 427
Overview of Body Fluid Compartments 428
Water: The Solvent of Body Fluids 428
Distribution of Fluids in the Body 428
Water Movement Between Fluid Compartments 429
Kidney Structure 430
Nephron Structure 430
Glomerular Function 431
Glomerular Vascular Structure and Glomerular Filtration Barriers 431
Peritubular Capillary Reabsorption and Secretion 434
Understanding Renal Clearance and Glomerular Filtration Rate 435
Thought Questions 1 and 2 436

GLOMERULAR INJURIES 436
Glomerular Injury by Immune Mechanisms 436
Diabetic Nephropathy 436
Hypertensive Nephropathy 438
Thought Questions 3 and 4 438

REGULATION OF RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE 438
Autoregulation of Renal Blood Flow 438
Extrinsic Regulation of RBF and GFR 439
Importance of eGFR as the Indicator of Renal Function 440
Factors Reducing RBF and GFR in Disease States 440
Thought Questions 5 and 6 441

STRUCTURE AND FUNCTION OF THE RENAL TUBULE 441
Tubular Transport Overview 441
Segmental Tubular Processing 442
Proximal Tubule 442
Loop of Henle 443
Distal Tubule 443

Late Distal Tubule and Collecting Duct 443
Thought Questions 7 and 8 446

REGIONAL KIDNEY FUNCTION 447
Corticomедullary Osmolarity Gradient 447
Production of Concentrated Urine and Homeostatic Regulation of Urine Composition and Osmolarity 447

CONCEPTS IN FLUID, ELECTROLYTE, AND ACID–BASE BALANCE 448
Renal Compensation in States of Hypovolemia and Hypotension 450
Renal Compensation in States of Hypervolemia and Hypertension 450
Thought Question 9 450

ACUTE KIDNEY INJURY–CHRONIC KIDNEY DISEASE CONTINUUM 451
Assessment of Kidney Function 451
Mechanisms and Manifestations of Acute Kidney Injury 451
Kidney Stones 452
Thought Question 10 453
Mechanisms and Manifestations of Chronic Kidney Disease 453
End-Stage Renal Disease 453
Thought Questions 11–13 454
APOL1 and CKD Progression 454

PEDIATRIC CONSIDERATIONS 456
Theresa Kyle
Urinary System Development 456
Pediatric Disorders of Urinary Tract and Kidneys 456

GERONTOLOGICAL CONSIDERATIONS 459
Ryan Prince
Age-Related Changes in the Kidney 459
Clinical Considerations in Older Adults 460
Summary of Age-Related Concerns 461

CASE STUDY 12.1
A Patient With Chronic Kidney Disease 461
Kim Zuber and Jane S. Davis

CASE STUDY 12.2
A Patient With a Kidney Stone 462
Kim Zuber and Jane S. Davis

BRIDGE TO CLINICAL PRACTICE 462
Ben Cocchiaro

KEY POINTS 463
References 465
Suggested Resources 466

13. GASTROINTESTINAL TRACT 467

Wilson Crone

THE CLINICAL CONTEXT 467

OVERVIEW OF GASTROINTESTINAL STRUCTURE AND FUNCTION 467
Alimentary Canal Structure and Motor Activity 468
Neural, Humoral, and Immune Regulation of Gastrointestinal Function 470
Gastrointestinal Innervation 470
Gastrointestinal Hormones and Mediators Modulate Gastrointestinal Function 471
Gastrointestinal Amine Neurotransmitters and Mediators 472
Gastrointestinal Immunology 473

Thought Questions 1–3 475

PROPERTIES AND DISORDERS OF DIGESTIVE TRACT ORGANS 475
Mouth 475
Salivary Glands 475
Esophagus 475
Disorders of the Esophagus 476
Esophageal obstruction 476
Esophageal varices 476
Esophagitis and gastroesophageal reflux disease 476
Esophageal cancer 476
Stomach 476
Disorders of the Stomach 479
Peptic ulcers 479
Gastroparesis 479
Vomiting 479

Thought Questions 4 and 5 481
Small and Large Intestines 481
Pancreas 483
Acute pancreatitis 483

DIGESTION AND ABSORPTION 484
Overview of Macronutrient Digestion and Absorption 484

Thought Questions 6 and 7 488
Principles of Micronutrient Absorption 488
Principles of Fluid and Electrolyte Absorption 488

IMMUNE-RELATED GASTROINTESTINAL DISORDERS 490
Celiac Disease 490
Inflammatory Bowel Disease 490

ABDOMINAL PAIN PATTERNS 492
Irritable Bowel Syndrome 493
Hemorrhoids 493

INTESTINAL FAILURE AND SHORT BOWEL SYNDROME 493

Thought Questions 8 and 9 494

MALNUTRITION AND OBESITY 494
Lynch Syndrome 495

PEDIATRIC CONSIDERATIONS 496
Randall L. Johnson
Gastrointestinal Development and Function in Childhood 496
Gastroenteritis 496
Gastroesophageal Reflux 497

Hypertrophic Pyloric Stenosis 497
Intussusception 498
Hirschsprung Disease 498

GERONTOLOGICAL CONSIDERATIONS 499
Rosanna Reda
Age-Related Changes of the Gastrointestinal Tract 499
Age-Associated Alterations in Mastication 499
Dysphagia 499
Gastroesophageal Reflux Disease in Older Adults 500
Altered Digestion 500
Peptic Ulcer Disease 500
Constipation 500
Diverticular Disease 501

CASE STUDY 13.1
A Patient With Peptic Ulcer Disease 502
Amanda Chaney and Michelle Zappas

CASE STUDY 13.2
A Teenage Boy With Celiac Disease 503
Amanda Chaney and Michelle Zappas

BRIDGE TO CLINICAL PRACTICE 504
Ben Cocchiaro

KEY POINTS 505

14. LIVER 509

Jennifer Andres, Adam Diamond, Kimberly A. Miller, Nicole E. Omecene, and Dusty Lisi

THE CLINICAL CONTEXT 509

OVERVIEW OF LIVER STRUCTURE AND FUNCTION 509
Liver Structure 510
Liver Cells 511

Thought Questions 1 and 2 513
Liver Function 513
Energy Metabolism 513
Synthetic Processes of the Liver 515

Thought Questions 3 and 4 516
Liver Clearance Mechanisms 516
Metabolism of bilirubin 516
Hormone and drug (xenobiotics) metabolism 517

Thought Question 5 519
Other Functions of the Liver 519
Reticuloendothelial system 519
Vitamin and mineral storage 519
Regenerative capacity 519

LIVER DISORDERS 520

Measures of Liver Function and Dysfunction 520
Acute Liver Disorders 520
Connections Between the Central Nervous System and the Periphery 543
Structural Brain Protection 543
Neurons 543
The Functional Units of the Brain 543
Electrically Excitable Cells 544
Synaptic Transmission 546
Synapse Structure 546
Electrical and Chemical Events of Synaptic Transmission 547
Neurotransmitter Receptors 548
Termination of Synaptic Transmission 549
Thought Questions 1–3 546
Thought Questions 4–7 551
NEUROTRANSMITTERS 551
Two Main Transmitter Families 551
Glutamate 552
Gamma-Aminobutyric Acid 553
Epilepsy results from excessive excitation or insufficient inhibition 554
Thought Questions 8 and 9 556
Neuromodulatory Transmitters: Amines 556
Acetylcholine 556
Catecholamines 557
Dopamine 557
Norepinephrine 559
Serotonin 560
Histamine 561
Neuromodulatory Transmitters: Peptides 561
Opioid Peptides 562
Orexins 563
Application of Neurotransmitter Concepts 563
Summary of Neurotransmitter Concepts 565
Thought Questions 10–12 567
SENSORY NEUROPHYSIOLOGY 567
Overview of Spinal Cord Anatomy 567
Somatic Sensory Function 567
Dorsal Column/Medial Lemniscus System 568
Spinothalamic Tract System 569
Pathological States of Sensory Function 570
Thought Questions 13 and 14 570
PAIN 570
Neurophysiology of Pain 570
Nociceptors 571
Spinothalamic Tract Neurons 571
Ascending Pain Pathways: A Site of Pain Modulation 572
Descending Pain Modulation 572
Sensitization 574
Referred Pain 575
Pharmacological Modulation of Pain 575
Nonpharmacological Modulation of Pain 575
Thought Questions 15–17 576
16. MUSCULOSKELETAL SYSTEM 619

Connie B. Scanga and Joseph J. Curci

THE CLINICAL CONTEXT 619

OVERVIEW OF BONES AND SKELETAL PHYSIOLOGY 619

Bone Histology 619
Osteogenesis and Bone Remodeling 620

Thought Questions 1 and 2 620

BONE FRACTURES 621

Types of Fractures 621
Fracture Healing 621
Recovery from Fracture 621

Thought Questions 3 and 4 623

JOINTS 626

Functional Classification 626
Structural Classification 626
Fibrous Joints 626
Cartilaginous Joints 626
Synovial Joints 627

Thought Questions 5 and 6 632

STRAINS AND SPRAINS 632

Ankle Sprains 632
Structure and Conditions of the Knee 634
Anatomy of the Knee 634
Ligamentous and Meniscal Injuries of the Knee 635
Medial ligament tears 635
Lateral ligament tears 636
Cruciate ligament tears 636
Meniscal injuries 637

Thought Questions 7 and 8 638

HERNIATED DISC DISEASE 638

Pathophysiology of Disc Herniation 638
Anatomical Correlations 639
Clinical Presentation and Management 639

CUMULATIVE TRAUMA DISORDERS 641

Causes of Cumulative Stress Injury 641
Clinical Syndromes 642
Carpal Tunnel Syndrome 642
Cubital Tunnel Syndrome 642
Lateral Epicondylosis 642
Trigger Finger 643
Hip Bursitis 643
Thoracic Outlet Syndrome 644

Thought Questions 9 and 10 645

PEDIATRIC CONSIDERATIONS 646

Theresa Kyle

Musculoskeletal Development 646
Youth Sports and Musculoskeletal Injuries 648
Genetic Musculoskeletal Conditions 650
GERONTOLOGICAL CONSIDERATIONS     652
Rudy Tassy
Aging and Muscle Integrity: Sarcopenia and Frailty  652
Bone Density And Osteoporosis  653
Joint Disorders In Older Adults   653
Parkinson Disease and Pisa Syndrome  655

CASE STUDY 16.1
A Patient With a Sprained Ankle  656
Allison Rusgo and Michelle Zappas

CASE STUDY 16.2
A Patient With Acute Gouty Arthritis     657
Michelle Zappas and Allison Rusgo

BRIDGE TO CLINICAL PRACTICE      658
Ben Cocchiaro

KEY POINTS   659
References   660
Suggested Resources   660

17.  ENDOCRINE SYSTEM   663
Christine Yedinak, Carolina R. Hurtado, Angela M. Leung,
Meredith Annon, Hanne S. Harbison, Diane L. Spatz, Gioia
Petrigli Polidori, and Victoria Fischer

THE CLINICAL CONTEXT  663

PRINCIPLES OF ENDOCRINE FUNCTION   664
Christine Yedinak

Hormone Structures  664
Cell Signaling by Hormones  666
Circulating Hormone Levels   669
Hormone Control Axes  670
Thought Questions 1 and 2   671

HYPOTHALAMUS AND PITUITARY GLAND   671
Christine Yedinak

STRUCTURE OF THE HYPOTHALAMUS  671

FUNCTIONS OF THE HYPOTHALAMUS  672
Thirst and Fluid Balance Control  672
Regulation of Uterine Contractility 673
Regulation of Body Energy Balance
and Weight     673
Thought Questions 3–5   674

DEVELOPMENT OF THE HYPOTHALAMUS AND
RELATIONSHIP WITH THE PITUITARY GLAND  674

ENDOCRINE CELLS OF THE ANTERIOR
PITUITARY   675
Corticotroph Cells: Adrenocorticotropic
Hormone  676
Corticotroph Dysfunction 677
Lactotroph Cells: Prolactin 678
Lactotroph Dysfunction  678
Somatotroph Cells: Growth Hormone  679

Somatotroph Dysfunction   680
Gonadotroph Cells: Luteinizing Hormone and
Follicle-Stimulating Hormone   680
Gonadotroph Dysfunction  682
Thyrotroph Cells: Thyroid-stimulating Hormone  682
Thyrotroph Dysfunction   683

POSTERIOR PITUITARY HORMONES   683
Vasopressin: Antidiuretic Hormone  683
Diabetes Insipidus  683
Syndrome of Inappropriate Antidiuretic Hormone
Secretion   683
Oxytocin  684
Thought Questions 6 and 7   684

ADRENAL GLANDS   684
Christine Yedinak

DEVELOPMENT, STRUCTURE, AND FUNCTION
OF THE ADRENAL GLANDS   684

ADRENAL CORTEX ZONES AND HORMONES   686
Zona Glomerulosa: Aldosterone  686
Hypoadrenalinism   687
Primary Aldosteronism   687
Zona Fasciculata: Glucocorticoids and Cortisol
Production  687
Adrenocortical Dysfunction  688
Hypocortisolism (Adrenal Insufficiency)  688
Adrenal hypercortisolism   689
Zona Reticularis: Androgens  690

ADRENAL MEDULLA AND CATECHOLAMINES   690
Adrenomedullary Dysfunction   690
Thought Questions 8–10   692

PEDIATRIC CONSIDERATIONS: HYPOTHALAMUS,
PITUITARY, AND ADRENAL GLANDS   693
Randall L. Johnson
Endocrine Control of Growth  693
Genetic Disorder: Congenital Adrenal
Hyperplasia   693

GERONTOLOGICAL CONSIDERATIONS:
HYPOTHALAMUS, PITUITARY, AND ADRENAL
GLANDS   694
Stacy M. Alabastro and Linda L. Herrmann
Decline in Growth Hormone   694
Adrenal Gland Changes  694

KEY POINTS: ENDOCRINE CONCEPTS; HYPOTHALAMUS,
PITUITARY, AND ADRENAL GLANDS   695

THYROID GLAND   696
Carolina R. Hurtado and Angela M. Leung

STRUCTURE AND FUNCTION OF THE
THYROID GLAND   696
THYROID HORMONE SYNTHESIS   696
THYROIDINE METABOLISM   697
Alterations of Serum Thyroid-Binding Globulin
Concentrations   698
THYROID HORMONE ACTIONS  699
  Screening for Serum Thyroid Dysfunction  700

THOUGHT QUESTIONS 11–13  701

THYROID DISORDERS  701
  Hypothyroidism  701
    Mechanisms of Hypothyroidism  701
    Laboratory Evaluation of Hypothyroidism  703
  Hyperthyroidism  703
    Mechanisms of Hyperthyroidism  703
    Laboratory Evaluation of Hyperthyroidism  704
  Nonthyroidal Illness with Altered Thyroid Function Tests (Euthyroid Sick Syndrome)  704

THOUGHT QUESTIONS 14 and 15  704

PEDIATRIC CONSIDERATIONS: THYROID GLAND  705
  Randall L. Johnson

GERONTOLOGICAL CONSIDERATIONS: THYROID GLAND  706
  Stacy M. Alabastro and Linda L. Herrmann

CASE STUDY 17.1 706
  A Patient With Graves Disease
  Linda W. Good

BRIDGE TO CLINICAL PRACTICE: Thyroid  707
  Ben Cocchiaro

KEY POINTS: THYROID GLAND  708
  Meredith Annon, Hanne S. Harbison, and Diane L. Spatz

OVERVIEW OF THE REPRODUCTIVE SYSTEM  709

THE FEMALE REPRODUCTIVE SYSTEM  709
  Structure and Functions of the Female Reproductive System  709
  Female Hypothalamic-Pituitary-Gonadal Function  711
  THOUGHT QUESTIONS 16 and 17  712
  Abnormalities of the Menstrual Cycle, Ovaries, and Endometrium  715
    Amenorrhea  715
    Abnormal Uterine Bleeding  715
    Polycystic Ovary Syndrome  715
    Endometriosis  717
  THOUGHT QUESTION 18  718
  Breast Cancer  718
  Menopausal Transition and Aging  718
  Osteoporosis in Postmenopausal Women (and Older Men)  719
  THOUGHT QUESTION 19  720

CASE STUDY 17.2 726
  A Patient With Hyperparathyroidism
  Nancy C. Tracs

THE MALE REPRODUCTIVE SYSTEM  721
  Structures and Functions of the Male Reproductive System  721

  Regulation and Spermatogenesis of the Male Reproductive System  722
    Hypothalamic-Pituitary-Gonadal Axis  722
    Spermatogenesis  723
    Erectile Dysfunction  724

  Prostate Disorders  724
    Benign Prostatic Hyperplasia  724
    Prostate Cancer  725
  THOUGHT QUESTIONS 20 and 21  726

KEY POINTS: THE GONADS  727

METABOLISM AND THE PANCREAS  728
  Gioia Polidori and Victoria Fischer

OVERVIEW  728

REVIEW OF METABOLISM  728
  Metabolic Processes in the Fed State  729
    Liver Processes  729
    Skeletal Muscle Processes  729
    Adipose Tissue Processes  730
    Summary of the Fed State  730
  Metabolic Processes in the Fasting State  731
    Liver Processes  731
    Skeletal Muscle Processes  732
    Adipose Tissue Processes  733
    Ketogenesis is an additional catabolic pathway  733
    Summary of the Fasting State  734
  THOUGHT QUESTIONS 22 and 23  734

HORMONAL REGULATION OF METABOLISM  734
  Insulin  734
    Cellular Mechanisms of Insulin Action  734
    Effects of Insulin on the Liver  735
    Effects of Insulin on Muscle  736
    Effect of Insulin on Fat Cells  736
    Effects of Insulin on the Brain  738
    Regulation of Insulin Secretion  738
    Oral Glucose Tolerance Testing  738
  Additional Hormones Regulating Metabolic Homeostasis  738
    Glucagon  740
    Cortisol  740
    Epinephrine  740
    Growth Hormone  741
    Chorionic Somatomammotropin  741
  THOUGHT QUESTIONS 24–26  741

DIABETES MELLITUS  741
  Diagnostic Criteria  742
  Type 1 Diabetes Mellitus  742
    Pathogenesis  742
    Presentation  743
    Clinical Management  743
    Diabetic Ketoacidosis  743
    Hypoglycemia  744
  Type 2 Diabetes Mellitus  745
    Risk Factors  745
Diabetes Screening 745
Pathogenesis 745
Insulin resistance 745
β-Cell Dysfunction 746
Interrelation of obesity and T2DM 747
Clinical Management 747
Lifestyle modifications 747
Pharmacological interventions 748
Complications of Diabetes Mellitus 748
Acute Complications of Type 2 Diabetes Mellitus 748
Hypoglycemia 748
Hyperosmolar hyperglycemic syndrome 748
Chronic Complications of T1DM and T2DM 748
Hyperglycemia and diabetes complications 748
Diabetic microangiopathy 748
Diabetic nephropathy 749
Diabetic retinopathy 749
Diabetic neuropathy 749
Susceptibility to Infections 749
Thought Questions 27–29 749

OTHER FORMS OF DIABETES AND DIABETES-
RELATED CONDITIONS 749
Gestational Diabetes 749
Latent Autoimmune Diabetes in Adults 750
Polycystic Ovary Syndrome 750
Obstructive Sleep Apnea 750
Cognitive Decline and Alzheimer Disease 750

SUMMARY 750

PEDIATRIC CONSIDERATIONS: METABOLISM AND THE PANCREAS 751
Randall L. Johnson
Type 1 Diabetes Mellitus 751
Type 2 Diabetes Mellitus 751

GERONTOLOGICAL CONSIDERATIONS:
METABOLISM AND THE PANCREAS 752
Stacy M. Alabastro and Linda L. Herrmann
Type 2 Diabetes Mellitus 752

CASE STUDY 17.3
A Patient With Gestational Diabetes 752
Kimberly K. Trout

BRIDGE TO CLINICAL PRACTICE: Diabetes 753
Ben Cocchiaro

KEY POINTS: METABOLISM AND THE PANCREAS 755

SUMMARY: ENDOCRINE PHYSIOLOGY AND PATHOPHYSIOLOGY 757

References 757
Suggested Resources 761
List of Abbreviations 763
Index 773
List of Disorders Inside back cover
CASE STUDIES

CASE STUDY 5.1
A Patient With Acute HIV Infection  148
Sampath Wijesinghe

CASE STUDY 5.2
A Child With Hand, Foot, and Mouth Disease  149
Stephanie L. Carper

CASE STUDY 6.1
A Patient With Allergic Rhinitis  209
Linda W. Good

CASE STUDY 7.1
A Patient With Breast Cancer  235
Beth Boyer

CASE STUDY 8.1
A Patient With Pernicious Anemia  270
Allison Rusgo

CASE STUDY 8.2
A Patient With Deep Venous Thrombosis  271
Allison Rusgo and Michelle Zappas

CASE STUDY 9.1
A Patient With Hypertension  318
David A. Roberts and Michelle Zappas

CASE STUDY 9.2
A Patient With Edema  319
David A. Roberts and Michelle Zappas

CASE STUDY 10.1
A Patient With Heart Failure Symptoms  381
Lisa Rathman

CASE STUDY 10.2
A Patient With Angina  382
David A. Roberts

CASE STUDY 10.3
A Patient With Atrial Fibrillation  383
Linda W. Good

CASE STUDY 11.1
A Child With Asthma  420
Stephanie L. Carper

CASE STUDY 11.2
A Patient With Chronic Bronchitis  421
Linda W. Good

CASE STUDY 12.1
A Patient With Chronic Kidney Disease  461
Kim Zuber and Jane S. Davis

CASE STUDY 12.2
A Patient With a Kidney Stone  462
Kim Zuber and Jane S. Davis

CASE STUDY 13.1
A Patient With Peptic Ulcer Disease  502
Amanda Chaney and Michelle Zappas

CASE STUDY 13.2
A Teenage Boy With Celiac Disease  503
Amanda Chaney and Michelle Zappas

CASE STUDY 14.1
A Patient With Hepatitis A Virus Infection  535
Amanda Chaney and Michelle Zappas

CASE STUDY 14.2
A Patient With Nonalcoholic Fatty Liver Disease  536
Amanda Chaney and Michelle Zappas

CASE STUDY 15.1
A Teenage Girl With Migraine  611
Michelle Zappas and Colleen Diering

CASE STUDY 15.2
A Child With a Seizure Disorder  611
Melissa Assaf and Katherine Edwards

CASE STUDY 15.3
A Patient With Depression  612
Linda W. Good

CASE STUDY 16.1
A Patient With a Sprained Ankle  656
Allison Rusgo and Michelle Zappas

CASE STUDY 16.2
A Patient With Acute Gouty Arthritis  657
Michelle Zappas and Allison Rusgo

CASE STUDY 17.1
A Patient With Graves Disease  706
Linda W. Good

CASE STUDY 17.2
A Patient With Hyperparathyroidism  726
Nancy C. Tkacs

CASE STUDY 17.3
A Patient With Gestational Diabetes  752
Kimberly K. Trout
Dr. Tkacs and I “met” when she emailed me about an error she spotted in my physiology textbook. Perhaps a surprising start to a warm friendship, but I was immediately taken by Dr. Tkacs’s thorough understanding of a tricky topic and I wrote back to express gratitude to her for taking the time to improve my book. Thus began our correspondence on matters of physiology teaching. I was thrilled to learn that she was writing a physiology and pathophysiology book for advanced practitioners, as it was clear that she has the gift for explaining difficult topics.

Students in advanced practice programs face the monumental challenge of applying knowledge of pathophysiology to clinical practice. To do this, the student must first have solid command of the principles of physiology, translate those principles to the pathophysiology of diseases, and then translate them again to the clinical setting. Each step must be undergirded by a firm understanding of the “whys” of the physiologic mechanisms.

Dr. Tkacs’s book guides the student through those “whys”—in a step-wise fashion that is logical and systematic. The physiology of each system is presented at the appropriate level, in an easily accessible book that is complemented by clear tables and figures. Throughout, she provides relevant examples and metaphors to help the student visualize and relate to complex pathophysiologic mechanisms. Thought-provoking questions challenge the student and offer practice for long-term retention. Equations—which are inescapable in physiology—are explained in words to make them less daunting to the student; every equation is also presented in the context of its pathophysiological application. Pathophysiology and case studies are integrated throughout the text, serving to link the physiology with clinical practice and treatment.

Dr. Tkacs’s credentials ideally qualify her to write a pathophysiology book for advanced practice students. Her credibility derives from the depth of her graduate and postgraduate training in nursing and physiology and her many years of experience in the trenches teaching advanced practice students. In other words, she is the “real deal” author—a serious, practicing physiologist and an educator with vast experience, who can translate her depth of knowledge at the appropriate level for her students.

I heartily recommend Dr. Tkacs’s exceptional book and wish you well on your pathophysiology journey with her.

Linda S. Costanzo, PhD
Professor of Physiology and Biophysics
Virginia Commonwealth University
School of Medicine
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CONTRIBUTORS

Stacy M. Alabastro, MS, AGACNP-BC, RN, SCRN
Nurse Practitioner
Critical Care Medicine
Memorial Sloan Kettering Cancer Center
New York, New York
Chapter 17: Endocrine System

Sheila A. Alexander, BSN, PhD, FCCM
Associate Professor
University of Pittsburgh School of Nursing
Pittsburgh, Pennsylvania
Chapter 3: Molecular Biology, Genetics, and Genetic Diseases

Jennifer Andres, PharmD, BCPS
Clinical Associate Professor of Pharmacy Practice
Temple University School of Pharmacy
Philadelphia, Pennsylvania
Chapter 14: Liver

Meredith Annon, MSN, CNM, WHNP-BC
Women’s Health Nurse Practitioner
The Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 17: Endocrine System

Melissa Assaf, DNP, CPNP-PC, APN-Genetics
Pediatric Nurse Practitioner
Advanced Practice Nurse in Genetics
Banner Children’s Specialists, Child Neurology
Scottsdale, Arizona
Chapter 15: Nervous System

Patrick C. Auth, PhD, PA-C
Clinical Professor
Philadelphia, Pennsylvania
Chapter 8: Blood and Clotting

Jennifer Bailey, PharmD, BCPS, AAHIVP
Assistant Professor
Department of Clinical and Administrative Sciences
School of Pharmacy
Notre Dame of Maryland University
Baltimore, Maryland
Chapter 5: Infectious Disease

Nicholas A. Barker, PharmD, BCCCP
Clinical Pharmacy Specialist, Cardiology
Emory Saint Joseph’s Hospital
Atlanta, Georgia
Chapter 11: Lungs

Thomas M. Bodenstine, PhD
Assistant Professor
Biochemistry and Molecular Genetics Department
Midwestern University
Downers Grove, Illinois
Chapter 7: Neoplasia

Alyssa Bondy, PA-C, MMS, EMT-B
Physician Assistant
Department of Internal Medicine
New York Presbyterian Weill Cornell Medicine
New York, New York
Chapter 5: Infectious Disease

Stephanie L. Carper, MSN, APRN, CPNP-PC
Nurse Practitioner
Rainbow Pediatric Center
Jacksonville, Florida
Chapter 8: Blood and Clotting
Mary B. Mehta, MD, FACC, FAAP  
Pediatric Cardiology  
Nemours Children's Specialty Care  
Pensacola, Florida  
Chapter 10: Heart  

Kimberly A. Miller, PharmD  
Assistant Professor of Pharmacology  
Geisinger Commonwealth School of Medicine  
Scranton, Pennsylvania  
Chapter 14: Liver  

Mariah Morris, DNP, CPNP  
Lecturer  
University of West Florida  
Pensacola, Florida  
Chapter 14: Liver  

Sandy Noronha, MD  
Associate Professor  
Physician Assistant Department  
Midwestern University  
Downers Grove, Illinois  
Chapter 7: Neoplasia  

Nicole E. Omecene, PharmD, BCPPS  
Assistant Professor  
Virginia Commonwealth University School of Pharmacy  
Richmond, Virginia  
Chapter 14: Liver  

Kara Pavone, RN, PhD  
Assistant Professor  
Northeastern University School of Nursing  
Boston, Massachusetts  
Chapter 15: Nervous System  

Gioia Petrighi Polidori, MS, PhD  
Assistant Professor of Teaching  
University of Southern California  
Los Angeles, California  
Chapter 2: Chemical and Biochemical Foundations  
Chapter 17: Endocrine System  

Charrell S. Porter, PharmD, BCACP  
Assistant Professor of Clinical Pharmacy  
University of the Sciences, Philadelphia College of Pharmacy  
Philadelphia, Pennsylvania  
Chapter 11: Lungs  

Ryan Prince, MS, PA-C  
Physician Assistant  
Department of Internal Medicine  
New York Presbyterian Weill Cornell Medicine  
New York, New York  
Chapter 12: Kidneys  

Rosanna Reda, PA-C  
Physician Assistant  
Department of Internal Medicine  
New York Presbyterian Weill Cornell Medicine  
New York, New York  
Chapter 13: Gastrointestinal Tract  

Spencer A. Rhodes, OMS-III  
William Carey University  
College of Osteopathic Medicine  
Hattiesburg, Mississippi  
Chapter 10: Heart  

Laura Roettger, MSN, CPNP-PC  
Director, Pediatric Nurse Practitioner Program  
Thomas Jefferson University  
Philadelphia, Pennsylvania  
Chapter 5: Infectious Disease  

Allison Rusgo, MPH, PA-C  
Assistant Clinical Professor  
Physician Assistant Program  
Drexel University  
Philadelphia, Pennsylvania  
Chapter 8: Blood and Clotting  

Connie B. Scanga, PhD  
Practice Professor of Nursing  
University of Pennsylvania School of Nursing  
Philadelphia, Pennsylvania  
Chapter 12: Kidneys  
Chapter 16: Musculoskeletal System  

Megan E. Schneider, MMS, MSPH, PA-C  
Assistant Clinical Professor  
Drexel University  
Philadelphia, Pennsylvania  
Chapter 8: Blood and Clotting  

Loretta A. Sernekos, MSN, PhD, AGPCNP-BC, PMHNP-BC, CNE  
Senior Lecturer  
University of Pennsylvania School of Nursing  
Philadelphia, Pennsylvania  
Chapter 1: The Foundational Concepts of Clinical Practice  

Diane L. Spatz, PhD, RN-BC, FAAN  
Professor of Perinatal Nursing and Helen M. Shearer Professor of Nutrition  
University of Pennsylvania School of Nursing  
Philadelphia, Pennsylvania  
Chapter 17: Endocrine System
CASE STUDY CONTRIBUTORS

Melissa Assaf, DNP, CPNP-PC, APN-Genetics  
Pediatric Nurse Practitioner  
Advanced Practice Nurse in Genetics  
Banner Children's Specialists, Child Neurology  
Glendale, Arizona  
Perseverance Research Center  
Scottsdale, Arizona  
*Case Study 15.2: A Child With a Seizure Disorder*

Beth Boyer, PA-C, MS  
Physician Assistant, Hematology/Oncology  
Mayo Clinic  
Jacksonville, Florida  
*Case Study 7.1: A Patient With Breast Cancer*

Stephanie L. Carper, MSN, APRN, CPNP-PC  
Nurse Practitioner  
Rainbow Pediatric Center  
Jacksonville, Florida  
*Case Study 5.2: A Child With Hand, Foot, and Mouth Disease*  
*Case Study 11.1: A Child With Asthma*

Amanda Chaney, DNP, APRN, FNP-BC, FAANP  
Transplant Nurse Practitioner/Chair, Advanced Practice Provider Subcommittee  
Mayo Clinic  
Jacksonville, Florida  
*Case Study 13.1: A Patient With Peptic Ulcer Disease*  
*Case Study 13.2: A Teenage Boy With Celiac Disease*  
*Case Study 14.1: A Patient With Hepatitis A Virus Infection*  
*Case Study 14.2: A Patient With Nonalcoholic Fatty Liver Disease*

Jane S. Davis, CRNP, DNP  
Division of Nephrology  
University of Alabama at Birmingham  
Birmingham, Alabama  
*Case Study 12.1: A Patient With Chronic Kidney Disease*  
*Case Study 12.2: A Patient With a Kidney Stone*

Colleen Diering, DNP, APRN  
Advanced Practice Provider, Neurology  
Mayo Clinic  
Jacksonville, Florida  
*Case Study 15.1: A Teenage Girl With Migraine*

Katherine Edwards, PA-C  
Advanced Practice Provider, Neurology  
Mayo Clinic  
Jacksonville, Florida  
*Case Study 15.2: A Child With a Seizure Disorder*

Linda W. Good, MD  
Family Practice Physician  
Mt. Airy Family Practice  
Philadelphia, Pennsylvania  
*Case Study 6.1: A Patient With Allergic Rhinitis*  
*Case Study 10.3: A Patient With Atrial Fibrillation*  
*Case Study 11.2: A Patient With Chronic Bronchitis*  
*Case Study 15.3: A Patient With Depression*  
*Case Study 17.1: A Patient With Graves Disease*

Lisa Rathman, MSN, CRNP, CHFN  
Lead Nurse Practitioner  
The Heart Group of Lancaster General Health/PENN Medicine Heart Failure Program  
Lancaster, Pennsylvania  
*Case Study 10.1: A Patient With Heart Failure Symptoms*

David A. Roberts, MSPAS, PA-C  
Heart and Vascular Center of West Tennessee  
Jackson, Tennessee  
*Case Study 9.1: A Patient With Hypertension*  
*Case Study 9.2: A Patient With Edema*  
*Case Study 10.2: A Patient With Angina*
Allison Rusgo, MPH, PA-C
Assistant Clinical Professor
Physician Assistant Program
Drexel University
Philadelphia, Pennsylvania
Case Study 8.1: A Patient With Pernicious Anemia
Case Study 8.2: A Patient With a Deep Venous Thrombosis
Case Study 16.1: A Patient With a Sprained Ankle
Case Study 16.2: A Patient With Acute Gouty Arthritis

Nancy C. Tkacs, PhD, RN
Associate Professor Emerita
University of Pennsylvania School of Nursing
Philadelphia, Pennsylvania
Case Study 17.2: A Patient With Hyperparathyroidism

Kimberly K. Trout, PhD, CNM, APRN, FAAN
Assistant Professor of Women’s Health
University of Pennsylvania School of Nursing
Philadelphia, Pennsylvania
Case Study 17.3: A Patient With Gestational Diabetes

Sampath Wijesinghe, DHSc, MS, MPAS, AAHIVS, PA-C
Principal Faculty and Clinical Site Director, Central Valley MSPA Program, School of Medicine
Stanford University
Stanford, California
Case Study 5.1: A Patient With Acute HIV Infection

Michelle Zappas, DNP, FNP-BC
Clinical Associate Professor
School of Social Work, Department of Nursing
University of Southern California
Los Angeles, California
Case Study 8.2: A Patient With a Deep Venous Thrombosis
Case Study 9.1: A Patient With Hypertension
Case Study 9.2: A Patient With Edema
Case Study 13.1: A Patient With Peptic Ulcer Disease
Case Study 13.2: A Teenage Boy With Celiac Disease
Case Study 14.1: A Patient With Hepatitis A Virus Infection
Case Study 14.2: A Patient With Nonalcoholic Fatty Liver Disease
Case Study 15.1: A Teenage Girl With Migraine
Case Study 16.1: A Patient With a Sprained Ankle
Case Study 16.2: A Patient With Acute Gouty Arthritis

Kim Zuber, PA-C, DFAAPA
Executive Director
American Academy of Nephrology PAs
St. Petersburg, Florida
Case Study 12.1: A Patient With Chronic Kidney Disease
Case Study 12.2: A Patient With a Kidney Stone
REVIEWERS

Rebecca Baldwin
Physician Assistant Student
Drexel University
Philadelphia, Pennsylvania

Joseph Boullata, PharmD, RPh, CNS-S, FASPEN, FACN
Clinical Professor
Department of Nutrition Sciences
Drexel University

Patrick Brown, MSPAS, PA-C
Assistant Professor of Clinical Medicine
Bethel University
Paris, Tennessee

Rachel Cloutier, MS, RN, ACNP-BC
Clinical Instructor
School of Nursing
Virginia Commonwealth University
Richmond, Virginia

Lisa Connor, PhD
School of Biological Sciences
Victoria University of Wellington
Wellington, New Zealand

Margaret Eckert-Norton, RN, PhD, FNP-BC, CDE, CNE
Associate Professor
St. Joseph's College/SUNY Downstate
Brooklyn, New York

Desiree Fleck, PhD, ACNP-BC, CPNP-BC
Nurse Practitioner
The Children's Hospital of Philadelphia
Lecturer
University of Pennsylvania School of Nursing
Philadelphia, Pennsylvania

Cecilia Follin, PhD
Associate Professor
Lund University
Lund, Sweden

Lynda A. Frassetto, MD, FASN
Professor Emerita of Medicine and Nephrology
University of California, San Francisco
San Francisco, California

Ranjodh S. Gill, MD, FACP
Professor
Department of Internal Medicine
Division of Endocrinology, Diabetes, & Metabolism
Virginia Commonwealth University
VA Medical Center
Richmond, Virginia

Lexy Kristen Green
Acute Care Nurse Practitioner Student
New York University
Rory Meyers College of Nursing
New York, New York

Lisa M. Harrison-Bernard, PhD, FAHA, FASN, FAPS
Associate Professor
Department of Physiology
Louisiana State University School of Medicine
New Orleans, Louisiana

Jonathan Howard, MD
Associate Professor of Neurology and Psychiatry and
Clerkship Director
Clinical Neurological Sciences
NYU Langone Medical Center
New York, New York
Tracie Kirkland, DNP, ANP-BC, CPNP
Clinical Assistant Professor
Suzanne Dworak-Peck School of Social Work
Department of Nursing
University of Southern California
Los Angeles, California

Kathryn Evans Kreider, DNP, APRN, FNP-BC
Associate Professor
Duke University School of Nursing
Durham, North Carolina

Mary Ann Lafferty-DellaValle, PhD
Practice Professor (Retired)
University of Pennsylvania School of Nursing
Philadelphia, Pennsylvania

Laura Gunder McClary, DHSc, MHE, PA-C
Professor, Doctor of Medical Science
Rocky Mountain University of Health Professions
Provo, Utah

Amanda Miller
Physician Assistant Student
Midwestern University
Downers Grove, Illinois

Lynn M. Oswald, PhD, MSN, RN
Associate Professor
Department of Family and Community Health
University of Maryland School of Nursing
Baltimore, Maryland

Sherry Pikul, MSN, APRN, FNP-C
Family Nurse Practitioner
Bozeman Creek Family Health
Bozeman, Montana

David A. Roberts, MSPAS, PA-C
Assistant Professor
Bethel University
Paris, Tennessee

Loretta A. Sernekos, PhD, MSN, AGPCNP-BC, PMHNP-BC, CNE
Senior Lecturer
University of Pennsylvania School of Nursing
Philadelphia, Pennsylvania

Dexter F. Speck, PhD
Professor of Physiology
University of Kentucky College of Medicine
Lexington, Kentucky

Ignacio Valencia, MD
Professor of Pediatrics
Drexel University College of Medicine
Philadelphia, Pennsylvania

William F. Wright, DO, MPH
Division of Infectious Diseases
Department of Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland

Michael Zychowicz, DNP, ANP, ONP, FAAN, FAANP
Professor and Director, MSN Program
Duke University School of Nursing
Durham, North Carolina
HOW TO USE THIS BOOK

Physiology and pathophysiology are subjects that are loved by some students even as they scare others! These disciplines cover challenging topics that, while necessary for success in future clinical courses, can be seen as a painful rite of passage or as an enlightening journey to clinical competence. The features of the book were developed by master pathophysiology teachers and clinician faculty members with the goal of helping students to synthesize complex content and extend that synthesis to clinical application. The following features, recognizable by their easy-to-find design elements, appear consistently in the chapters to help reinforce the physiologic and pathophysiologic concepts discussed in this book.

THE CLINICAL CONTEXT

Each chapter begins with a short introduction that sets the stage for the content’s relevance to clinical practice. This section introduces the common disease states of that organ system, briefly highlighting their incidence and prevalence.

THOUGHT QUESTIONS

In each chapter, major subtopics conclude with questions to improve student mastery of information. These open-ended questions require students to pause and reflect on the section they have just read, to recall important facts, and often to use higher-level thinking to synthesize and apply what they have learned. Answers are provided in the online student supplement on Springer Publishing Company Connect™ to encourage self-instruction, immediate feedback, and remediation.

PEDIATRIC CONSIDERATIONS

These sections briefly review prenatal and postnatal development as it relates to physiology and pathophysiology. Congenital malformations and genetic conditions generally present at birth or in the pediatric population. Additionally, children metabolize therapeutic agents differently than adults—critical information to understand when treating children. All the system chapters as well...
GERONTOLOGICAL CONSIDERATIONS

Understanding how aging affects organ systems is imperative in providing competent patient care. Healthy aging is inevitably associated with certain trends in organ function, for example, reduced liver biotransformation of drugs, decreased renal glomerular filtration, and other alterations that must be considered when assessing disease and planning management in older adults. Additionally, certain diseases are more prevalent in older adults, and phenomena such as frailty and complex comorbidities become more common with aging. All of these considerations factor into the special care that must be taken when providing clinical care to older adults. This section appears in all system chapters as well as in Chapter 4, Cell Physiology and Pathophysiology.

CASE STUDY 9.2: A Patient With Hypertension

Patient Complaint: “I was kept a couple of weeks ago for a checkup. The nurse said my blood pressure was high. She gave me a medicine, and I have been taking my pressures at home since then. I was told to come back today. I feel fine.”

History of Present Illness/Review of Systems: A 43-year-old African American man presents to the office for a blood pressure recheck. On his two previous visits to the office, his blood pressure was 142/88 mm Hg and 154/92 mm Hg, respectively. After the most recent visit, he was sent home with a blood pressure cuff to perform at-home blood pressure monitoring. The results of his home blood pressure readings reveal a mean systolic blood pressure that is 150 mm Hg or higher, and a diastolic pressure that is 80 mm Hg or higher. Based on the home readings, white coat hypertension is ruled out and he is diagnosed with essential hypertension. The review of systems finds no chest pain or shortness of breath. Right foot pain and stiffness are noted, but all other findings are negative.

Past Medical History: The patient’s past medical history is significant for obesity and osteoarthritis of his knees. He works a desk job and is sedentary most days. He frequently consumes fast food for convenience. His family history is significant for prostate cancer, hypertension, and hyperlipidemia on his father’s side, and hyperlipidemia, and type 2 diabetes mellitus on his mother’s side. He currently takes naproxen, 500 mg twice a day as needed, for knee pain.

Physical Examination: You observe a well-appearing obese man in no acute distress. His body mass index (BMI) is 31 kg/m². General appearance: The patient is alert and oriented. Funduscopic examination is negative for hemorrhage, papilledema, cotton wool spots, arteriolar narrowing, and arteriovenous nicking. Neck is supple, with no carotid bruits, thyromegaly, or nodules. Lungs are clear to auscultation bilaterally. Abdomen is soft, nontender, and nontender, with no renal masses or aortic or renal artery bruits. Extremities reveal no edema bilaterally, and peripheral pulses are normal. Neurological examination is grossly intact, with no focal weakness.

Laboratory and Diagnostic Findings: You perform baseline tests, including electrolytes and serum creatinine, fasting glucose, urinalysis, CBC, TSH, and lipid profile. An ECG, and initiate amiodipine, 5 mg by mouth daily. You set a follow-up appointment in 2 weeks to check on this patient’s blood pressure and review the laboratory results.

CASE STUDY 9.1 QUESTIONS

• Amiodipine is a calcium channel blocker. What site of blood pressure regulation does this medication work on, and why does it help?

• What could systolic hypertension be reduced in a patient taking amiodipine, a nonselective alpha-adrenergic receptor blocker?

• Long-standing blood pressure control is mediated by endothelial and renal function. Describe the hormones involved and how they contribute to blood pressure control.

CASE STUDIES

This unique feature is designed to help students transition from the basic pathophysiology covered in the chapter to the implications for the clinical role. For each system this section provides a succinct summary of system-specific aspects of the history and physical examination, the most common laboratory tests and diagnostic tools, major drug classes used for disorders of that system, and other commonly used non-pharmacologic modalities that students will encounter as they transition into clinical settings.
This feature highlights the important takeaways for which students should be able to demonstrate an understanding at the conclusion of each chapter. These points are not intended as a comprehensive summary of the chapter; instead, they capture the main ideas conveyed throughout the chapter in short bullet points that students can reflect upon as they assess their mastery of the content.

As noted in the chapter introduction, kidney disease encompasses several entities, including acute kidney injury (AKI), which is often, but not always, reversible, and chronic kidney disease (CKD), which tends to progress through several stages until ending at stage 5 (also known as end-stage renal disease [ESRD]). The definitions of these terms and stages usually depend on laboratory assessments of kidney function, evaluation of the history and physical findings, and presence of comorbidities. For the CKD-ESRD continuum, global prevalence is estimated at 13.4%. Prevalence by stage was determined based on the eGFR and ACR (Table 12.3). CKD staging has evolved to include consideration of both eGFR and ACR, as some individuals have eGFR within the normal range but demonstrate renal impairment in the form of excessive urinary albumin excretion.11

KEY DISORDERS

All disorders reviewed in this book are highlighted within the text to facilitate quick identification and discovery. These disorders are also listed in the List of Disorders to help students locate content rapidly. Highlighted disorders appear throughout each chapter, in the main discussion as well as in the pediatric and geriatric consideration sections.

GENETIC CONDITIONS

As the fields of molecular biology and genetics provide ever more understanding of the genetic basis of disease and disease risk factors, the book uses an easily identifiable icon next to all genetic conditions described throughout the text for quick reference and discovery. These disorders are also included among the key disorders found in the List of Disorders.

SHARE YOUR FEEDBACK AND FOLLOW DR. TKACS ON TWITTER

The editors would like to hear your feedback on this first edition. If you would like to share your thoughts on potential additions, corrections, or updates that you believe should be incorporated into this book, please contact Nancy Tkacs at tkacs@nursing.upenn.edu.

You can also follow Dr. Tkacs on Twitter: @DrTkacsPatho.
Advanced Physiology and Pathophysiology: Essentials for Clinical Practice includes a robust ancillary package that qualified instructors may obtain by emailing textbook@springerpub.com

Instructor’s Manual
- Chapter Outline
- Chapter Summary
- Objectives
- Connecting the Dots (Tips and Pointers for Faculty on How to Approach the Content of the Chapter With Their Students)
- Key Points
- Thought Questions and Suggested Answers
- Case Studies Suggested Answers
- Discussion Questions
- Assignment Suggestions (Individual and Group) and Suggested Answers
- Additional Resources

Chapter-Based PowerPoint Presentations

Test Bank
- Multiple Choice Questions With Rationales
- Essay Questions and Suggested Answers

Image Bank
Clinicians’ ability to correctly identify disease processes and develop management plans with their patients relies on a deep knowledge of the pathophysiology of disease. This book was developed to meet that clinical need. Physiology seeks to understand the mechanisms of body function, and pathophysiology seeks to understand the mechanisms of altered body function due to pathological states. People, whether patients or clinicians, often fail to appreciate the finely tuned machine that is the human body until they experience alterations in function that lead to signs and symptoms of disease. Pathophysiology can be viewed with the same lens: Studying the manifestations of body function loss can illuminate the exquisite and intricate functions of our organs that we do not even think about when we are healthy. For every physiological function, there is a pathophysiological consequence when that normal function goes awry. Clinicians-in-training are well positioned to reinforce their knowledge of normal physiological principles when they are presented as the context for disease development, as we have in this book.

In disease states, one or more normal homeostatic mechanisms malfunction, and the organism increasingly relies on compensatory mechanisms to maintain homeostasis. The clinician must know the principles of normal function, the alteration of these functions during disease states, and the benefits and risks of compensatory mechanisms. In addition, one cannot study physiology and pathophysiology in isolation. To understand the complex mechanisms of body function requires application of fundamental principles from chemistry, genetics, cell biology, and other basic sciences.

The data gathered during the clinical encounter include details from the history and physical examination, comprising both subjective and objective findings; results of laboratory studies; results of imaging studies; and other measurements. The clinician must then evaluate these data, consider the differential diagnosis, and formulate a plan. At each step, knowledge of pathophysiology is integral to the process. The aims of this book are to:

- Provide a foundation of core principles of physiology for each system and organ discussed
- Link the pathophysiology of common and selected less common disorders to those core principles
- Alternate discussion of each core principle with the clinical applications, sequencing the content to emphasize the application of those core principles and mechanisms
- Present in-depth life span considerations for each organ and system as developed by geriatric and pediatric content experts who
  - Emphasize developmental aspects of organ functions and their relationships to disorders commonly encountered in infants and children
  - Describe organ and system alterations of normal healthy aging and their relationships to disorders commonly encountered in older adults
- Provide a bridge between pathophysiology and concurrent or later coursework on health history and physical assessment, diagnostic tools and laboratory testing, pharmacology, and nonpharmacologic management strategies
Offer an interdisciplinary perspective on the intricacies of the body’s systems in both a normal and a diseased state, with an author team comprising experienced clinicians and educators: nurses and nurse practitioners, physician assistants, dietitians, doctors of pharmacy, physicians, and basic scientists.

At the same time, we endeavored to avoid redundancy with topics covered more extensively in other courses in the graduate curriculum of advanced practitioners. The book does not have a freestanding chapter on the skin, for example. The most common skin disorders have unique presentations that are well described in physical assessment books and clinical lectures on dermatology. We feel that these disorders are best covered in textbooks associated with those topics. Rather than devoting a lengthy chapter to this topic, the mechanisms of selected skin disorders are covered within the context of infectious disease (Chapter 5, Infectious Disease) and immune and leukocyte function (Chapter 6, The Immune System and Leukocyte Function), which are the primary origins of many skin disorders and consistent with our approach of discussing disease in the context of alterations of existing physiological principles and mechanisms.

Similarly, we have selected certain common and uncommon disorders for discussion in the book because of their educational value and the way they illustrate an underlying principle of function. In many curricula, the pathophysiology course spans only one semester, making it impossible to describe an exhaustive list of diseases in detail. While this book explores a wide range of disorders, our approach aims to provide mastery of concepts, vocabulary, and diagnostic evaluation strategies that students can use throughout their remaining clinical semesters to broaden their knowledge of diseases they encounter. Each principle-focused segment ends with Thought Questions to immediately engage the students in reflection and analysis of their level of mastery of that chunk of content. Chapters conclude with Key Points to return students to the big picture of function and dysfunction for the chapter’s main topics. We sincerely hope that this approach produces a resource that students will actually read and keep reading as a companion to their subsequent coursework.

CHEMISTRY (CHAPTER 2)
All body functions can ultimately be described in terms of chemical interactions. The body’s chemistry begins at the level of single atoms, including many of the electrolytes. Sodium, chloride, potassium, calcium, and hydrogen ions must be kept within a normal range of concentration in both the intracellular and extracellular fluid. Ion imbalance can lead to cardiac arrhythmias, paresthesias, and acidosis. Minerals, including those present in small amounts (trace minerals), are required for proper function of many enzymes. Iron is the site of oxygen binding within hemoglobin and myoglobin molecules, and iodine is required for thyroid hormone synthesis. The chemistry of the body has an undisputed role in health and disease.

Atoms combine through ionic and covalent bonds to form molecules. In addition to the previously listed elements, key atoms that make up the molecules of the body are carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur. Molecular oxygen \( (\text{O}_2) \) is needed by all cells for synthesis of adenosine triphosphate (ATP) and other energy sources. This role of oxygen comes with a cost, in that oxidative metabolism generates oxygen-derived free radicals that can damage cell components.

The most abundant molecule in the body is water, and the polar nature of water’s molecular structure is a major determinant of physiological function. The aqueous environment of the body’s extracellular and intracellular fluids creates the shape and interactions of proteins, lipids, and carbohydrates to sustain life. The nonpolar, hydrophobic molecular nature of fatty acids underlies the function of the plasma membrane as a barrier between intracellular and extracellular fluids. With a hydrophobic fatty acid core, the plasma membrane defines the cell, the smallest unit of biological function.

Solubility, diffusion, equilibrium reactions, and many other core concepts of atomic and molecular function will appear throughout this book.
BIOCHEMISTRY (CHAPTER 2)
The biomolecules—carbohydrates, lipids, proteins, and nucleic acids—are the workhorses of cell and organ function. Abnormalities in metabolism, such as phenylketonuria, result in abnormally high levels of certain biomolecules and abnormally low levels of others, transforming function in devastating ways. Nutritional deficiencies (iron-deficiency anemia) and excesses (obesity) underlie many disease processes and may be preventable or readily treatable, once recognized.

MOLECULAR BIOLOGY AND GENETICS (CHAPTER 3)
The human genome project was completed in 2003, and was followed by additional haplotype mapping studies to identify common variant alleles and single-nucleotide polymorphisms (SNPs). The impact of these developments on clinical practice is profound and far reaching. Understanding heredity, single gene disorders, penetrance, expressivity, and the impact of human gene variants on disease risk is integral to clinicians entering independent practice. Common genetic disorders and variants are discussed in this book, and each chapter features one or more highlighted genetic disorders. Some less common genetic disorders are included because they illustrate important concepts in genetic disease.

The consequences of many genetic disorders are detectable in the perinatal period, as described in the Pediatric Considerations section of this chapter. Prenatal genetic screening and diagnosis are discussed here, along with genetic disorders identified after birth. Newborn screening programs continually expand their targets—identifying genetic and biochemical abnormalities in enzymes and other biomolecules within a few days after birth, allowing early intervention and management that prevents or lessens long-term disability.

CELL BIOLOGY (CHAPTER 4)
As molecular biology knowledge has expanded, so too has knowledge of cell biology. Membrane transport proteins and membrane-bound receptors are the targets of many drug classes in common use, and new subtypes of these membrane proteins continue to be discovered. Knowledge of intracellular signaling cascades involved in immune function and neoplastic transformation is growing rapidly, leading to better tools for management of autoimmunity, hypersensitivity, and cancer.

A fundamental understanding of the impact of aging at cellular, tissue, organ, and systemic levels is crucial in order for clinicians to tailor individualized age-appropriate interventions, given the demographics on aging domestically and abroad. By 2060, 23% of U.S. residents will be aged 65 and older, an increase from 16% in 2018. In 2015, the number of persons aged 60 and older worldwide was 900 million; this is expected to increase to 2 billion people by 2050. Knowledge of the pathophysiological underpinnings of age-related changes, both normal and abnormal, is paramount when considering changes in implicit body regulatory mechanisms, metabolism, and nutrition; selecting pharmacotherapy; and critically analyzing the interplay of systemic manifestations of disease, clinical data, and patient presentation. Hypotheses of aging at the cellular level are described in the Gerontological Considerations section of Chapter 4.

INFECTIOUS DISEASE (CHAPTER 5)
In keeping with our emphasis on principles and concepts, this chapter begins with an overview of the interactions between humans and microbes, and concepts such as infection versus colonization, pathogen virulence, and host characteristics that determine infection severity. A brief review of characteristics of bacteria, viruses, protozoa, fungi, and yeasts is provided, followed by clinical concepts of pathogen identification strategies, drug resistance, and antimicrobial stewardship. This chapter concludes with snapshots of the structure and function of selected microbes commonly encountered in clinical settings in the United States or globally. Selected infectious diseases are further discussed in the relevant organ systems chapters; for example, pneumonia in Chapter 11, Lungs, and infectious diarrheas in Chapter 13, Gastrointestinal Tract.
THE IMMUNE SYSTEM AND LEUKOCYTE FUNCTION (CHAPTER 6)

Knowledge of immunology continues to grow exponentially, and identification of lymphocyte subsets, cytokines, and other members of the immune system’s “cast of characters” continues to provide new targets for biologic drugs. At the same time, innate immunity (inflammation) continues to cause a great deal of morbidity and mortality, wreaking havoc in the blood vessels of patients with atherosclerosis, the adipose tissue of persons with obesity and metabolic syndrome, and the joints of patients with rheumatoid arthritis. This chapter explores the latest concepts of innate and adaptive immunity; details the pathophysiology of hypersensitivity, autoimmunity, and immunodeficiency; and builds the foundation for understanding the pharmacology of biological therapies for immune-related disorders. The waxing and waning of immune function across the life span, and implications for care of both children and older adults, are placed in that context.

NEOPLASIA (CHAPTER 7)

This chapter focuses on the principles underlying a cell’s movement into the cell cycle and cell division—the critical event that is inappropriately activated in cells that have undergone neoplastic transformation. Characteristics of cancer cells are described, with emphasis on the implications for current and projected treatments of certain cancers. The discussion of genetic and viral causes of cancer highlights the critical role of genotyping in cancer care. The most common cancers of children are described, as well as specific aspects of cancer pathophysiology in older adults.

BLOOD AND CLOTTING (CHAPTER 8)

This chapter builds on the content of Chapter 6, The Immune System and Leukocyte Function, by focusing on red blood cells in health and disease and the processes of blood clotting. The concept of anemia and the principles underlying the different forms of anemia provide the foundation for developing differential diagnoses in patients with suspected anemia based on clinical manifestations and diagnostic findings. The process of hemostasis is described, focusing on the complementary roles of platelets and coagulation factors, as well as relevant laboratory assessments. This underpins the subsequent discussion of pathophysiological and genetic causes of states of excess clotting and excess bleeding. Life span considerations include the unique changes in red blood cell size and number in the perinatal period, and the bone marrow–related changes of older adults.

CIRCULATION (CHAPTER 9)

The circulatory system receives the output of the heart and channels the blood flow through a series of tubes that diverge and narrow as they proceed outward to the tissues, and then converge and enlarge as they return to the heart. Although some aspects of this flow are true for all segments of the circulation, structural and biophysical characteristics of each segment determine the pathophysiological vulnerabilities of each. The large muscular arteries move blood rapidly and efficiently
to various body sites but are prone to atherosclerosis, as well as hypertrophy and aneurysm. The arterioles provide vascular resistance that helps to maintain organ perfusion pressures—they are the site of blood pressure control by neural and humoral mediators, and their dysfunction is associated with hypertension and shock. The capillaries exchange essential substances with the tissues, and are also the locus of physiological and pathophysiological edema formation. The veins are low-pressure storage vessels that are vulnerable to gravitational influences, varicosities, and coagulability. Hypertension can occur in children as well as adults, and recognizing this disorder depends on knowledge of age-related population norms. Older adults have additional clinical concerns related to vascular stiffness due to age-related collagen deposition in vessel walls.

HEART (CHAPTER 10)
The heart is an autonomously functioning pump, ejecting a volume of blood (stroke volume) with each beat into the circulation for delivery to the body. Heart function is critically dependent on electrical automaticity of pacemaker cells and rapid action potential propagation that produces coordinated chamber contractions. Cardiac cells have unique action potentials that can be vulnerable to abnormal cardiac beats and rhythms (arrhythmias). These electrical signals are linked to calcium entry that initiates the mechanical steps of contraction—the pumping action of the heart. The mechanical properties of the heart determine the stroke volume—the amount of blood pumped with each beat, at rest and during exercise, to meet the body’s need for oxygen delivery and carbon dioxide removal. Ischemic heart disease results in both electrical and mechanical dysfunction. Recently, research has begun to illuminate how the pathophysiology and presentation of ischemic heart disease differ in men and women, and clinical practice is beginning to change accordingly.

Heart failure can result from ischemic heart disease, among other causes, and is a chronic, progressive loss of pumping capacity that ultimately limits physical activity and can result in death. Structural cardiac disorders range from valve diseases in children and adults to malformations arising during embryonic and fetal development. Many of these are managed surgically, albeit with varying degrees of success depending on severity. Cardiac changes during healthy aging generally do not result in activity limitations; however, many disorders, such as atrial fibrillation, show increased prevalence with aging.

LUNGS (CHAPTER 11)
The lungs interface with the environment, bringing in atmospheric air during inspiration, and expelling mixed airway and alveolar air during expiration. Thus, the airways—the diverging and narrowing tubes that lead to the alveoli—are exposed to pollutants, irritants, and pathogens. Several mechanisms, including antimicrobial and mucociliary responses, protect the airways from these damaging substances. The lungs’ delicate structure is encased in a more rigid thoracic chamber, surrounded by the chest wall (ribs, sternum, associated muscles and lining), and bounded below by the diaphragm. The ability of inspiratory muscles (diaphragm and others) to inflate the lungs depends on compliance of the lungs and the chest wall, and pathophysiological changes in either component can alter the amount of effort required for inspiration. The airways are the site of airway resistance that must be overcome to generate inspiratory and expiratory airflow. Airway diameter can be pathologically altered in a variety of disease processes, leading to acute or chronic obstructive disease.

Gas exchange occurs in the alveoli and depends on lung mechanics (for ventilation) as well as blood flow (for perfusion) in taking up oxygen and releasing carbon dioxide. Diseases may alter blood oxygenation (and carbon dioxide removal) through their effects on ventilation, perfusion, or the diffusion barrier of the alveolar wall. The lungs receive all of the blood flow of the right heart, a low-pressure system that perfuses the millions of alveolar capillaries for gas exchange. Abnormalities of lung blood flow can lead to secondary heart disease, lung fluid accumulation, and acutely impaired oxygenation. Much of the alveolar development occurs postnatally, and preterm birth is associated with persistent lung pathology. In older adults, pneumonia is a common occurrence, related in part to decreased protective mechanisms.

KIDNEYS (CHAPTER 12)
The kidneys are highly vascular organs that filter the blood, removing wastes for excretion and returning the rest of the blood to the vascular system. The functional units of the kidneys are nephrons, each composed of a glomerulus and a tubule. In a two-step process, the glomeruli receive blood for filtration and release an ultrafiltrate of plasma into the tubules, which then process the filtrate and greatly reduce its volume, leading to the final step of urine production. The extremely high blood flow and capillary permeability of the glomeruli relative to other vascular beds make them vulnerable to damage by hypertension, diabetic hyperglycemia, antibodies, and complement components. The tubules are transport membranes that return most of the glomerular filtrate to the circulation, while secreting substances destined for clearance, including many drugs. Tubules can be damaged by many filtered and secreted substances, including proteins such as myoglobin and certain medications. Hypotension and hypovolemia can also lead to tubular necrosis in the renal medulla, which receives relatively low blood flow and is prone to hypoxia. Acute kidney injury may resolve, but
compromised function may progress to chronic kidney injury and end-stage renal disease. At both ends of the life span, childhood and older age, the kidneys are more vulnerable to damage owing to decreased number or function of nephrons.

**GASTROINTESTINAL TRACT (CHAPTER 13)**

Similar to the circulatory system, the basic structure of the gastrointestinal tract is a generalized tube with a series of segments that are specialized in structure and function. Similar to the respiratory tract, the gut is exposed to environmental toxins—in this case, a wide variety of ingested foods and beverages, as well as pathogens. In addition to a sequential description of structure, function, and disorders of the esophagus, stomach, and small and large intestines, this chapter emphasizes general concepts of gut control by neurotransmitters and hormones that are the basis for many of the drugs used to manage gastrointestinal disorders. The abundant and intricate immune system of the gut plays a role in development of immune responses in early life and is protective against ingested pathogens, but also is implicated in inflammatory bowel disease. Life span considerations include structural disorders as well as common infectious diarrheas of children, and structural disorders of older adults, including greater occurrence of reflux and diverticular disease.

**LIVER (CHAPTER 14)**

This book places a substantial emphasis on the physiology and pathophysiology of the liver, providing a critical foundation for clinicians who will be responsible for prescribing medications. We have dedicated a chapter solely to this organ rather than including it in the gastrointestinal tract chapter because drug-induced liver injury is extremely common, and prescribers must appreciate the role of the liver in drug metabolism and excretion. Understanding the metabolic functions of the liver is also key to appreciating its significance in diabetes, the metabolic syndrome, and nonalcoholic fatty liver disease—a disorder with steadily increasing prevalence in the developed world. Infectious hepatitis is common in the United States and globally; an understanding of the patterns of dysfunction and laboratory assessment of different subtypes of hepatitis is critical for advanced practice. Individuals at both ends of the life span are more vulnerable to liver injury—children, because of the relative immaturity of many of the drug-metabolizing enzymes, and older adults, because of reduced liver mass and blood flow.

**NERVOUS SYSTEM (CHAPTER 15)**

The nervous system is arguably the most complex body system, with both physiological and behavioral components, all of which make up the whole person cared for by clinicians. To provide a strong foundation of knowledge for practitioners with prescriptive privileges, this chapter focuses in detail on concepts of neurotransmission and functions of major neurotransmitters. In primary care, a clinician can expect to spend a significant portion of each day interacting with patients who are trying to manage anxiety, depression, pain, or substance use disorders. Antidepressants, anxiolytics, anesthetics, and nonpharmacologic modalities are widely prescribed. Although our knowledge of exact mechanisms of many neurological and affective disorders is incomplete, this chapter presents current hypotheses, concepts, and vocabulary. Knowledge of the long-term effects of adverse childhood experiences and other contributing factors can help clinicians explain the biological basis of these disorders to patients experiencing mental health challenges. Having this understanding also helps the clinician to reduce stigma and promote adherence to management approaches.

The section on sensory function and dysfunction emphasizes pain, as this is a major patient complaint. Motor disorders are very common and must be carefully evaluated and described, so they are given expanded coverage in this chapter. The major disorders of brain function in children include epilepsy and developmental delay, as well as headache and concussion. Cerebrovascular structural changes in older adults increase risk of subdural hematomas, and functional losses can accompany cognitive dysfunction as well as neurodegenerative disorders. Neurovascular disorders are also emphasized in the Gerontological Considerations section of this chapter.

**MUSCULOSKELETAL SYSTEM (CHAPTER 16)**

The musculoskeletal system is responsible for the structure of the body and the ability to have purposeful movements. This chapter begins with a review of structure and function of bones, with an emphasis on the remodeling process of dynamic bone maintenance. A discussion of fractures and the fracture healing process follows. The structure and function of joints are described, emphasizing synovial joints and the manifestations of sprains and strains. Particular emphasis is placed on the knee, and the associated ligament and meniscal injuries. This chapter also discusses other common structural and functional disorders, such as herniated disc disease and cumulative trauma disorders. Developmental disorders and sports injuries in children, as well as genetic conditions of muscles and bones, are the focus of the Pediatric Considerations section. Disorders in older adults include general principles of sarcopenia and frailty, as well as osteoporosis, osteoarthritis, and Parkinson-associated Pisa syndrome.

**ENDOCRINE SYSTEM (CHAPTER 17)**

The book concludes with the longest chapter, focusing on the endocrine system. This is the third integrative
system of the body, along with the nervous and immune systems. Found in many locations throughout the body, endocrine glands and cells secrete hormones that act locally and also travel through the circulation to alter the activities of target cells in other organs. General concepts of endocrine signaling are described first, focusing on cellular mechanisms of hormone action, hormone control axes, feedback mechanisms, and temporal regulation of hormone secretion. An important principle of endocrine pathophysiology is that the most common sources of dysfunction fall into three major categories: pathological increases of hormone levels (which are often produced by hormone-secreting tumor cells), pathological decreases of hormone levels (which can be caused by autoimmune destruction of hormone-secreting cells), and insensitivity of target tissues to hormone actions (some of which have genetic causes).

Following the introduction, this chapter content is divided into six major sections that group key content blocks. The initial section provides an overview of the endocrine system. Following this overview begins a more in-depth look at the various parts of the endocrine system. The section covering hypothalamus and pituitary glands provides an in-depth overview of these structures—as sources of direct-acting hormones (oxytocin, vasopressin, growth hormone, and prolactin) and master regulators of other endocrine glands and tissues. The focus then turns to those glands, with separate sections covering adrenals, thyroid, and female and male gonads. The final section of this chapter opens with a review of metabolic physiology that prepares students for detailed coverage of pancreatic hormones and diabetes mellitus. This section begins with an extensive discussion of the hormone insulin, including its mechanisms of signaling and cellular actions, followed by descriptions of the hormones that oppose the actions of insulin. Included are extensive discussions of type 1 and type 2 diabetes, as well as other types of diabetes and related conditions of dysregulated metabolism. Reflecting the unique organization of this chapter, Pediatric and Gerontological Considerations and Key Points appear at the end of each main section rather than at the end of this chapter. Bridge to Clinical practice segments appear in the sections on the thyroid gland and metabolism and diabetes, as management of these disorders is common in primary care settings.

**CONNECTING THE DOTS**

As this content overview has emphasized, the conceptually driven organization of this book, linking principles with their clinical applications, aims to reinforce the unique aspects of each organ or system’s function and the ways in which alterations of these functions contribute to disease. The rationale for this approach was derived from clinical practice and refined through teaching pathophysiology courses at an advanced level for over 25 years. Having mastered the concepts and vocabulary of function for each system in this way, the reader will best be prepared for later or concurrent courses in pharmacology, clinical diagnosis, and management.

The ability to connect the dots between pathophysiological principles and clinical applications is a major emphasis in this book. This knowledge can provide a rational basis for clinical decision-making and can make it easier to generalize knowledge to new pathological conditions encountered in practice. Knowledge of these core principles assists in learning the strategies and medications used to manage disease states, ultimately facilitating safe and effective advanced patient care.

**PATHOPHYSIOLOGY AND THE INDEPENDENT CLINICIAN**

The ultimate goal of graduate education in healthcare practice is to prepare to deliver the highest and safest care possible. This entails knowing not only what signs and symptoms are associated with a certain disorder but why they are associated. Knowing about compensatory mechanisms for impaired oxygen delivery, for example, helps the clinician immediately recognize that a patient presenting with dyspnea and tachypnea is likely hypoxic, even before applying a pulse oximeter or listening to the lungs. Knowing about the oxygen-carrying capacity of hemoglobin helps the clinician put iron-deficiency anemia at the top of the differential diagnosis list when a patient presents with fatigue, dyspnea on exertion, and pallor.

Knowledge of pathophysiology also directs the logical choice of diagnostic tests. This is something that all novice clinicians struggle with. Which blood test(s) should be ordered? Does this patient need imaging and, if so, which type of imaging will yield the most diagnostically relevant information? One may know to order a complete blood count for suspected anemia, but what other tests will be informative and narrow the differential diagnosis? When the results are obtained, how should they be interpreted? The answers to many of these questions are clearer when there is a strong grounding in pathophysiology. Likewise, the knowledge of normal and abnormal physiology is essential for understanding which medications are the logical choices and why—and equally if not more importantly, why certain medications should not be used in people with certain disease states.

Knowledge of core principles emphasized in this book will make it easier to generalize knowledge to
new pathological conditions encountered in practice. Novice clinicians should anticipate that they cannot possibly graduate with knowledge of every disease and disorder. There will be times when their patients are diagnosed—usually by a specialist—with a disease they have never heard of or one that was only briefly touched on in their training. A strong foundation in pathophysiology makes it possible to read an online update or journal article about a disease, to understand what normal function is altered, and by extension, how the abnormal state is treated.

Finally, patients and their families expect clinicians to be able to explain and interpret for them what is going on in their particular disease state. Understanding the pathophysiology of a disease is essential to being able to explain the disease in ways your patients will understand. It also helps patients own their disease. With knowledge of what is going on and why certain tests are ordered or why certain medications are prescribed, patients are more likely to take responsibility for those aspects of their illness that they can influence. A clinician can order many tests and prescribe many medications, but ultimately the patient must go get the tests and take the medications. The more successful the clinician is in patient teaching, the greater the likelihood that the patient will feel a partnership with the clinician in the journey to wellness. A deep understanding of pathophysiology facilitates clear explanations tailored to the patient’s level of understanding.

REFERENCES