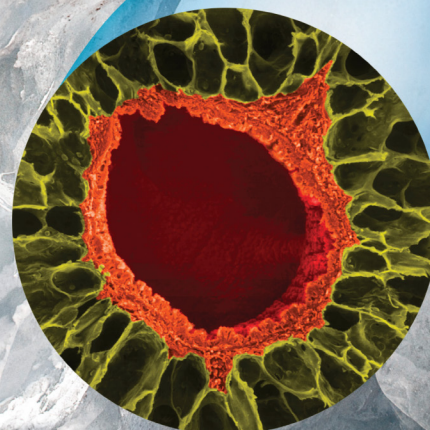
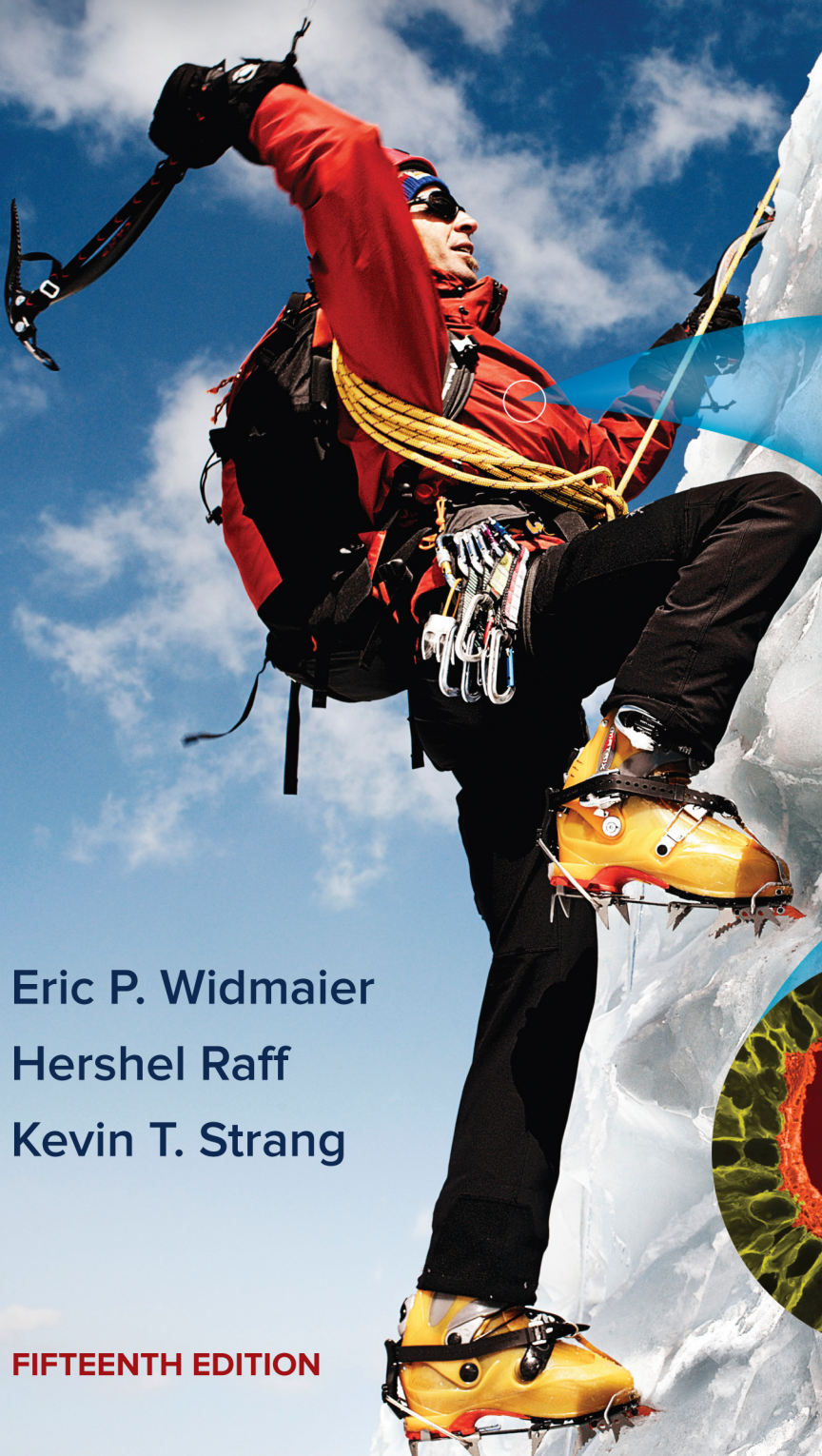


VANDER'S

Human Physiology

**THE MECHANISMS
OF BODY FUNCTION**



Eric P. Widmaier
Hershel Raff
Kevin T. Strang

FIFTEENTH EDITION

**Mc
Graw
Hill
Education**



FIFTEENTH EDITION

VANDER'S

Human Physiology

The Mechanisms of Body Function

ERIC P. WIDMAIER

BOSTON UNIVERSITY

HERSHEL RAFF

MEDICAL COLLEGE OF WISCONSIN
AURORA ST. LUKE'S MEDICAL CENTER

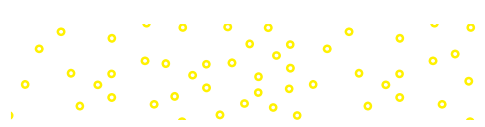
KEVIN T. STRANG

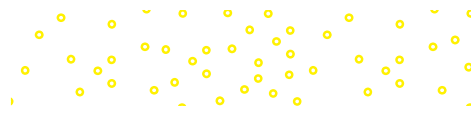
UNIVERSITY OF WISCONSIN-MADISON

TODD C. SHOEPE, DIGITAL AUTHOR

LOYOLA MARYMOUNT UNIVERSITY

**Mc
Graw
Hill**
Education





VANDER'S HUMAN PHYSIOLOGY: THE MECHANISMS OF BODY FUNCTION, FIFTEENTH EDITION

Published by McGraw-Hill Education, 2 Penn Plaza, New York, NY 10121. Copyright © 2019 by McGraw-Hill Education. All rights reserved. Printed in the United States of America. Previous editions © 2016, 2014, and 2011. No part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written consent of McGraw-Hill Education, including, but not limited to, in any network or other electronic storage or transmission, or broadcast for distance learning.

Some ancillaries, including electronic and print components, may not be available to customers outside the United States.

This book is printed on acid-free paper.

1 2 3 4 5 6 7 8 9 LWI 21 20 19 18

ISBN 978-1-259-90388-5

MHID 1-259-90388-5

Portfolio Manager: *Amy Reed*

Product Developer: *Michelle Gaseor*

Marketing Manager: *James Connely*

Content Project Manager: *Ann Courtney*

Buyer: *Sandy Ludovissy*

Design: *Tara McDermott*

Content Licensing Specialist: *Lori Hancock*

Cover Image: *Mountain climber*: ©David Trood/Getty Images; *3D illustration of lungs*: ©yodiyim/Getty Images; *human lung*:

©Dennis Kunkel Microscopy/Science Source

Compositor: *SPi Global*

All credits appearing on page or at the end of the book are considered to be an extension of the copyright page.

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained, from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Library of Congress Cataloging-in-Publication Data

Names: Widmaier, Eric P., author. | Vander, Arthur J., 1933- Human physiology.

Title: Vander's human physiology : the mechanisms of body function.

Other titles: Human physiology

Description: Fifteenth edition / Eric P. Widmaier, Boston University [and three others]. | New York, NY : McGraw-Hill Education, [2019] | Includes index.

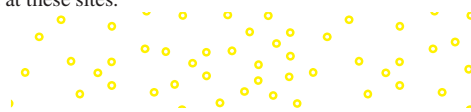
Identifiers: LCCN 2017048599 | ISBN 9781259903885 (alk. paper)

Subjects: LCSH: Human physiology. | Human physiology—Problems, exercises, etc.

Classification: LCC QP34.5 .W47 2019 | DDC 612—dc23 LC record available at <https://lccn.loc.gov/2017048599>

The Internet addresses listed in the text were accurate at the time of publication. The inclusion of a website does not indicate an endorsement by the authors or McGraw-Hill Education, and McGraw-Hill Education does not guarantee the accuracy of the information presented at these sites.

mheducation.com/highered





Brief Contents

- **1** Homeostasis: A Framework for Human Physiology 1
 - **2** Chemical Composition of the Body and Its Relation to Physiology 20
 - **3** Cellular Structure, Proteins, and Metabolic Pathways 44
 - SECTION A Cell Structure 45
 - SECTION B Protein Synthesis, Degradation, and Secretion 57
 - SECTION C Interactions Between Proteins and Ligands 66
 - SECTION D Chemical Reactions and Enzymes 71
 - SECTION E Metabolic Pathways 77
 - **4** Movement of Solutes and Water Across Cell Membranes 95
 - **5** Cell Signaling in Physiology 118
 - **6** Neuronal Signaling and the Structure of the Nervous System 136
 - SECTION A Cells of the Nervous System 137
 - SECTION B Membrane Potentials 143
 - SECTION C Synapses 158
 - SECTION D Structure of the Nervous System 172
 - **7** Sensory Physiology 189
 - SECTION A General Principles 190
 - SECTION B Specific Sensory Systems 200
 - **8** Consciousness, the Brain, and Behavior 234
 - **9** Muscle 257
 - SECTION A Skeletal Muscle 258
 - SECTION B Smooth and Cardiac Muscle 287
 - **10** Control of Body Movement 301
 - **11** The Endocrine System 320
 - SECTION A General Characteristics of Hormones and Hormonal Control Systems 321
 - SECTION B The Hypothalamus and Pituitary Gland 333
 - SECTION C The Thyroid Gland 339
 - SECTION D The Endocrine Response to Stress 344
 - SECTION E Endocrine Control of Growth 348
 - SECTION F Endocrine Control of Ca^{2+} Homeostasis 352
 - **12** Cardiovascular Physiology 362
 - SECTION A Overview of the Circulatory System 363
 - SECTION B The Heart 372
 - SECTION C The Vascular System 390
 - SECTION D Integration of Cardiovascular Function: Regulation of Systemic Arterial Pressure 411
 - SECTION E Cardiovascular Patterns in Health and Disease 419
 - SECTION F Hemostasis: The Prevention of Blood Loss 431
 - **13** Respiratory Physiology 445
 - **14** The Kidneys and Regulation of Water and Inorganic Ions 488
 - SECTION A Basic Principles of Renal Physiology 489
 - SECTION B Regulation of Ion and Water Balance 503
 - SECTION C Hydrogen Ion Regulation 520
 - **15** The Digestion and Absorption of Food 531
 - **16** Regulation of Organic Metabolism and Energy Balance 572
 - SECTION A Control and Integration of Carbohydrate, Protein, and Fat Metabolism 573
 - SECTION B Regulation of Total-Body Energy Balance 587
 - SECTION C Regulation of Body Temperature 593
 - **17** Reproduction 604
 - SECTION A Gametogenesis, Sex Determination, and Sex Differentiation; General Principles of Reproductive Endocrinology 605
 - SECTION B Male Reproductive Physiology 614
 - SECTION C Female Reproductive Physiology 623
 - SECTION D Pregnancy, Contraception, Infertility, and Hormonal Changes Through Life 636
 - **18** The Immune System 655
 - **19** Medical Physiology: Integration Using Clinical Cases 694
 - SECTION A Case Study of a Woman with Palpitations and Heat Intolerance 695
 - SECTION B Case Study of a Man with Chest Pain After a Long Airplane Flight 699
 - SECTION C Case Study of a Man with Abdominal Pain, Fever, and Circulatory Failure 702
 - SECTION D Case Study of a College Student with Nausea, Flushing, and Sweating 706
- APPENDIX A A-1
APPENDIX B A-17
APPENDIX C A-21
GLOSSARY/INDEX GI-1

Meet the Authors



©Maria Widmaier

ERIC P. WIDMAIER received his Ph.D. in 1984 in Endocrinology from the *University of California at San Francisco*. His postdoctoral training was in molecular endocrinology, neuroscience and physiology at the *Worcester Foundation for Experimental Biology* in Shrewsbury, Massachusetts, and *The Salk Institute* in La Jolla, California. His research is focused on the control of body mass and metabolism in mammals, the mechanisms of hormone action, and molecular mechanisms of intestinal and hypothalamic adaptation to high-fat diets. He is currently Professor of Biology at *Boston University*, where he teaches Human Physiology and has been recognized with the Gitner Award for Distinguished Teaching by the College of Arts and Sciences, and the Metcalf Prize for Excellence in Teaching by Boston University. He is the author of many scientific and lay publications, including books about physiology for the general reader. He has two grown children, Rick and Carrie; he and his wife Maria split their time between Massachusetts and Florida.



©Tonya Limberg

HERSHEL RAFF received his Ph.D. in Environmental Physiology from the *Johns Hopkins University* in 1981 and did postdoctoral training in Endocrinology at the *University of California at San Francisco*. He is now a Professor of Medicine (Endocrinology, Metabolism, and Clinical Nutrition), Surgery, and Physiology in the School of Medicine, and Professor in the School of Pharmacy at the *Medical College of Wisconsin*. He is Director of the Endocrine Research Laboratory at *Aurora St. Luke's Medical Center/Aurora Research Institute*. He teaches physiology and pathophysiology to medical, pharmacy, and graduate students as well as medical residents and clinical fellows. At the Medical College of Wisconsin, he is the Endocrinology/Reproduction Course Director for second-year medical students. He was an inaugural inductee into the Society of Teaching Scholars, received the Beckman Basic Science Teaching Award from the senior MD class four times, and has been one of the MCW's Outstanding Medical Student Teachers in multiple years. He is also an Adjunct Professor of Biomedical Sciences at *Marquette University*. Dr. Raff's basic research focuses on the adaptation to low oxygen (hypoxia). His clinical interest focuses on pituitary and adrenal diseases, with a special focus on laboratory tests for the diagnosis of Cushing's syndrome. He resides outside Milwaukee with his wife Judy and son Jonathan.



©Kevin Strang

KEVIN T. STRANG received his Master's Degree in Zoology (1988) and his Ph.D. in Physiology (1994) from the *University of Wisconsin at Madison*. His research area is cellular mechanisms of contractility modulation in cardiac muscle. He teaches a large undergraduate systems physiology course in the *UW-Madison School of Medicine and Public Health*. He was elected to UW-Madison's Teaching Academy and as a Fellow of the Wisconsin Initiative for Science Literacy. He is a frequent guest speaker at colleges and high schools on the physiology of alcohol consumption. He has twice been awarded the UW Medical Alumni Association's Distinguished Teaching Award for Basic Sciences, and also received the University of Wisconsin System's Underkofler/Alliant Energy Excellence in Teaching Award. In 2012 he was featured in *The Princeton Review* publication, "*The Best 300 Professors.*" Interested in teaching technology, Dr. Strang has produced numerous animations of figures from *Vander's Human Physiology* available to instructors and students. He has two adult children, Jake and Amy, and lives in Madison with his wife Sheryl.



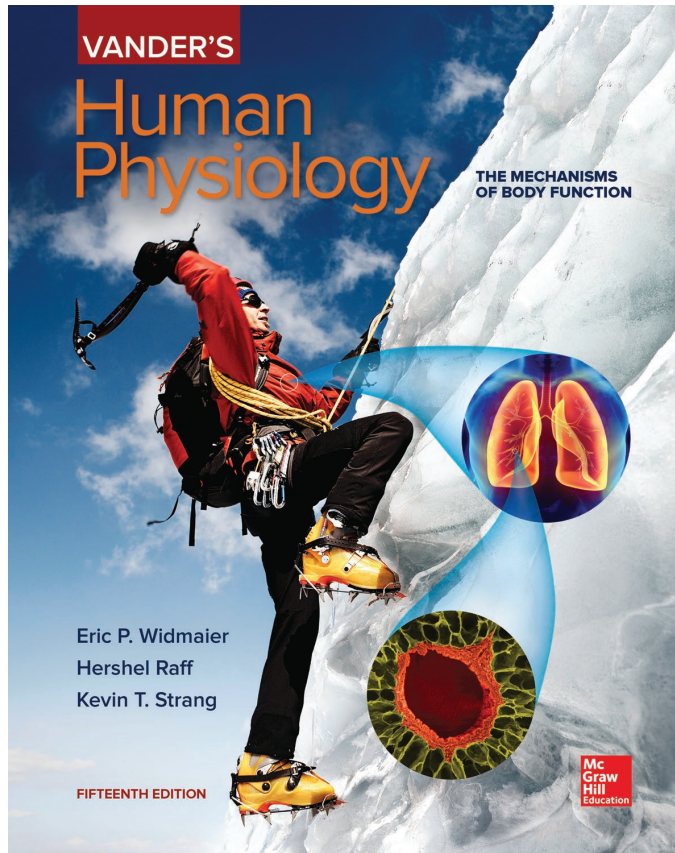
©Jon Rou

TODD C. SHOEPE received his B.S. degree in Fitness Program Management in 1998 and his M.S. degree in Exercise Physiology in 2001 both from *Oregon State University*. In 2013 he received an Ed.D. degree in Learning Technologies from *Pepperdine University*. He has been a faculty member at *Loyola Marymount University* since 2005 where he is currently an Associate Professor in the *Department of Health and Human Sciences*. He has been teaching undergraduate anatomy and physiology for the past 12 years in addition to courses in exercise physiology, biomechanics, and strength and conditioning, along with online courses in nutrition. He has served as both a Master Teacher and Faculty Associate for the Loyola Marymount University *Center for Teaching Excellence*. His research pursuits span functional analysis of muscle biopsies to changes in muscular fitness after exercise training in cancer survivors, while also studying the incorporation of technology in science education. He is a member of the American College of Sports Medicine as well as the National Strength and Conditioning Association where he has held certifications since 2000 and 2005, respectively. He is also an active member of the Human Anatomy and Physiology Society, American Association of Anatomists, and Sigma Xi. He lives in Los Angeles with his wife Dr. Hawley Almstedt, who is also a professor of Health and Human Sciences at *Loyola Marymount University*.

TO OUR FAMILIES: MARIA, CAROLINE, AND RICHARD; JUDY AND JONATHAN; SHERYL, JAKE, AND AMY; HAWLEY

From the Authors

Lifeline to success in physiology



We are pleased to offer an integrated package of textual and digital material to help deliver basic and clinical content, real-life applications, and educational technologies to students of physiology. With the 15th edition of *Vander's Human Physiology*, all these pieces come together to facilitate learning and enthusiasm for understanding the mechanisms of body function.

The cover of this edition reflects the book's focus on homeostasis, one of the key "General Principles of Physiology" elaborated upon in Chapter 1 and reinforced throughout. In addition, the cover illustrates the book's emphasis on processes at all levels of system, organ, tissue, and cellular function. As in previous editions, these themes are always related to pathophysiology through the use of compelling clinical case studies in all chapters, and a final chapter with several cases that integrate material across the entire book.

An exciting development with this edition is the addition to the author team of Todd Shoepe from Loyola Marymount University. In addition to his background in exercise physiology, Professor Shoepe is an expert in cutting-edge learning technologies and has assumed the role of digital author beginning with this edition. The big winners in this context will be students using the book, who will benefit from the combined expertise of Professor Shoepe and the skilled editorial team that created the extremely successful Connect digital content for McGraw-Hill Education.

We are certain that you will find the 15th edition of this textbook to be the most up-to-date and comprehensive book available for students of physiology. Thank you and happy reading!

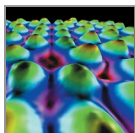
Table of Contents

MEET THE AUTHORS IV ■ FROM THE AUTHORS V ■ INDEX OF EXERCISE PHYSIOLOGY XV ■ GUIDED TOUR THROUGH A CHAPTER XVI
■ UPDATES AND ADDITIONS XX ■ CONNECT XXII ■ ACKNOWLEDGMENTS XXV



1 Homeostasis: A Framework for Human Physiology 1

- 1.1 The Scope of Human Physiology 2**
- 1.2 How Is the Body Organized? 2**
 - Muscle Cells and Tissue 3*
 - Neurons and Nervous Tissue 3*
 - Epithelial Cells and Epithelial Tissue 3*
 - Connective-Tissue Cells and Connective Tissue 4*
 - Organs and Organ Systems 4*
- 1.3 Body Fluid Compartments 4**
- 1.4 Homeostasis: A Defining Feature of Physiology 5**
- 1.5 General Characteristics of Homeostatic Control Systems 7**
 - Feedback Systems 8*
 - Resetting of Set Points 8*
 - Feedforward Regulation 9*
- 1.6 Components of Homeostatic Control Systems 9**
 - Reflexes 9*
 - Local Homeostatic Responses 11*
- 1.7 The Role of Intercellular Chemical Messengers in Homeostasis 11**
- 1.8 Processes Related to Homeostasis 12**
 - Adaptation and Acclimatization 12*
 - Biological Rhythms 13*
 - Balance of Chemical Substances in the Body 14*
- 1.9 General Principles of Physiology 14**
- Chapter 1 Clinical Case Study 17**
 - ASSORTED ASSESSMENT QUESTIONS 19
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 19



2 Chemical Composition of the Body and Its Relation to Physiology 20

- 2.1 Atoms 21**
 - Components of Atoms 21*
 - Atomic Number 22*
 - Atomic Mass 22*
 - Ions 23*
 - Atomic Composition of the Body 23*
- 2.2 Molecules 23**
 - Covalent Chemical Bonds 23*
 - Ionic Bonds 25*

- Hydrogen Bonds 25*
- Molecular Shape 25*
- Ionic Molecules 26*
- Free Radicals 26*

2.3 Solutions 27

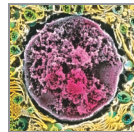
- Water 27*
- Molecular Solubility 28*
- Concentration 28*
- Hydrogen Ions and Acidity 29*

2.4 Classes of Organic Molecules 30

- Carbohydrates 30*
- Lipids 31*
- Proteins 34*
- Nucleic Acids 38*

Chapter 2 Clinical Case Study 41

- ASSORTED ASSESSMENT QUESTIONS 42
- ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 43



3 Cellular Structure, Proteins, and Metabolic Pathways 44

SECTION A Cell Structure 45

- 3.1 Microscopic Observations of Cells 45**
- 3.2 Membranes 46**
 - Membrane Structure 46*
 - Membrane Junctions 49*
- 3.3 Cell Organelles 51**
 - Nucleus 51*
 - Ribosomes 51*
 - Endoplasmic Reticulum 51*
 - Golgi Apparatus 52*
 - Endosomes 52*
 - Mitochondria 52*
 - Lysosomes 53*
 - Peroxisomes 54*
 - Vaults 54*
 - Cytoskeleton 55*

SECTION B Protein Synthesis, Degradation, and Secretion 57

- 3.4 Genetic Code 57**
- 3.5 Protein Synthesis 58**
 - Transcription: mRNA Synthesis 58*
 - Translation: Polypeptide Synthesis 60*
 - Regulation of Protein Synthesis 63*
 - Mutation 64*

3.6 Protein Degradation 64

3.7 Protein Secretion 64

SECTION C Interactions Between Proteins and Ligands 66

3.8 Binding Site Characteristics 66

Chemical Specificity 67

Affinity 68

Saturation 68

Competition 69

3.9 Regulation of Binding Site Characteristics 69

Allosteric Modulation 69

Covalent Modulation 70

SECTION D Chemical Reactions and Enzymes 71

3.10 Chemical Reactions 72

Determinants of Reaction Rates 72

Reversible and Irreversible Reactions 72

Law of Mass Action 73

3.11 Enzymes 73

Cofactors 74

3.12 Regulation of Enzyme-Mediated Reactions 74

Substrate Concentration 74

Enzyme Concentration 75

Enzyme Activity 75

3.13 Multienzyme Reactions 76

SECTION E Metabolic Pathways 77

3.14 Cellular Energy Transfer 78

Glycolysis 78

Krebs Cycle 80

Oxidative Phosphorylation 82

3.15 Carbohydrate, Fat, and Protein Metabolism 83

Carbohydrate Metabolism 83

Fat Metabolism 86

Protein and Amino Acid Metabolism 87

Metabolism Summary 88

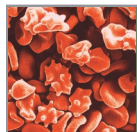
3.16 Essential Nutrients 89

Vitamins 89

Chapter 3 Clinical Case Study 92

ASSORTED ASSESSMENT QUESTIONS 93

ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 94



4 Movement of Solutes and Water Across Cell Membranes 95

4.1 Diffusion 96

Magnitude and Direction of Diffusion 96

Diffusion Rate Versus Distance 97

Diffusion Through Membranes 97

4.2 Mediated-Transport Systems 100

Facilitated Diffusion 101

Active Transport 102

4.3 Osmosis 105

Extracellular Osmolarity and Cell Volume 108

4.4 Endocytosis and Exocytosis 109

Endocytosis 109

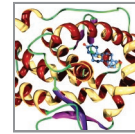
Exocytosis 111

4.5 Epithelial Transport 111

Chapter 4 Clinical Case Study 114

ASSORTED ASSESSMENT QUESTIONS 115

ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 117



5 Cell Signaling in Physiology 118

5.1 Receptors 119

Types of Receptors 119

Interactions Between Receptors and Ligands 119

Regulation of Receptors 122

5.2 Signal Transduction Pathways 122

Pathways Initiated by Lipid-Soluble Messengers 122

Pathways Initiated by Water-Soluble Messengers 123

Major Second Messengers 126

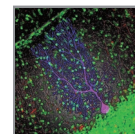
Other Messengers 129

Cessation of Activity in Signal Transduction Pathways 131

Chapter 5 Clinical Case Study 133

ASSORTED ASSESSMENT QUESTIONS 134

ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 135



6 Neuronal Signaling and the Structure of the Nervous System 136

SECTION A Cells of the Nervous System 137

6.1 Structure and Maintenance of Neurons 137

6.2 Functional Classes of Neurons 138

6.3 Glial Cells 140

6.4 Neural Growth and Regeneration 141

Growth and Development of Neurons 141

Regeneration of Axons 142

SECTION B Membrane Potentials 143

6.5 Basic Principles of Electricity 143

6.6 The Resting Membrane Potential 144

Nature and Magnitude of the Resting Membrane Potential 144

Contribution of Ion Concentration Differences 145

Contribution of Different Ion Permeabilities 147

Contribution of Ion Pumps 148

Summary of the Development of a Resting Membrane Potential 148

6.7 Graded Potentials and Action Potentials 149

Graded Potentials 149

Action Potentials 150

SECTION C Synapses 158

6.8 Functional Anatomy of Synapses 158

Electrical Synapses 158
Chemical Synapses 159

6.9 Mechanisms of Neurotransmitter Release 159

6.10 Activation of the Postsynaptic Cell 160

Binding of Neurotransmitters to Receptors 160
Removal of Neurotransmitter from the Synapse 160
Excitatory Chemical Synapses 160
Inhibitory Chemical Synapses 161

6.11 Synaptic Integration 161

6.12 Synaptic Strength 163

Presynaptic Mechanisms 163
Postsynaptic Mechanisms 164
Modification of Synaptic Transmission by Drugs and Disease 164

6.13 Neurotransmitters and Neuromodulators 165

Acetylcholine 166
Biogenic Amines 166
Amino Acid Neurotransmitters 168
Neuropeptides 169
Gases 170
Purines 170
Lipids 170

6.14 Neuroeffector Communication 170

SECTION D Structure of the Nervous System 172

6.15 Central Nervous System: Brain 172

Forebrain: The Cerebrum 173
Forebrain: The Diencephalon 175
Hindbrain: The Cerebellum 175
Brainstem: The Midbrain, Pons, and Medulla Oblongata 175

6.16 Central Nervous System: Spinal Cord 176

6.17 Peripheral Nervous System 176

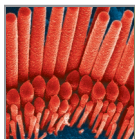
6.18 Autonomic Nervous System 177

6.19 Protective Elements Associated with the Brain 181

Meninges and Cerebrospinal Fluid 181
The Blood–Brain Barrier 184

Chapter 6 Clinical Case Study 185

ASSORTED ASSESSMENT QUESTIONS 186
ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 188



7 Sensory Physiology 189

SECTION A General Principles 190

7.1 Sensory Receptors 190

The Receptor Potential 191

7.2 Primary Sensory Coding 192

Stimulus Type 192
Stimulus Intensity 193
Stimulus Location 193
Central Control of Afferent Information 196

7.3 Ascending Neural Pathways in Sensory Systems 196

7.4 Association Cortex and Perceptual Processing 198

Factors That Affect Perception 198

SECTION B Specific Sensory Systems 200

7.5 Somatic Sensation 200

Touch and Pressure 200
Posture and Movement 200
Temperature 201
Pain and Itch 201
Neural Pathways of the Somatosensory System 204

7.6 Vision 205

Light 205
Overview of Eye Anatomy 206
The Optics of Vision 207
Photoreceptor Cells and Phototransduction 209
Neural Pathways of Vision 211
Color Vision 214
Color Blindness 214
Eye Movement 215
Common Diseases of the Eye 216

7.7 Audition 216

Sound 216
Sound Transmission in the Ear 217
Hair Cells of the Organ of Corti 220
Neural Pathways in Hearing 220

7.8 Vestibular System 221

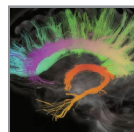
The Semicircular Canals 222
The Utricle and Saccule 222
Vestibular Information and Pathways 223

7.9 Chemical Senses 224

Gustation 224
Olfaction 225

Chapter 7 Clinical Case Study 229

ASSORTED ASSESSMENT QUESTIONS 231
ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 232



8 Consciousness, the Brain, and Behavior 234

8.1 States of Consciousness 235

Electroencephalogram 235
The Waking State 236
Sleep 236
Neural Substrates of States of Consciousness 238
Coma and Brain Death 240

8.2 Conscious Experiences 241

Selective Attention 241
Neural Mechanisms of Conscious Experiences 242

8.3 Motivation and Emotion 243

Motivation 243
Emotion 244

- 8.4 Altered States of Consciousness 245**
 - Schizophrenia* 245
 - The Mood Disorders: Depression and Bipolar Disorders* 246
 - Psychoactive Substances, Tolerance, and Substance Use Disorders* 247

- 8.5 Learning and Memory 248**
 - Memory* 248
 - The Neural Basis of Learning and Memory* 249
- 8.6 Cerebral Dominance and Language 250**

Chapter 8 Clinical Case Study 253

- ASSORTED ASSESSMENT QUESTIONS 255
- ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 255



9 Muscle 257

SECTION A Skeletal Muscle 258

- 9.1 Structure 258**
 - Cellular Structure* 258
 - Connective Tissue Structure* 259
 - Filament Structure* 260
 - Sarcomere Structure* 260
 - Other Myofibril Structures* 261
- 9.2 Molecular Mechanisms of Skeletal Muscle Contraction 262**
 - Membrane Excitation: The Neuromuscular Junction* 262
 - Excitation–Contraction Coupling* 265
 - Sliding-Filament Mechanism* 267
- 9.3 Mechanics of Single-Fiber Contraction 269**
 - Twitch Contractions* 270
 - Load–Velocity Relation* 272
 - Frequency–Tension Relation* 272
 - Length–Tension Relation* 273
- 9.4 Skeletal Muscle Energy Metabolism 275**
 - Creatine Phosphate* 275
 - Oxidative Phosphorylation* 276
 - Glycolysis* 276
 - Muscle Fatigue* 276
- 9.5 Types of Skeletal Muscle Fibers 277**
- 9.6 Whole-Muscle Contraction 278**
 - Control of Muscle Tension* 278
 - Control of Shortening Velocity* 280
 - Muscle Adaptation to Exercise* 280
 - Lever Action of Muscles and Bones* 281
- 9.7 Skeletal Muscle Disorders 282**
 - Muscle Cramps* 283
 - Hypocalcemic Tetany* 283
 - Muscular Dystrophy* 283
 - Myasthenia Gravis* 284

SECTION B Smooth and Cardiac Muscle 287

- 9.8 Structure of Smooth Muscle 287**
- 9.9 Smooth Muscle Contraction and Its Control 288**
 - Cross-Bridge Activation* 288
 - Sources of Cytosolic Ca²⁺* 289

- Membrane Activation* 290
- Types of Smooth Muscle* 292

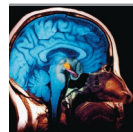
- 9.10 Cardiac Muscle 293**
 - Cellular Structure of Cardiac Muscle* 293
 - Excitation–Contraction Coupling in Cardiac Muscle* 293
- Chapter 9 Clinical Case Study 296**

- ASSORTED ASSESSMENT QUESTIONS 298
- ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 299



10 Control of Body Movement 301

- 10.1 Motor Control Hierarchy 302**
 - Voluntary and Involuntary Actions* 304
- 10.2 Local Control of Motor Neurons 304**
 - Interneurons* 304
 - Local Afferent Input* 304
- 10.3 The Brain Motor Centers and the Descending Pathways They Control 308**
 - Cerebral Cortex* 308
 - Subcortical and Brainstem Nuclei* 309
 - Cerebellum* 311
 - Descending Pathways* 311
- 10.4 Muscle Tone 312**
 - Abnormal Muscle Tone* 313
- 10.5 Maintenance of Upright Posture and Balance 313**
- 10.6 Walking 314**
- Chapter 10 Clinical Case Study 316**
- ASSORTED ASSESSMENT QUESTIONS 317
- ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 318



11 The Endocrine System 320

SECTION A General Characteristics of Hormones and Hormonal Control Systems 321

- 11.1 Hormones and Endocrine Glands 321**
- 11.2 Hormone Structures and Synthesis 323**
 - Amine Hormones* 323
 - Peptide and Protein Hormones* 323
 - Steroid Hormones* 324
- 11.3 Hormone Transport in the Blood 327**
- 11.4 Hormone Metabolism and Excretion 327**
- 11.5 Mechanisms of Hormone Action 327**
 - Hormone Receptors* 327
 - Events Elicited by Hormone–Receptor Binding* 328
 - Pharmacological Effects of Hormones* 329
- 11.6 Inputs That Control Hormone Secretion 329**
 - Control by Plasma Concentrations of Mineral Ions or Organic Nutrients* 329
 - Control by Neurons* 330
 - Control by Other Hormones* 330

11.7 Types of Endocrine Disorders 330

Hyposecretion 330

Hypersecretion 331

Hyporesponsiveness and Hyperresponsiveness 331

SECTION B The Hypothalamus and Pituitary Gland 333

11.8 Control Systems Involving the Hypothalamus and Pituitary Gland 333

Posterior Pituitary Hormones 334

Anterior Pituitary Gland Hormones and the Hypothalamus 334

SECTION C The Thyroid Gland 339

11.9 Synthesis of Thyroid Hormone 339

11.10 Control of Thyroid Function 341

11.11 Actions of Thyroid Hormone 341

Metabolic Actions 342

Permissive Actions 342

Growth and Development 342

11.12 Hypothyroidism and Hyperthyroidism 342

SECTION D The Endocrine Response to Stress 344

11.13 Physiological Functions of Cortisol 344

11.14 Functions of Cortisol in Stress 345

11.15 Adrenal Insufficiency and Cushing's Syndrome 346

11.16 Other Hormones Released During Stress 347

SECTION E Endocrine Control of Growth 348

11.17 Bone Growth 348

11.18 Environmental Factors Influencing Growth 349

11.19 Hormonal Influences on Growth 349

Growth Hormone and Insulin-Like

Growth Factors 349

Thyroid Hormone 351

Insulin 351

Sex Steroids 351

Cortisol 351

SECTION F Endocrine Control of Ca²⁺ Homeostasis 352

11.20 Effector Sites for Ca²⁺ Homeostasis 352

Bone 352

Kidneys 353

Gastrointestinal Tract 353

11.21 Hormonal Controls 353

Parathyroid Hormone 353

1,25-Dihydroxyvitamin D 354

Calcitonin 355

11.22 Metabolic Bone Diseases 355

Hypercalcemia 355

Hypocalcemia 356

Chapter 11 Clinical Case Study 357

ASSORTED ASSESSMENT QUESTIONS 359

ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 360



12 Cardiovascular Physiology 362

SECTION A Overview of the Circulatory System 363

12.1 Components of the Circulatory System 363

Blood 363

Plasma 364

The Blood Cells 364

Blood Flow 367

Circulation 368

12.2 Pressure, Flow, and Resistance 369

SECTION B The Heart 372

12.3 Anatomy 372

Cardiac Muscle 373

12.4 Heartbeat Coordination 375

Sequence of Excitation 375

Cardiac Action Potentials and Excitation of the SA Node 376

The Electrocardiogram 378

Excitation–Contraction Coupling 378

Refractory Period of the Heart 380

12.5 Mechanical Events of the Cardiac Cycle 380

Mid-Diastole to Late Diastole 383

Systole 383

Early Diastole 383

Pulmonary Circulation Pressures 384

Heart Sounds 384

12.6 The Cardiac Output 385

Control of Heart Rate 385

Control of Stroke Volume 386

12.7 Measurement of Cardiac Function 388

SECTION C The Vascular System 390

12.8 Arteries 392

Arterial Blood Pressure 392

Measurement of Systemic Arterial Pressure 394

12.9 Arterioles 394

Local Controls 396

Extrinsic Controls 397

Endothelial Cells and Vascular Smooth Muscle 398

Arteriolar Control in Specific Organs 399

12.10 Capillaries 399

Anatomy of the Capillary Network 400

Velocity of Capillary Blood Flow 401

Diffusion Across the Capillary Wall: Exchanges of Nutrients and Metabolic End Products 402

Bulk Flow Across the Capillary Wall: Distribution of the Extracellular Fluid 403

12.11 Venules and Veins 406

Determinants of Venous Pressure 406

12.12 The Lymphatic System 407

Mechanism of Lymph Flow 409

SECTION D Integration of Cardiovascular Function: Regulation of Systemic Arterial Pressure 411

- 12.13 Baroreceptor Reflexes 414**
 - Arterial Baroreceptors 414*
 - The Medullary Cardiovascular Center 415*
 - Operation of the Arterial Baroreceptor Reflex 416*
 - Other Baroreceptors 416*
- 12.14 Blood Volume and Long-Term Regulation of Arterial Pressure 417**
- 12.15 Other Cardiovascular Reflexes and Responses 417**

SECTION E Cardiovascular Patterns in Health and Disease 419

- 12.16 Hemorrhage and Other Causes of Hypotension 419**
 - Shock 420*
- 12.17 The Upright Posture 420**
- 12.18 Exercise 421**
 - Maximal Oxygen Consumption and Training 424*
- 12.19 Hypertension 424**
- 12.20 Heart Failure 425**
- 12.21 Hypertrophic Cardiomyopathy 427**
- 12.22 Coronary Artery Disease and Heart Attacks 427**
 - Causes and Prevention 428*
 - Drug Therapy 429*
 - Interventions 429*
 - Stroke and TIA 429*

SECTION F Hemostasis: The Prevention of Blood Loss 431

- 12.23 Formation of a Platelet Plug 431**
- 12.24 Blood Coagulation: Clot Formation 432**
- 12.25 Anticlotting Systems 435**
 - Factors That Oppose Clot Formation 435*
 - The Fibrinolytic System 436*
- 12.26 Anticlotting Drugs 436**
- Chapter 12 Clinical Case Study 438**
 - ASSORTED ASSESSMENT QUESTIONS 441
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 442



13 Respiratory Physiology 445

- 13.1 Organization of the Respiratory System 446**
 - The Airways and Blood Vessels 446*
 - Site of Gas Exchange: The Alveoli 447*
 - Relation of the Lungs to the Thoracic (Chest) Wall 449*
- 13.2 Principles of Ventilation 449**
 - Ventilation 450*
 - Boyle's Law 450*
 - Transmural Pressures 451*
 - How Is a Stable Balance of Transmural Pressures Achieved Between Breaths? 451*
 - Inspiration 453*
 - Expiration 453*

13.3 Lung Mechanics 453

- Lung Compliance 453*
- Airway Resistance 456*
- Lung Volumes and Capacities 458*

13.4 Alveolar Ventilation 458

- Dead Space 458*

13.5 Exchange of Gases in Alveoli and Tissues 460

- Partial Pressures of Gases 461*
- Alveolar Gas Pressures 462*
- Gas Exchange Between Alveoli and Blood 463*
- Matching of Ventilation and Blood Flow in Alveoli 464*
- Gas Exchange Between Tissues and Blood 465*

13.6 Transport of Oxygen in Blood 465

- What Is the Effect of P_{O_2} on Hemoglobin Saturation? 466*
- Effects of Other Factors on Hemoglobin Saturation and Oxygen-Carrying Capacity 468*

13.7 Transport of Carbon Dioxide in Blood 470

13.8 Transport of Hydrogen Ion Between Tissues and Lungs 471

13.9 Control of Respiration 471

- Neural Generation of Rhythmic Breathing 471*
- Control of Ventilation by P_{O_2} , P_{CO_2} , and H^+ Concentration 473*
- Control of Ventilation During Exercise 477*
- Other Ventilatory Responses 478*

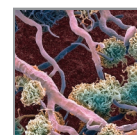
13.10 Hypoxia 479

- Why Do Ventilation–Perfusion Abnormalities Affect O_2 More Than CO_2 ? 479*
- Emphysema 479*
- Acclimatization to High Altitude 480*

13.11 Nonrespiratory Functions of the Lungs 480

Chapter 13 Clinical Case Study 484

- ASSORTED ASSESSMENT QUESTIONS 485
- ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 487



14 The Kidneys and Regulation of Water and Inorganic Ions 488

SECTION A Basic Principles of Renal Physiology 489

14.1 Renal Functions 489

14.2 Structure of the Kidneys and Urinary System 489

14.3 Basic Renal Processes 493

- Glomerular Filtration 494*
- Tubular Reabsorption 497*
- Tubular Secretion 499*
- Metabolism by the Tubules 499*
- Regulation of Membrane Channels and Transporters 499*
- “Division of Labor” in the Tubules 499*

14.4 The Concept of Renal Clearance 499

14.5 Micturition 500

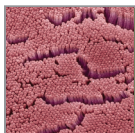
- Involuntary (Spinal) Control 500*
- Voluntary Control 501*
- Incontinence 501*

SECTION B Regulation of Ion and Water Balance 503

- 14.6 Total-Body Balance of Sodium and Water 503**
- 14.7 Basic Renal Processes for Sodium and Water 503**
 - Primary Active Na⁺ Reabsorption 503*
 - Coupling of Water Reabsorption to Na⁺ Reabsorption 504*
 - Urine Concentration: The Countercurrent Multiplier System 506*
- 14.8 Renal Sodium Regulation 510**
 - Control of GFR 510*
 - Control of Na⁺ Reabsorption 511*
- 14.9 Renal Water Regulation 513**
 - Osmoreceptor Control of Vasopressin Secretion 513*
 - Baroreceptor Control of Vasopressin Secretion 514*
- 14.10 A Summary Example: The Response to Sweating 515**
- 14.11 Thirst and Salt Appetite 515**
- 14.12 Potassium Regulation 516**
 - Renal Regulation of K⁺ 516*
- 14.13 Renal Regulation of Calcium and Phosphate Ions 517**
- 14.14 Summary—Division of Labor 517**
- 14.15 Diuretics 517**

SECTION C Hydrogen Ion Regulation 520

- 14.16 Sources of Hydrogen Ion Gain or Loss 520**
- 14.17 Buffering of Hydrogen Ion in the Body 521**
- 14.18 Integration of Homeostatic Controls 521**
- 14.19 Renal Mechanisms 522**
 - HCO₃⁻ Handling 522*
 - Addition of New HCO₃⁻ to the Plasma 522*
- 14.20 Classification of Acidosis and Alkalosis 523**
- Chapter 14 Clinical Case Study 525**
 - ASSORTED ASSESSMENT QUESTIONS 528
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 529



15 The Digestion and Absorption of Food 531

- 15.1 Overview of the Digestive System 532**
- 15.2 Structure of the Gastrointestinal Tract Wall 535**
- 15.3 How Are Gastrointestinal Processes Regulated? 536**
 - Neural Regulation 536*
 - Hormonal Regulation 537*
 - Phases of Gastrointestinal Control 537*
- 15.4 Mouth, Pharynx, and Esophagus 538**
 - Saliva 538*
 - Chewing 539*
 - Swallowing 539*
- 15.5 The Stomach 541**
 - Anatomy 541*
 - Secretions of the Stomach 541*
 - Gastric Motility 545*
- 15.6 The Small Intestine 547**
 - Anatomy 547*
 - Secretions 548*

- Digestion and Absorption in the Small Intestine 553*
- Motility of the Small Intestine 558*

- 15.7 The Large Intestine 559**
 - Anatomy 559*
 - Secretion, Digestion and Absorption in the Large Intestine 560*
 - Motility of the Large Intestine and Defecation 560*
- 15.8 Pathophysiology of the Digestive System 561**
 - Ulcers 561*
 - Vomiting 562*
 - Gallstones 562*
 - Lactose Intolerance 564*
 - Constipation and Diarrhea 564*
- Chapter 15 Clinical Case Study 568**
 - ASSORTED ASSESSMENT QUESTIONS 570
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 571



16 Regulation of Organic Metabolism and Energy Balance 572

SECTION A Control and Integration of Carbohydrate, Protein, and Fat Metabolism 573

- 16.1 Events of the Absorptive and Postabsorptive States 573**
 - Absorptive State 573*
 - Postabsorptive State 576*
- 16.2 Endocrine and Neural Control of the Absorptive and Postabsorptive States 578**
 - Insulin 580*
 - Glucagon 582*
 - Epinephrine and Sympathetic Nerves to Liver and Adipose Tissue 583*
 - Cortisol 583*
 - Growth Hormone 584*
 - Hypoglycemia 584*
- 16.3 Energy Homeostasis in Exercise and Stress 584**

SECTION B Regulation of Total-Body Energy Balance 587

- 16.4 General Principles of Energy Expenditure 587**
 - Metabolic Rate 587*
- 16.5 Regulation of Total-Body Energy Stores 589**
 - Regulation of Food Intake 589*
 - Overweight and Obesity 591*
 - Eating Disorders: Anorexia Nervosa and Bulimia Nervosa 592*
 - What Should We Eat? 592*

SECTION C Regulation of Body Temperature 593

- 16.6 General Principles of Thermoregulation 593**
 - Mechanisms of Heat Loss or Gain 593*
 - Temperature-Regulating Reflexes 594*
 - Temperature Acclimatization 596*
- 16.7 Fever and Hyperthermia 596**
- Chapter 16 Clinical Case Study 599**
 - ASSORTED ASSESSMENT QUESTIONS 601
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 602



17 Reproduction 604

SECTION A Gametogenesis, Sex Determination, and Sex Differentiation; General Principles of Reproductive Endocrinology 605

- 17.1 Gametogenesis 605**
- 17.2 Sex Determination 607**
- 17.3 Sex Differentiation 607**
 - Differentiation of the Gonads 607*
 - Differentiation of Internal and External Genitalia 607*
 - Fetal and Neonatal Programming 611*
 - Sexual Differentiation of the Brain 611*
- 17.4 General Principles of Reproductive Endocrinology 611**
 - Androgens 611*
 - Estrogens and Progesterone 611*
 - Effects of Gonadal Steroids 612*
 - Hypothalamo–Pituitary–Gonadal Control 612*

SECTION B Male Reproductive Physiology 614

- 17.5 Anatomy 614**
- 17.6 Spermatogenesis 615**
 - Sertoli Cells 616*
 - Leydig Cells 616*
 - Production of Mature Sperm 616*
- 17.7 Transport of Sperm 617**
 - Erection 618*
 - Ejaculation 618*
- 17.8 Hormonal Control of Male Reproductive Functions 619**
 - Control of the Testes 619*
 - Testosterone 620*
- 17.9 Puberty 620**
 - Secondary Sex Characteristics and Growth 620*
 - Behavior 621*
 - Anabolic Steroid Use 621*
- 17.10 Hypogonadism 621**
- 17.11 Andropause 622**

SECTION C Female Reproductive Physiology 623

- 17.12 Anatomy 623**
- 17.13 Ovarian Functions 624**
 - Oogenesis 624*
 - Follicle Growth 625*
 - Formation of the Corpus Luteum 626*
 - Sites of Synthesis of Ovarian Hormones 627*
- 17.14 Control of Ovarian Function 627**
 - Follicle Development and Estrogen Synthesis During the Early and Middle Follicular Phases 628*
 - LH Surge and Ovulation 629*
 - The Luteal Phase 629*
- 17.15 Uterine Changes in the Menstrual Cycle 631**
- 17.16 Additional Effects of Gonadal Steroids 632**

- 17.17 Puberty 633**
- 17.18 Female Sexual Response 634**
- 17.19 Menopause 634**

SECTION D Pregnancy, Contraception, Infertility, and Hormonal Changes through Life 636

- 17.20 Fertilization and Early Development 636**
 - Egg Transport 636*
 - Intercourse, Sperm Transport, and Capacitation 636*
 - Fertilization 636*
 - Early Development, Implantation, and Placentation 637*
- 17.21 Hormonal and Other Changes During Pregnancy 641**
 - Preeclampsia and Pregnancy Sickness 642*
- 17.22 Parturition and Lactation 643**
 - Parturition 643*
 - Lactation 645*
- 17.23 Contraception and Infertility 647**
 - Contraception 647*
 - Infertility 648*
- 17.24 Summary of Reproductive Hormones Through Life 648**
- Chapter 17 Clinical Case Study 651**
 - ASSORTED ASSESSMENT QUESTIONS 652
 - ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 654



18 The Immune System 655

- 18.1 Cells and Secretions Mediating Immune Defenses 656**
 - Immune Cells 656*
 - Immune Cell Secretions: Cytokines 657*
- 18.2 Innate Immune Responses 657**
 - Defenses at Body Surfaces 657*
 - Inflammation 657*
 - Interferons 662*
 - Toll-Like Receptors 663*
- 18.3 Adaptive Immune Responses 664**
 - Overview 664*
 - Lymphoid Organs and Lymphocyte Origins 664*
 - Humoral and Cell-Mediated Responses: Functions of B Cells and T Cells 666*
 - Lymphocyte Receptors 668*
 - Antigen Presentation to T Cells 670*
 - NK Cells 671*
 - Development of Immune Tolerance 672*
 - Antibody-Mediated Immune Responses: Defenses Against Bacteria, Extracellular Viruses, and Toxins 672*
 - Defenses Against Virus-Infected Cells and Cancer Cells 676*
- 18.4 Systemic Manifestations of Infection 677**
- 18.5 Factors That Alter the Resistance to Infection 679**
 - Acquired Immune Deficiency Syndrome (AIDS) 680*
 - Antibiotics 681*
- 18.6 Harmful Immune Responses 681**
 - Graft Rejection 681*

Transfusion Reactions 681
Hypersensitivities 682
Autoimmune Disease 684
Excessive Inflammatory Responses 684

Chapter 18 Clinical Case Study 690

ASSORTED ASSESSMENT QUESTIONS 692
ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS 693



19 Medical Physiology: Integration Using Clinical Cases 694

SECTION A Case Study of a Woman with Palpitations and Heat Intolerance 695

- 19.1 Case Presentation 695
- 19.2 Physical Examination 695
- 19.3 Laboratory Tests 696
- 19.4 Diagnosis 696
- 19.5 Physiological Integration 698
- 19.6 Therapy 698

SECTION B Case Study of a Man with Chest Pain After a Long Airplane Flight 699

- 19.7 Case Presentation 699
- 19.8 Physical Examination 699
- 19.9 Laboratory Tests 700
- 19.10 Diagnosis 700

19.11 Physiological Integration 701

19.12 Therapy 701

SECTION C Case Study of a Man with Abdominal Pain, Fever, and Circulatory Failure 702

- 19.13 Case Presentation 702
- 19.14 Physical Examination 702
- 19.15 Laboratory Tests 702
- 19.16 Diagnosis 703
- 19.17 Physiological Integration 704
- 19.18 Therapy 705

SECTION D Case Study of a College Student with Nausea, Flushing, and Sweating 706

- 19.19 Case Presentation 706
- 19.20 Physical Examination 706
- 19.21 Laboratory Tests 707
- 19.22 Diagnosis 707
- 19.23 Physiological Integration 707
- 19.24 Therapy 708

APPENDIX A: ANSWERS TO TEST QUESTIONS A-1

APPENDIX B: INDEX OF CLINICAL TERMS A-17

APPENDIX C: CONCENTRATION RANGES OF COMMONLY MEASURED
VARIABLES IN BLOOD A-21

GLOSSARY/INDEX GI-1

Table of Contents credits: Ch. 1 ©Andre Schoenherr/Stone/Getty Images; Ch. 2 ©Andrew Dunn/Alamy Stock Photo; Ch. 3 ©Professors Pietro M. Motta & Tomonori Naguro/Science Source; Ch. 4 ©VVG/Science Photo Library/Science Source; Ch. 5 ©Dr. Mark J. Winter/Science Source; Ch. 6 ©David Becker/Science Source; Ch. 7 ©Dr. Robert Fettiplace; Ch. 8 ©Sherbrooke Connectivity Imaging Lab (SCIL)/Getty Images; Ch. 9 ©Steve Gschmeissner/Science Source; Ch. 10 ©Erik Isakson/Blend Images/Getty Images; Ch. 11 ©ISM/Medical Images; Ch. 12 ©SPL/Science Source; Ch. 13 ©SPL/Science Source; Ch. 14 ©Science Photo Library/Getty Images; Ch. 15 ©Steve Gschmeissner/Science Photo Library/Science Source; Ch. 16 ©The Rockefeller University/AP Images; Ch. 17 ©David M. Phillips/Science Source; Ch. 18 Source: Frederick Murphy/CDC; Ch. 19 ©Comstock Images/Getty Images



Index of Exercise Physiology

EFFECTS ON CARDIOVASCULAR SYSTEM, 421–24

- Atrial pumping (atrial fibrillation), 384
- Cardiac output (increases), 385, 421–24, 421*f*–22*f*, 423*t*, 424*f*
 - Distribution during exercise, 421, 421*f*
- Control mechanisms, 422*f*, 423
- Coronary blood flow (increases), 421, 421*f*
- Gastrointestinal blood flow (decreases), 421, 421*f*
- Heart attacks (protective against), 429
- Heart rate (increases), 422–23, 422*f*, 423*t*, 424*f*
- Lymph flow (increases), 408
- Maximal oxygen consumption (increases), 424, 424*f*
- Mean arterial pressure (increases), 412, 421–23, 422*f*, 423*t*
- Renal blood flow (decreases), 366, 421, 421*f*
- Skeletal muscle blood flow (increases), 277, 396, 412, 421, 421*f*, 422–23
- Skin blood flow (increases), 421*f*
- Stroke volume (increases), 422–23, 422*f*, 423*t*, 424*f*
- Summary, 430
- Venous return (increases), 422–23
 - Role of respiratory pump, 406–7, 422*f*, 424
 - Role of skeletal muscle pump, 406–7, 422*f*, 424

EFFECTS ON ORGANIC METABOLISM, 583–84

- Cortisol secretion (increases), 583–84
- Diabetes mellitus (protects against), 600
- Epinephrine secretion (increases), 583
- Fuel homeostasis, 580–582
- Fuel source, 80, 83, 276, 581
- Glucagon secretion (increases), 582–83, 582*f*
- Glucose mobilization from liver (increases), 581–82
- Glucose uptake by muscle (increases), 276, 580–82, 582*f*
- Growth hormone secretion (increases), 584
- Insulin secretion (decreases), 580–82, 582*f*
- Metabolic rate (increases), 585
- Plasma glucose changes, 276, 580–82, 582*f*
- Plasma lactic acid (increases), 276, 476
- Sympathetic nervous system activity (increases), 582

EFFECTS ON RESPIRATION, 477, 478

- Airflow (increases), 446
- Alveolar gas pressures (no change in moderate exercise), 463, 477, 478*f*
- Capillary diffusion, 464
- Control of respiration in exercise, 471–77, 478*f*
- Oxygen debt, 276

- Ventilation (increases), 477, 478*f*
 - Breathing depth (increases), 276, 460
 - Expiration, 453, 472*f*
 - Respiratory rate (increases), 460, 473
 - Role of Hering-Breuer reflex, 473

EFFECTS ON SKELETAL MUSCLE

- Adaptation to exercise, 280–282
- Arterioles (dilate), 412, 421–23, 422*f*
- Changes with aging, 281
- Cramps, 283
- Fatigue, 276, 276*f*
- Glucose uptake and utilization (increase), 276, 582–83, 582*f*
- Hypertrophy, 259, 280
- Local blood flow (increases), 277, 396, 412, 421–22, 421*f*
- Local metabolic rate (increases), 585
- Local temperature (increases), 296–97, 421
- Nutrient utilization, 276, 580–82
- Oxygen extraction from blood (increases), 467
- Recruitment of motor units, 280
- Soreness, 281
- Summary, 285*t*–286*t*

OTHER EFFECTS

- Aging, 281
- Body temperature (increases), 74, 593, 593*f*
- Central command fatigue, 276
- Gastrointestinal blood flow (decreases), 421, 421*f*
- Immune function, 679
- Menstrual function, 633
- Metabolic acidosis, 524*t*
- Metabolic rate (increases), 585
- Muscle fatigue, 276, 276*f*
- Osteoporosis (protects against), 355
- Stress, 344
- Sweating, 515
- Weight loss, 585, 600

TYPES OF EXERCISE

- Aerobic, 280
- Endurance exercise, 280–81, 424, 600
- Long-distance running, 276, 281, 423, 423*t*, 477
- Moderate exercise, 423, 478
- Swimming, 423, 478
- Weightlifting, 276, 280, 422

Guided Tour Through a Chapter

CHAPTER 12
Cardiovascular Physiology



Color-enhanced angiographic image of coronary arteries. © SPL/Science Source

SECTION A
Overview of the Circulatory System

12.1 Components of the Circulatory System
Blood
Plasma
The Blood Cells
Blood Flow

12.2 Pressure, Flow, and Resistance

SECTION B
The Heart

12.3 Anatomy
Cardiac Muscle
Heartbeat Coordination

12.4 Heartbeat Coordination
Sequence of Excitation
Cardiac Action Potentials and Excitation of the SA Node
The Electrocardiogram
Excitation–Contraction Coupling
Refractory Period of the Heart

12.5 Mechanical Events of the Cardiac Cycle
Mid-Diastole to Late Diastole
Early Diastole

12.6 The Cardiac Output
Control of Heart Rate
Control of Stroke Volume
Measurement of Cardiac Function

SECTION C
The Vascular System

12.8 Arteries
Arterial Blood Pressure
Measurement of Systemic Arterial Pressure

12.9 Arterioles
Local Controls
Extrinsic Controls
Endothelial Cells and Vascular Smooth Muscle

12.10 Capillaries
Arteriolar Control in Specific Organs
Anatomy of the Capillary Network
Velocity of Capillary Blood Flow
Diffusion Across the Capillary Wall
Exchanges of Nutrients and Metabolic End Products
Bulk Flow Across the Capillary Wall
Distribution of the Extracellular Fluid

12.11 Venules and Veins
Determinants of Venous Pressure

12.12 The Lymphatic System
Mechanism of Lymph Flow

SECTION D
Integration of Cardiovascular Function: Regulation of Systemic Arterial Pressure

12.13 Baroreceptor Reflexes
Arterial Baroreceptors
The Medullary Cardiovascular Center
Operation of the Arterial Baroreceptor
Other Baroreceptors

12.14 Blood Volume and Long-Term Regulation of Arterial Pressure

12.15 Other Cardiovascular Reflexes and Responses

SECTION E
Cardiovascular Patterns in Health and Disease

12.16 Hemorrhage and Other Causes of Hypotension
Shock

12.17 The Upright Posture

12.18 Exercise
Metabolic Oxygen Consumption and Training

12.19 Hypertension

12.20 Heart Failure

12.21 Hypertrophic Cardiomyopathy

12.22 Coronary Artery Disease and Heart Attacks
Causes and Prevention
Drug Therapy
Interventions
Stroke and TIA

SECTION F
Hemostasis: The Prevention of Blood Loss

12.23 Formation of a Platelet Plug

12.24 Blood Coagulation: Clot Formation

12.25 Anticlotting Systems
Factors That Oppose Clot Formation
The Fibrinolytic System

12.26 Anticlotting Drugs

Chapter 12 Clinical Case Study

Chapter Outline

Every chapter starts with an introduction giving the reader a brief overview of what is to be covered in that chapter. Included in the introduction for the fifteenth edition is a feature that provides students with a preview of those General Principles of Physiology (introduced in Chapter 1) that will be covered in the chapter.

General Principles of Physiology

First introduced in the 13th edition to wide acclaim, General Principles of Physiology have been integrated throughout each chapter in order to continually reinforce their importance. Each chapter opens with a preview of those principles that are particularly relevant for the material covered in that chapter. The principles are then reinforced when specific examples arise within a chapter, including Physiological Inquiries associated with certain figures.

Beyond a distance of a few cell diameters, the random movement of substances from a region of higher concentration to one of lower concentration (diffusion) is too slow to meet the metabolic requirements of cells. Because of this, our large, multicellular bodies require an organ system to transport molecules and other substances rapidly over the long distances between cells, tissues, and organs. This is achieved by the **circulatory system** (also known as the **cardiovascular system**), which includes a pump (the heart); a set of interconnected tubes (**blood vessels or vascular system**); and a fluid connective tissue containing water, solutes, and cells that fills the tubes (**the blood**). Chapter 9 described the detailed mechanisms by which the cardiac and smooth muscle cells found in the heart and blood vessel walls, respectively, contract and generate force. In this chapter, you will learn how these contractions create pressures and move blood within the circulatory system.

The general principles of physiology described in Chapter 1 are abundantly represented in this chapter. In Section A, you will learn about the relationships between blood pressure, blood flow, and resistance to blood flow, a classic illustration of the

general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The general principle of physiology that structure is a determinant of—and has coevolved with—function is apparent throughout the chapter; as one example, you will learn how the structures of different types of blood vessels determine whether they participate in fluid exchange, regulate blood pressure, or provide a reservoir of blood (Section C). The general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition, is exemplified by the hormonal and neural regulation of blood vessel diameter and blood volume (Sections C and D), as well as by the opposing mechanisms that create and dissolve blood clots (Section F). Sections D and E explain how the regulation of arterial blood pressure exemplifies that homeostasis is essential for health and survival, yet another general principle of physiology. Finally, multiple examples demonstrate the general principle of physiology that the functions of organ systems are coordinated with each other; for example, the circulatory and urinary systems work together to control blood pressure, blood volume, and sodium balance. ■

Clinical Case Studies

The authors have drawn from their teaching and research experiences and the clinical experiences of colleagues to provide students with real-life applications through clinical case studies in each chapter. They have been redesigned to incorporate the format of Chapter 19. You will now find “Reflect and Review” in every case study.

CHAPTER 12 Clinical Case Study: Shortness of Breath on Exertion in a 72-Year-Old Man

A 72-year-old man saw his primary care physician, who was complaining of shortness of breath when doing his 15 min daily walk. His shortness of breath was worse when walking had been worsening over the past few weeks. He did not complain of chest pain during his walks. However, he did experience a pressure-like chest pain under the sternum (groin pectoral) when walking up several flights of stairs. He had also felt light-headed and as if he were going to faint when walking up the stairs, but both the pain and light-headedness passed when he sat down and rested. For the last few months, he has had to prop his head up using three pillows to keep from feeling short of breath when lying in bed. Occasionally the breathlessness would wake him up at night. This symptom was relieved by sitting upright and letting his legs hang off the side of the bed. His feet got swollen, particularly at the end of the day when he had been standing quite a bit. He had never smoked cigarettes and was not taking any prescription medications.

Reflect and Review #1
What are the potential causes of this condition that are standing for a significant portion of the day? (Hint: See Figures 12.4B and 12.6.3.)

The physician performed a complete physical exam. The man did not have a fever. His heart rate was 86 bpm, which was increased compared to a year before when it was 78 bpm. His systolic

blood pressure was 150 mmHg, which was increased compared to a year before when it was 120 mmHg. His diastolic blood pressure was 80 mmHg, which was increased compared to a year before when it was 60 mmHg. His pulse rate was 86 bpm, which was increased compared to a year before when it was 78 bpm. His oxygen saturation was 96% on room air, which was normal. His lungs were clear to auscultation. His jugular venous pressure was elevated. His lower extremities were swollen.

Reflect and Review #2
What is the patient's current pulse rate? What are the main determinants of pulse rate? Examination of his neck veins revealed that they were prominent and had very prominent "c" waves. This revealed a prominent systolic murmur in the aortic area (see Figure 12.5). When the patient's arms were raised, the strength of the pulse seemed to be decreased.

Reflect and Review #3
What clinical condition could this patient have? (Hint: See Section 12.1.)

The patient was showing all heart failure (see Figure 12.6B). This suggested that the failure of cardiac caused a backup of blood in the fluid that reduced the capacity for not a problem at rest but was oxygen consumption that occurred in the body. The feeling of light-headedness suggested that the brain was flow to maintain oxygen delivery at diastole. This is an additional evidence heart to adequately increase cardiac blood flow during exercise.

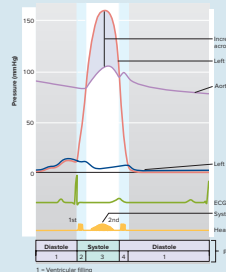


Figure 12.78 The effect of aortic stenosis on left ventricular and aortic pressures during the cardiac cycle. Compare to a normal functioning heart in Figure 12.22 to see the dramatic increase in the difference between left ventricular and aortic pressure during ejection (shaded area). Because of the reduction of the aortic orifice, the aortic pulse pressure is diminished. Also note the systolic ejection murmur in the heart sounds.

ing a weak pressure with the pulmonary capillaries and subsequent leakage of fluid from pulmonary capillaries. All of these factors indicated that the patient may have had fluid retention (see explanation of Figure 12.6B). As described in Section 12.20, this was likely due, at least in part, to decreased baroreceptor afferent activity that triggered the neuroendocrine components of the baroreceptor reflex; this increased the retention of fluid by the kidney. Although his mean arterial pressure was not decreased at the time he first presented to his physician, the smaller pulse pressure resulted in decreased baroreceptor firing (see Figure 12.57b). The baroreceptor reflex also accounted for the increased heart rate of this patient.

Reflect and Review #4
Explain how an increase in venous pressure can result in the development of peripheral edema. (Hint: See Figure 12.45.)

The history and physical findings (particularly the shortness of breath on exertion, systolic murmur, decreased pulse pressure,

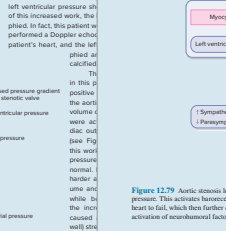


Figure 12.79 Aortic stenosis leading to heart failure. The narrowing of the aortic valve decreases pulse pressure and eventually causes arterial pressure. This activates baroreceptor reflex that increases stimulation of the heart to work harder. However, the increased workload causes the heart to fail, which then further decreases cardiac output and blood pressure. At the same time, increases in venous and capillary pressure and activation of neuroendocrine factors that increase fluid retention lead to the development of pulmonary and peripheral edema.

of fluid retention by the kidneys led to the propensity to develop pulmonary and peripheral edema. Remember that the rate of fluid filtration from the capillaries into the interstitial fluid is a balance between forces favoring filtration (capillary hydrostatic pressure and interstitial fluid protein osmotic pressure) and forces favoring absorption (interstitial fluid hydrostatic pressure and plasma protein osmotic pressure; see Figure 12.45). The increase in venous pressure is reflected back into the capillaries, increasing the capillary hydrostatic pressure, which increases the filtration of fluid into the interstitial space leading to the development of edema.

The best treatment for patients with aortic stenosis is surgical replacement of the poorly functioning aortic valve as soon as symptoms develop. Because our patient was in good physical condition before the symptoms started and he sought treatment quickly, he was a good candidate for surgical valve replacement. In patients who cannot have surgical valve replacement (myocardial infarction), the valve can be enlarged by **balloon valvuloplasty**. In this procedure, a cardiologist inserts a catheter (follow tube) across the valve

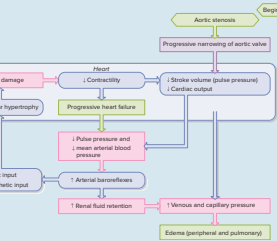


Figure 12.79 Aortic stenosis leading to heart failure. The narrowing of the aortic valve decreases pulse pressure and eventually causes arterial pressure. This activates baroreceptor reflex that increases stimulation of the heart to work harder. However, the increased workload causes the heart to fail, which then further decreases cardiac output and blood pressure. At the same time, increases in venous and capillary pressure and activation of neuroendocrine factors that increase fluid retention lead to the development of pulmonary and peripheral edema.

and inflates a balloon to try to break up the calcifications on the valve. This typically is only a temporary treatment as the valve usually calcifies again or leaks after the procedure.

An exciting new approach to valve replacement is called **percutaneous** (through the skin) **transcatheter aortic valve replacement (TAVR)**. In this technique, the cardiologist inserts a catheter containing a collapsed artificial aortic valve into the outflow from the left ventricle into the aorta. When the catheter is in proper position, the valve is deployed and expanded to its full size from the catheter and then anchored in place. This technique is primarily used in patients who are not candidates for standard surgical aortic valve replacement.

Our patient underwent a surgical valve replacement and is currently doing well.

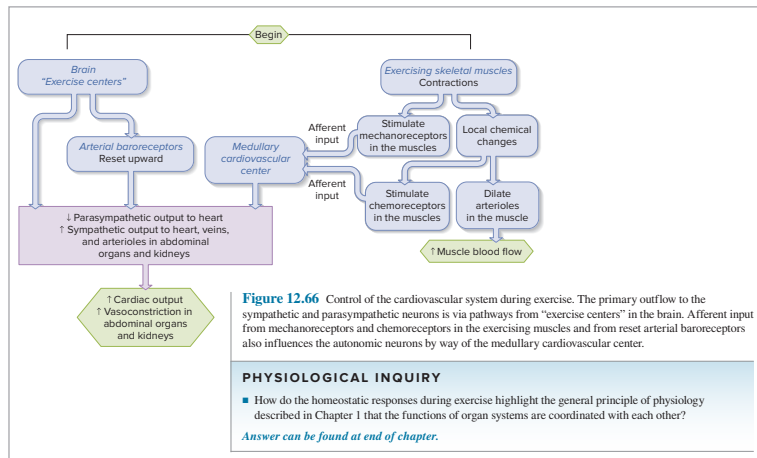
Clinical terms: balloon valvuloplasty, percutaneous transcatheter aortic valve replacement (TAVR)

Source: Adapted from Frye, McGowan, and McGowan, Medical Case Files, Access Medicine [© 2014] Case 72

Summary Tables

Summary tables are used to bring together large amounts of information that may be scattered throughout the book or to summarize small or moderate amounts of information. The tables complement the accompanying figures to provide a rapid means of reviewing the most important material in the chapter.

Component	Function
Heart	
Atria	Chambers through which blood flows from veins to ventricles. Atrial contraction adds to ventricular filling but is not essential for it.
Ventricles	Chambers whose contractions produce the pressures that drive blood through the pulmonary and systemic vascular systems and back to the heart.
Vascular system	
Arteries	Low-resistance tubes conducting blood to the various organs with little loss in pressure. They also act as pressure reservoirs for maintaining blood flow during ventricular relaxation.
Arterioles	Major sites of resistance to flow; responsible for regulating the pattern of blood-flow distribution to the various organs; participate in the regulation of arterial blood pressure.
Capillaries	Major sites of nutrient, gas, metabolic end product, and fluid exchange between blood and tissues.
Venules	Capacitance vessels that are sites of migration of leukocytes from the blood into tissues during inflammation and infection.
Veins	Low-resistance, high-capacitance vessels carrying blood back to the heart. Their capacity for blood is adjusted to facilitate this flow.
Blood	
Plasma	Liquid portion of blood that contains dissolved nutrients, ions, wastes, gases, and other substances. Its composition equilibrates with that of the interstitial fluid at the capillaries.
Cells	Includes erythrocytes that function mainly in gas transport, leukocytes that function in immune defenses, and



Physiological Inquiries

The authors have continued to refine and expand the number of higher Bloom's level critical-thinking questions based on many figures from all chapters. These concept checks were introduced in the eleventh edition and continue to prove extremely popular with users of the textbook. They are designed to help students become more engaged in learning a concept or process depicted in the art. These questions challenge a student to analyze the content of the figure and, occasionally, to recall information from previous chapters. Many of the questions also require quantitative skills. Many instructors find that these Physiological Inquiries make great exam questions. Numerous Physiological Inquiries are linked with General Principles of Physiology, providing students with two great learning tools in one!

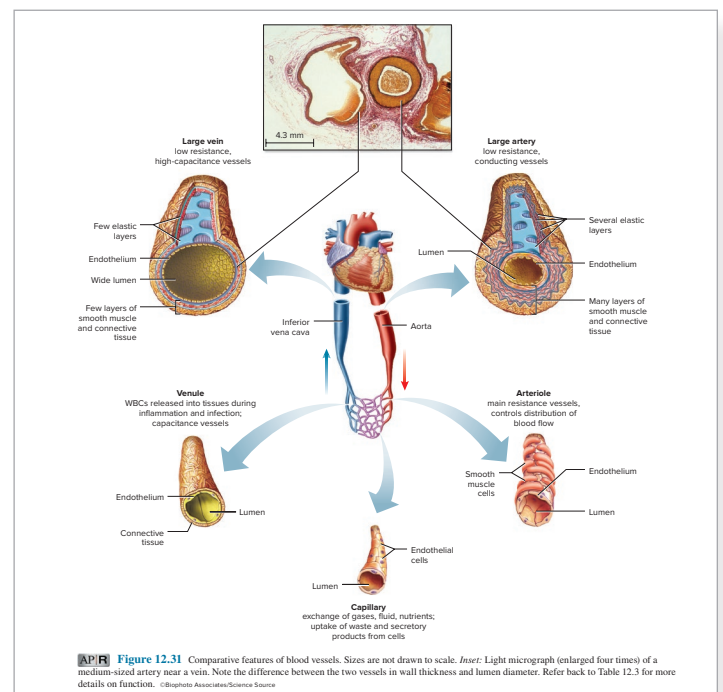
Anatomy and Physiology REVEALED® (APR) Icon

APR icons are found in figure legends. These icons indicate that APR related content is available to reinforce and enhance learning of the material.



Descriptive Art Style

A realistic three-dimensional perspective is included in many of the figures for greater clarity and understanding of concepts presented.



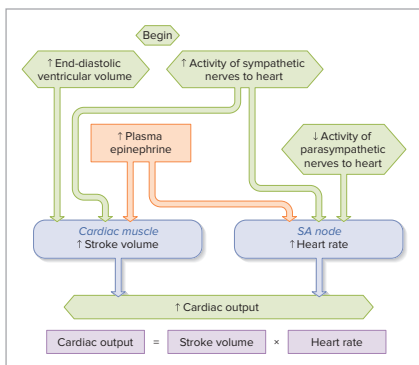


Figure 12.30 Major factors involved in increasing cardiac output. Reversal of all arrows in the boxes would illustrate how cardiac output can be decreased.

PHYSIOLOGICAL INQUIRY

- Recall from Figure 12.12 that parasympathetic nerves do not innervate the ventricles. Does this make it impossible for parasympathetic activity to influence stroke volume?

Answer can be found at end of chapter.

Flow Diagrams

Long a hallmark of this book, extensive use of flow diagrams is continued in this edition. They have been updated to assist in learning.

Key to Flow Diagrams

- The beginning boxes of the diagrams are color-coded green.
- Other boxes are consistently color-coded throughout the book.
- Structures are always shown in three-dimensional form.

Uniform Color-Coded Illustrations

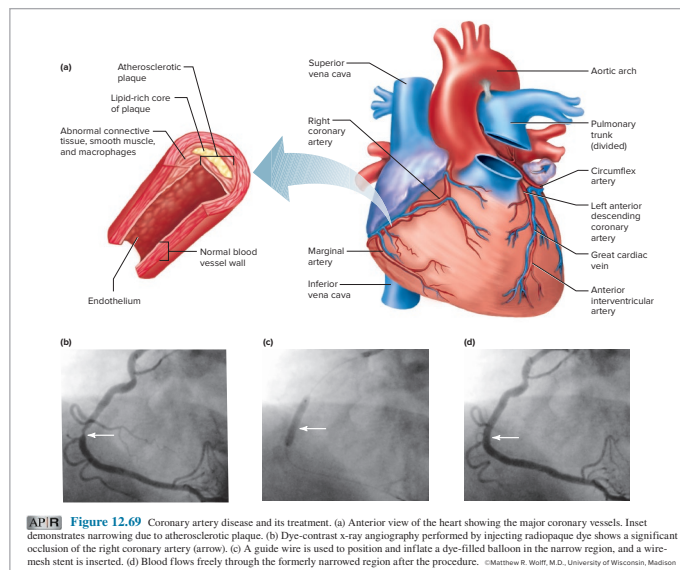
Color-coding is effectively used to promote learning. For example, there are specific colors for extracellular fluid, the intracellular fluid, muscle filaments, and transporter molecules.

Multilevel Perspective

Illustrations depicting complex structures or processes combine macroscopic and microscopic views to help students see the relationships between increasingly detailed drawings.

End of Section

At the end of sections throughout the book, you will find a summary, review questions, key terms, and clinical terms.



AP|R Figure 12.69 Coronary artery disease and its treatment. (a) Anterior view of the heart showing the major coronary vessels. Inset demonstrates narrowing due to atherosclerotic plaque. (b) Dye-contrast x-ray angiography performed by injecting radiopaque dye shows a significant occlusion of the right coronary artery (arrow). (c) A guide wire is used to position and inflate a dye-filled balloon in the narrow region, and a wire-mesh stent is inserted. (d) Blood flows freely through the formerly narrowed region after the procedure. © Matthew R. Wolff, M.D., University of Wisconsin, Madison

- | | | |
|---|--------------------------------------|-------------------------|
| 8. What is the oxygen status of arterial and venous blood in the systemic versus the pulmonary circulation? | nematopoietic growth factors (HGFs) | pulmonary trunk |
| 9. State the formula relating flow, pressure difference, and resistance. | hemoglobin | pulmonary veins |
| 10. What are the three determinants of resistance? | inferior vena cava | reticulocyte |
| 11. Which determinant of resistance is varied physiologically to alter blood flow? | intrinsic factor | serum |
| 12. How does variation in hematocrit influence the hemodynamics of blood flow? | leukocytes | superior vena cava |
| 13. Trace the path of a red blood cell through the entire circulatory system, naming all structures and vessel types it flows through, beginning and ending in a capillary of the left big toe. | lymphocytes | systemic circulation |
| | macrophages | transferrin |
| | megakaryocytes | veins |
| | microcirculation | ventricle |
| | monocytes | venules |
| | multipotent hematopoietic stem cells | vitamin B ₁₂ |

SECTION A KEY TERMS

blood	circulatory system
blood vessels	heart
cardiovascular system	vascular system

12.1 Components of the Circulatory System

albumin	bone marrow
aorta	bulk flow
arteries	capillaries
arterioles	defensins
atrium	eosinophils
basophils	erythrocytes
bilirubin	erythropoiesis

12.2 Pressure, Flow, and Resistance

hemodynamics	resistance (R)
hydrostatic pressure	viscosity
Poiseuille's law	

SECTION A CLINICAL TERMS

12.1 Components of the Circulatory System

anemia	malaria
hemochromatosis	pernicious anemia
iron deficiency	polycythemia
iron-deficiency anemia	sickle-cell disease

SECTION B

The Heart

12.3 Anatomy

The heart is a muscular organ enclosed in a protective fibrous sac, the **pericardium**, and located in the chest (Figure 12.9). A fibrous layer is also closely affixed to the heart and is called the

(a "mitre") has earned the left AV valve another commonly used name, **mitral valve**. The opening and closing of the AV valves are passive processes resulting from pressure differences across the valves. When the blood pressure in an atrium is greater than in the cor-

End of Chapter

At the end of the chapters, you will find

- Recall and Comprehend Questions that are designed to test student comprehension of key concepts.
- Apply, Analyze, and Evaluate Questions that challenge the student to go beyond the memorization of facts to solve problems and to encourage thinking about the meaning or broader significance of what has just been read.
- General Principles Assessment questions that test the student's ability to relate the material covered in a given chapter to one or more of the General Principles of Physiology described in Chapter 1. This provides a powerful unifying theme to understanding all of physiology and is also an excellent gauge of a student's progress from the beginning to the end of a semester.
- Answers to the Physiological Inquiries in that chapter.

CHAPTER 12 TEST QUESTIONS Recall and Comprehend

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Hematocrit is increased
 - a. when a person has a vitamin B₁₂ deficiency.
 - b. by an increase in secretion of erythropoietin.
 - c. when the number of white blood cells is increased.
 - d. by a hemorrhage.
 - e. in response to excess oxygen delivery to the kidneys.
2. The principal site of erythrocyte production is
 - a. the liver.
 - b. the kidneys.
 - c. the bone marrow.
 - d. the spleen.
 - e. the lymph nodes.
3. Which of the following contains blood with the lowest oxygen content?
 - a. aorta
 - b. left atrium
 - c. right ventricle
 - d. pulmonary veins
 - e. systemic arterioles
4. If other factors are equal, which of the following vessels would have the lowest resistance?
 - a. length = 1 cm, radius = 1 cm
 - b. length = 4 cm, radius = 1 cm
 - c. length = 8 cm, radius = 1 cm
 - d. length = 1 cm, radius = 2 cm
 - e. length = 0.5 cm, radius = 2 cm
5. Which of the following correctly ranks pressures during isovolumetric contraction of a normal cardiac cycle?
 - a. left ventricular > aortic > left atrial
 - b. aortic > left atrial > left ventricular
 - c. left atrial > aortic > left ventricular
 - d. aortic > left ventricular > left atrial
 - e. left ventricular > left atrial > aortic
6. Considered as a whole, the body's capillaries have
 - a. smaller cross-sectional area than the arteries.
 - b. less total blood flow than in the veins.
 - c. greater total resistance than the arterioles.
 - d. slower blood velocity than in the arteries.
 - e. greater total blood flow than in the arteries.
7. What is mainly responsible for the delay between the atrial and ventricular contractions?
 - a. the shallow slope of AV node pacemaker potentials
 - b. slow action potential conduction velocity of AV node cells
 - c. slow action potential conduction velocity along atrial muscle cell membranes
 - d. slow action potential conduction in the Purkinje network of the ventricles
 - e. greater parasympathetic nerve firing to the ventricles than to the atria
8. Which of the following pressures is closest to the mean arterial blood pressure in a person whose systolic blood pressure is 135 mmHg and pulse pressure is 50 mmHg?
 - a. 110 mmHg
 - b. 78 mmHg
 - c. 102 mmHg
 - d. 152 mmHg
 - e. 85 mmHg
9. Which of the following would help restore homeostasis in the first few moments after a person's mean arterial pressure became elevated?
 - a. a decrease in baroreceptor action potential frequency
 - b. a decrease in action potential frequency along parasympathetic neurons to the heart
 - c. an increase in action potential frequency along sympathetic neurons to the heart
 - d. a decrease in action potential frequency along sympathetic neurons to arterioles
 - e. an increase in total peripheral resistance
10. Which is false about L-type Ca²⁺ channels in cardiac ventricular muscle cells?
 - a. They are open during the plateau of the action potential.
 - b. They allow Ca²⁺ entry that triggers sarcoplasmic reticulum Ca²⁺ release.
 - c. They are found in the T-tubule membrane.
 - d. They open in response to depolarization of the membrane.
 - e. They contribute to the pacemaker potential.
11. Which correctly pairs an ECG phase with the cardiac event responsible?
 - a. P wave: depolarization of the ventricles
 - b. P wave: depolarization of the plateau of the action potential
 - c. QRS wave: depolarization of the ventricles
 - d. QRS wave: repolarization of the ventricles
 - e. T wave: repolarization of the atria

CHAPTER 12 TEST QUESTIONS Apply, Analyze, and Evaluate

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. A person is found to have a hematocrit of 35%. Can you conclude that there is a decreased volume of erythrocytes in the blood? Explain. *Hint:* See Figure 12.1 and remember the formula for hematocrit.
2. Which would cause a greater increase in resistance to flow, a doubling of blood viscosity or a halving of tube radius? *Hint:* See equation 12.2 in Section 12.2.

CHAPTER 12 TEST QUESTIONS General Principles Assessment

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. A general principle of physiology states that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes. How is this principle demonstrated by the relationship between the circulatory and endocrine systems?
2. The left AV valve has only two large leaflets, while the right AV valve has three smaller leaflets. It is a general principle of physiology that structure is a determinant of—and has coevolved with—function. Although it is unknown why the two valves differ in structure in this way, what difference in the functional demands of the left side of the heart might explain why there is one less valve leaflet than on the right side?
3. Two of the body's important fluid compartments are those of the interstitial fluid and plasma. How does the liver's production of plasma proteins interact with those compartments to illustrate the general principle of physiology, *Controlled exchange of materials occurs between compartments and across cellular membranes*?

CHAPTER 12 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 12.1 The hematocrit would be 33% because the red blood cell volume is the difference between total blood volume and plasma volume ($4.5 - 3.0 = 1.5$ L), and hematocrit is determined by the fraction of whole blood that is red blood cells ($1.5 / 4.5$ L = 0.33, or 33%).

Figure 12.6 The major change in blood flow would be an increase to certain abdominal organs, notably the stomach and small intestines. This change would provide the additional oxygen and nutrients required to meet the increased metabolic demands of digestion and absorption of the breakdown products of food. Blood flow to the brain and other organs would not be expected to change significantly, but there might be a small increase in blood flow to the skeletal muscles associated with chewing and swallowing. Consequently, the total blood flow in a resting person during and following a meal would be expected to increase.

Figure 12.8 No. The flow on side B would be doubled, but still less than that on side A. The summed wall area would be the same on both sides. The formula for circumference of a circle is $2\pi r$; so the wall circumference in side A would be $2 \times 3.14 \times 2 = 12.56$; for the two tubes on side B, it would be $(2 \times 3.14 \times 1) + (2 \times 3.14 \times 1) = 12.56$. However, the total cross section through which flow occurs would be larger in side A than in side B. The formula for cross-sectional area of a circle is πr^2 , so the area of side A would be $3.14 \times 2^2 = 12.56$, whereas the summed area of the tubes in side B would be $(3.14 \times 1^2) + (3.14 \times 1^2) = 6.28$. Thus, even with two outflow tubes on side B, there would be more flow through side A.

Figure 12.11 A: If this diagram included a systemic portal vessel, the order of structures in the lower box would be: aorta → arteries → arterioles →

ONLINE STUDY TOOLS



Test your recall, comprehension, and critical thinking skills with interactive questions about cardiovascular physiology assigned by your instructor. Also access McGraw-Hill LearnSmart™/SmartBook™ and Anatomy & Physiology REVEALED from your McGraw-Hill Connect® home page.



Do you have trouble accessing and retaining key concepts when reading a textbook? This personalized adaptive learning tool serves as a guide to your reading by helping you discover which aspects of cardiovascular physiology you have mastered, and which will require more attention.



A fascinating view inside real human bodies that also incorporates animations to help you understand cardiovascular physiology.

Updates and Additions

The 15th edition of Vander’s Human Physiology has been updated throughout to reflect the latest advances in our knowledge of physiological processes, including their cellular and molecular mechanisms. Each chapter has been carefully read for opportunities to improve clarity or flow, or to enhance artwork by editing existing art, improving the detail and sophistication of anatomical illustrations, or adding new art. As in previous editions, we have paid particular attention to the many different assessment tools that have been introduced into the text over several editions. In some cases, for example, new Physiological Inquiries have been added to key figures, and others have been modified to reflect feedback from users of the book. The previous edition included an overhaul of the digital content associated with the book. In this edition we have gone a step further with the addition of a new author who is fully vested in maintaining, updating, and introducing innovation to Connect, Learn Smart, and our other products in the digital realm. A brief overview of some key changes to chapters follows.

Chapter 1 A new figure has been added that demonstrates positive feedback, using blood clotting as a model. The section on adaptation and acclimatization has been expanded with examples.

Chapter 4 The concept of membrane potential is now expanded upon and treated in a new section called “Ion Movement and Membrane Potential.”

Chapter 5 Several Physiological Inquiries have been reworded for clarity and linked to relevant hints from prior readings in Chapter 3. Signaling and ligand/protein interactions are now better integrated with cross references throughout to key figures in Chapter 3. The treatment of specificity of signaling and receptor binding has been reworked for improved clarity. The mechanisms of cessation of cell signaling are more clearly explained with examples.

Chapter 6 Two new challenging and quantitative Physiological Inquiries have been added to two figures. A new section has been added on “lipid neurotransmitters” including a discussion of endocannabinoids.

Chapter 7 A new figure of cochlear hair cells has been added. A new figure illustrating tonotopic mapping of sound along the basilar membrane has been added. The depiction of the semicircular canals has been rendered for better 3D accuracy. A new Physiological Inquiry regarding the mechanisms by which NSAIDS block pain signals has been included. In the text, newly discovered itch receptors are discussed; the relationship between time indoors and the incidence of myopia is covered; and a new discussion about taste receptors found in the GI tract and respiratory epithelia and believed to be important in numerous reflexes such as coughing and sneezing has been added.

Chapter 8 Table 8.3 has been revised and updated. New ideas regarding the necessity for sleep have been incorporated. Statistics on ADHD have been updated, and the currently accepted term “Substance use disorder” has now been introduced and replaces “dependence.”

Chapter 9 Two new Physiological Inquiries, including one on a new term added to the text (calsequestrin), have been added to two figures. The presence of the protein nebulin in thin filaments is now mentioned. Muscle fiber types have been renamed to reflect current designations in human muscle (Types 1, 2A, and 2X). New research is cited regarding the mechanism by which spicy foods reduce muscle cramps. The description of depolarization block has been improved and updated.

Chapter 10 Discussion of golgi tendon organs has been updated and expanded. A description of the diseases amyotrophic lateral sclerosis and large fiber sensory neuropathy has been added.

Chapter 11 A new, full-page figure has been added to the beginning of the chapter, illustrating the location of major endocrine glands and other endocrine structures in humans. The hormones produced by these structures are named and a few key functions of each are given.

Chapter 12 Several figures have been redrawn to more accurately represent the functional anatomy of the heart and the effect of vasodilation on arteriolar and capillary pressures. The function of venules and veins in circulatory control has been updated. The tables describing the drugs to treat chronic hypertension and chronic heart failure have been updated.

Chapter 13 The chapter has been reorganized to better describe lung mechanics and alveolar ventilation. A new figure has been added to explain the effects of anemia and carbon monoxide poisoning on the transport of oxygen in the blood. Information has been added about the effects of shunt and of opiate overdose on the development of hypoxia.

Chapter 14 A new figure has been added to better show the functional anatomy of the bladder during micturition. A new figure has been added that explains the mechanisms of sodium and chloride reabsorption in the ascending limb of the loop of Henle via the Na-K-2Cl (NKCC) cotransporter.

Chapter 15 The chapter has been thoroughly reorganized such that following an overview of the digestive system, all of the functions of each segment along the alimentary canal are described in order. In addition, two new figures have been added, one on the hepatic portal system and another early in the chapter describing the ingested forms of macromolecules and the enzymes involved in their digestion.

Chapter 16 The regulation of body temperature is now treated in its own new section, with a new subsection called General

Principles of Thermoregulation. Lipoproteins are now described in detailed and distinguished from each other with additional text and a new figure showing their structures. A discussion of exercise-associated thermogenesis (EAT) and nonexercise activity thermogenesis (NEAT) has now been added to the section on energy balance. The terms *hunger*, *appetite*, and *satiety* are now defined and distinguished. Finally, the limitations of using BMI as an indicator of obesity and adiposity have been better elucidated.

Chapter 17 The chapter has been reorganized with a new section on pregnancy, contraception, infertility, and hormonal changes through life. New information has been added about epigenetic programming and ovary-determining genes. A new section and table has been added to compare and contrast male and female hormonal changes through life. The section on contraception and infertility has been updated.

Chapter 19 This chapter has been updated with treatment of thyrotoxicosis and the use of glucocorticoid therapy in septic shock.

McGraw-Hill Connect® is a highly reliable, easy-to-use homework and learning management solution that utilizes learning science and award-winning adaptive tools to improve student results.

Homework and Adaptive Learning

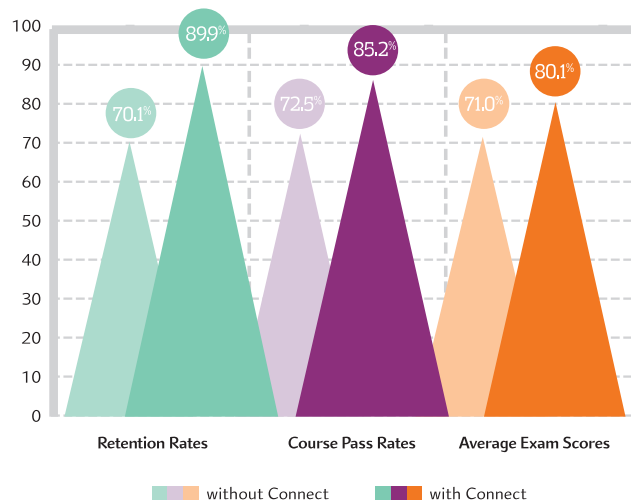
- Connect's assignments help students contextualize what they've learned through application, so they can better understand the material and think critically.
- Connect will create a personalized study path customized to individual student needs through SmartBook®.
- SmartBook helps students study more efficiently by delivering an interactive reading experience through adaptive highlighting and review.

Over 7 billion questions have been answered, making McGraw-Hill Education products more intelligent, reliable, and precise.

Quality Content and Learning Resources

- Connect content is authored by the world's best subject matter experts, and is available to your class through a simple and intuitive interface.
- The Connect eBook makes it easy for students to access their reading material on smartphones and tablets. They can study on the go and don't need internet access to use the eBook as a reference, with full functionality.
- Multimedia content such as videos, simulations, and games drive student engagement and critical thinking skills.

Connect's Impact on Retention Rates, Pass Rates, and Average Exam Scores



Using **Connect** improves retention rates by **19.8%**, passing rates by **12.7%**, and exam scores by **9.1%**.

73% of instructors who use **Connect** require it; instructor satisfaction increases by 28% when **Connect** is required.

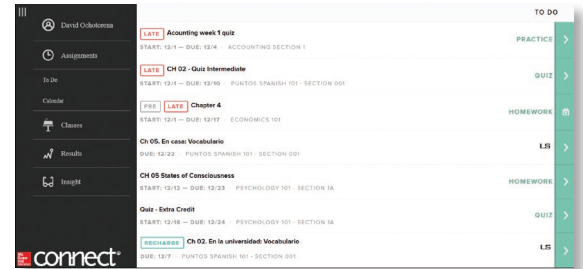


Robust Analytics and Reporting

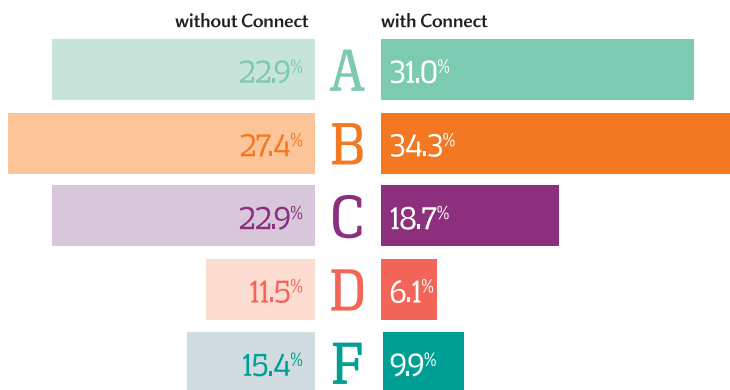
- Connect Insight® generates easy-to-read reports on individual students, the class as a whole, and on specific assignments.
- The Connect Insight dashboard delivers data on performance, study behavior, and effort. Instructors can quickly identify students who struggle and focus on material that the class has yet to master.
- Connect automatically grades assignments and quizzes, providing easy-to-read reports on individual and class performance.



©Hero Images/Getty Images



Impact on Final Course Grade Distribution



More students earn **As** and **Bs** when they use McGraw-Hill Education **Connect**.

Trusted Service and Support

- Connect integrates with your LMS to provide single sign-on and automatic syncing of grades. Integration with Blackboard®, D2L®, and Canvas also provides automatic syncing of the course calendar and assignment-level linking.
- Connect offers comprehensive service, support, and training throughout every phase of your implementation.
- If you're looking for some guidance on how to use Connect, or want to learn tips and tricks from super users, you can find tutorials as you work. Our Digital Faculty Consultants and Student Ambassadors offer insight into how to achieve the results you want with Connect.

50% of the country's students are not ready for A&P

LearnSmart® Prep can help!

Improve preparation for the course and increase student success with the only adaptive Prep tool available for students today. Areas of individual weaknesses are identified in order to help students improve their understanding of core course areas needed to succeed.

LEARNSMART®
Prep for A&P

Students seek lab time that fits their busy schedules. Anatomy & Physiology REVEALED 3.2, our Virtual Dissection tool, allows students to practice anytime, anywhere, and now features enhanced physiology interactives with clinical and 3D animations.

Anatomy & Physiology | **REVEALED®**
3.2
Virtual dissection

Bringing to life complex processes is a challenge. Ph.I.L.S. 4.0 is the perfect way to reinforce key physiology concepts with powerful lab experiments. Tools like physiology interactives, Ph.I.L.S., and world-class animations make it easier than ever.

Ph.I.L.S.
Physiology supplements

The Practice Atlas for Anatomy & Physiology is a new interactive tool that pairs images of common anatomical models with stunning cadaver photography. This atlas allows students to practice naming structures on both models and human bodies, anytime and anywhere.

*Practice Atlas for
Anatomy & Physiology*

Since 2009, our adaptive programs in A&P have hosted 1 million unique users who have answered more than 1 billion questions/probes, providing the only data-driven solutions to help students get from their first college-level course to program readiness.

Acknowledgments

In this fifteenth edition of *Vander's Human Physiology*, we are very excited to have been able to use real student data points derived from thousands of users to help guide our revision path. We are also deeply thankful to the following individuals for their contributions to the fifteenth edition. Any errors that may remain are solely the responsibility of the authors.

Mark Alston,
University of Tennessee Knoxville

Brian Antonsen,
Marshall University

Jeffery Betts,
Central Michigan University

Patrick Cafferty,
Emory University

Jennifer Carr,
Harvard University Cambridge

Colin Carriker,
High Point University

Pat Clark,
IUPUI Indianapolis

Robert Fettiplace,
University of Wisconsin-Madison

Paul Goldspink,
Medical College of Wisconsin

Andrew Greene,
Medical College of Wisconsin

Suzanna Lesko Gribble,
University of Pittsburgh

Michael T. Griffin,
Angelo State University

Michael Guralnick,
Medical College of Wisconsin

Lisa Harrison-Bernard,
Louisiana State University School of Medicine

Lois Heller,
University of Minnesota - Duluth

Albert Herrera,
University of Southern California

Cecilia Hillard,
Medical College of Wisconsin

Grace Lee,
University of Wisconsin-Madison

Andrew Lokuta,
University of Wisconsin-Madison

Julian Lombard,
Medical College of Wisconsin

Steven Magill,
Medical College of Wisconsin

David Mattson,
Medical College of Wisconsin

Leanne May,
Rose State College

Monica McCullough,
Western Michigan University Kalamazoo

T. Richard Nichols,
Georgia Tech

Sandra Pfister,
Medical College of Wisconsin

John Pooler,
Emory University

Laurel Roberts,
University of Pittsburg

Jennifer Rogers,
University of Iowa- Iowa City

Virginia Shea,
University of North Carolina School of Medicine

Roy Silverstein,
Medical College of Wisconsin

Robert Stark,
California State University Bakersfield

Curt Walker,
Dixie State University

The authors are indebted to the many individuals who assisted with the numerous digital and ancillary products associated with this text. Thank you to Beth Altschaf, Jacques Hill, Kip McGilliard, Linda Ogren, and Jennifer Rogers.

The authors are also indebted to the editors and staff at McGraw-Hill Education who contributed to the development and publication of this text, particularly Lead Product Developer Fran Simon and Product Developer Michelle Gaseor, Brand Managers Amy Reed and Mike Ivanov, Marketing Manager Jim Connely, Core Project Manager Ann Courtney, Assessment Content Project Manager Amber Bettcher, Buyer Sandy Ludovissy, Designer Matt Backhaus, and Content Licensing Specialist Lori Hancock. We also thank freelance copy editor Julie A. Kennedy. As always, we are grateful to the many students and faculty who have provided us with critiques and suggestions for improvement.

Eric P. Widmaier
Hershel Raff
Kevin T. Strang
Todd S. Shoen

Homeostasis:

A Framework for Human Physiology

CHAPTER

1

1.1 The Scope of Human Physiology

1.2 How Is the Body Organized?

Muscle Cells and Tissue

Neurons and Nervous Tissue

Epithelial Cells and Epithelial Tissue

Connective-Tissue Cells and Connective Tissue

Organs and Organ Systems

1.3 Body Fluid Compartments

1.4 Homeostasis: A Defining Feature of Physiology

1.5 General Characteristics of Homeostatic Control Systems

Feedback Systems

Resetting of Set Points

Feedforward Regulation

1.6 Components of Homeostatic Control Systems

Reflexes

Local Homeostatic Responses

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

1.8 Processes Related to Homeostasis

Adaptation and Acclimatization

Biological Rhythms

Balance of Chemical Substances in the Body

1.9 General Principles of Physiology

Chapter 1 Clinical Case Study



Coping with changes in external temperature and oxygen levels even in extreme conditions are examples of homeostasis. ©Andre Schoenherr/Stone/Getty Images

The purpose of this chapter is to provide an orientation to the subject of human physiology and the central role of homeostasis in the study of this science. The mountain climbers shown here and on the cover of the textbook are experiencing numerous challenges that must be met by their hearts, lungs, and other organs. An understanding of the functions of these and other organs of the body also requires knowledge of the structures and relationships of the body parts. For this reason, this chapter also introduces the way the body is organized into cells, tissues, organs, organ systems, and fluid compartments. Lastly, several “General Principles of Physiology” are introduced. These serve as unifying themes throughout the textbook, and the reader is encouraged to return to them often to see how they apply to the material covered in subsequent chapters. ■

1.1 The Scope of Human Physiology

Physiology is the study of how living organisms function. At one end of the spectrum, it includes the study of individual molecules—for example, how a particular protein’s shape and electrical charge, if any, allow it to function as a channel for ions to move into or out of a cell. At the other end, it is concerned with complex processes that depend on the integrated functions of many organs in the body—for example, how the heart, kidneys, and several glands all function together to cause the excretion of more sodium ions in the urine when a person has eaten salty food.

Physiologists are interested in function and integration—how parts of the body work together at various levels of organization and, most importantly, in the entire organism. Even when physiologists study parts of organisms, all the way down to individual molecules, the intention is ultimately to apply the information they gain to understanding the function of the whole body. As the nineteenth-century physiologist Claude Bernard put it, “After carrying out an analysis of phenomena, we must . . . always reconstruct our physiological synthesis, so as to see the *joint action* of all the parts we have isolated. . . .”

Finally, in many areas of this text, we will relate physiology to human health. Some disease states can be viewed as physiology “gone wrong,” or **pathophysiology**, which makes an understanding of physiology essential for the study and practice of medicine. Indeed, many physiologists are actively engaged in research on the physiological bases of a wide range of diseases. In this text, we will give many examples of the basic physiology that underlies disease. A handy index of all the diseases and medical conditions discussed in this text, and their causes and treatments, appears in Appendix B.

We turn first to an overview of the anatomical organization of the human body, including the ways in which the cells of the body are organized into higher levels of structure. As we will see throughout the text, the structures of objects—such as the heart, lungs, or kidneys—determine in large part their functions.

1.2 How Is the Body Organized?

The simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life are called **cells** (Figure 1.1). Each human being begins as a single cell, a fertilized egg, which divides to create two cells, each of which divides in turn to result in four cells, and so on. If cell multiplication were the only event occurring, the end result would be a spherical mass of identical cells. During development, however, each cell becomes specialized for the performance of a particular function, such as producing force and movement or generating electrical signals. The process of transforming an unspecialized cell into a specialized cell is known as **cell differentiation**, the study of which is one of the most exciting areas in biology today. About 200 distinct kinds of cells can be identified in the body in terms of differences in structure and function. When cells are classified according to the broad types of function they perform, however,

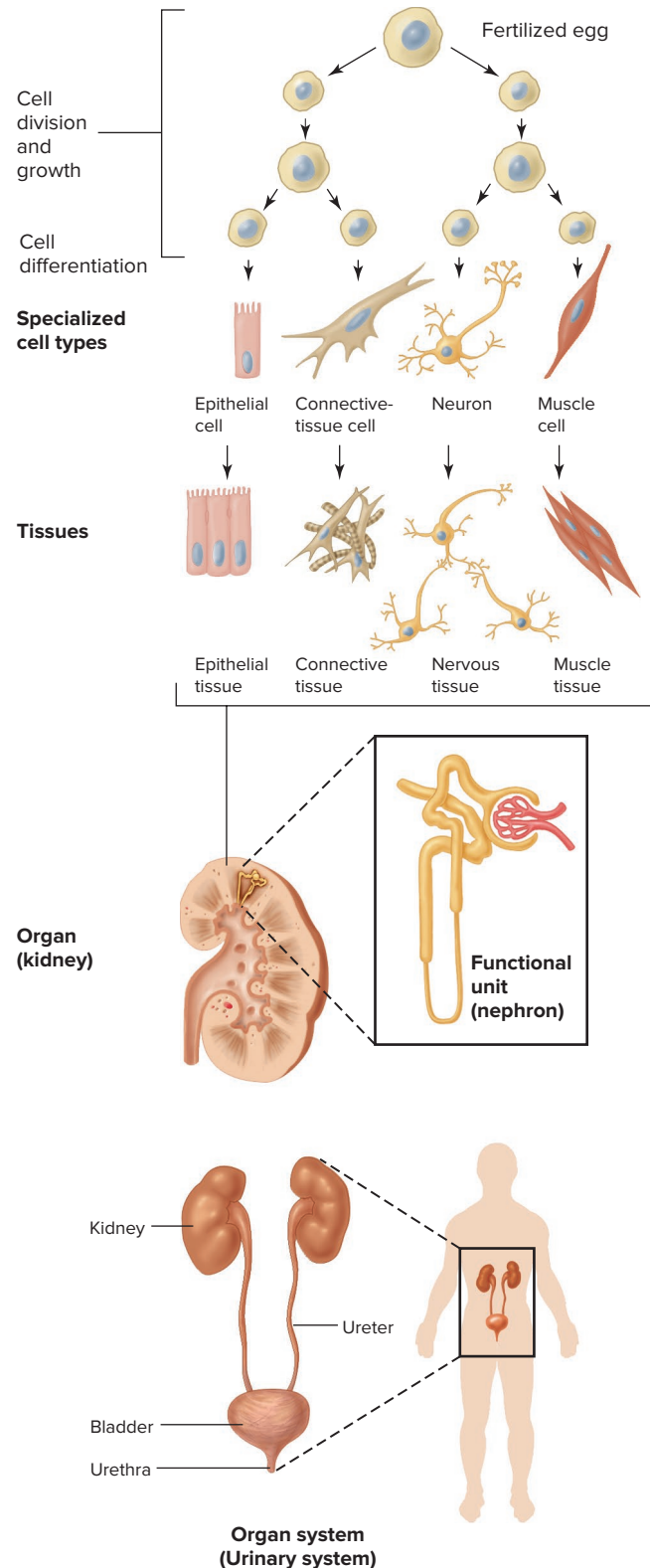


Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

four major categories emerge: (1) muscle cells, (2) neurons, (3) epithelial cells, and (4) connective-tissue cells. In each of these functional categories, several cell types perform variations of the specialized function. For example, there are three types of

muscle cells—skeletal, cardiac, and smooth. These cells differ from each other in shape, in the mechanisms controlling their contractile activity, and in their location in the various organs of the body, but each of them is a muscle cell.

In addition to differentiating, cells migrate to new locations during development and form selective adhesions with other cells to produce multicellular structures. In this manner, the cells of the body arrange themselves in various combinations to form a hierarchy of organized structures. Differentiated cells with similar properties aggregate to form **tissues**. Corresponding to the four general categories of differentiated cells, there are four general types of tissues: (1) **muscle tissue**, (2) **nervous tissue**, (3) **epithelial tissue**, and (4) **connective tissue**. The term *tissue* is used in different ways. It is formally defined as an aggregate of a single type of specialized cell. However, it is also commonly used to denote the general cellular fabric of any organ or structure—for example, kidney tissue or lung tissue, each of which in fact usually contains all four types of tissue.

One type of tissue combines with other types of tissues to form **organs**, such as the heart, lungs, and kidneys. Organs, in turn, work together as **organ systems**, such as the urinary system (see Figure 1.1). We turn now to a brief discussion of each of the four general types of cells and tissues that make up the organs of the human body.

Muscle Cells and Tissue

As noted earlier, there are three types of muscle cells. These cells form skeletal, cardiac, or smooth muscle tissue. All **muscle cells** are specialized to generate mechanical force. Skeletal muscle cells are attached through other structures to bones and produce movements of the limbs or trunk. They are also attached to skin, such as the muscles producing facial expressions. Contraction of skeletal muscle is under voluntary control, which simply means that you can choose to contract a skeletal muscle whenever you wish. Cardiac muscle cells are found only in the heart. When cardiac muscle cells generate force, the heart contracts and consequently pumps blood into the circulation. Smooth muscle cells make up part of the walls of many of the tubes in the body—blood vessels, for example, or the tubes of the gastrointestinal tract—and their contraction decreases the diameter or shortens the length of these tubes. For example, contraction of smooth muscle cells along the esophagus—the tube leading from the pharynx to the stomach—helps “squeeze” swallowed food down to the stomach. Cardiac and smooth muscle tissues are said to be “involuntary” muscle, because you cannot consciously alter the activity of these types of muscle. You will learn about the structure and function of each of the three types of muscle cells in Chapter 9.

Neurons and Nervous Tissue

A **neuron** is a cell of the nervous system that is specialized to initiate, integrate, and conduct electrical signals to other cells, sometimes over long distances. A signal may initiate new electrical signals in other neurons, or it may stimulate a gland cell to secrete substances or a muscle cell to contract. Thus, neurons provide a major means of controlling the activities of other cells. The incredible complexity of connections between neurons underlies such phenomena as consciousness and perception. A collection of neurons forms nervous tissue, such as that of the

brain or spinal cord. In some parts of the body, cellular extensions from many neurons are packaged together along with connective tissue (described shortly); these neuron extensions form a **nerve**, which carries the signals from many neurons between the nervous system and other parts of the body. Neurons, nervous tissue, and the nervous system will be covered in Chapter 6.

Epithelial Cells and Epithelial Tissue

Epithelial cells are specialized for the selective secretion and absorption of ions and organic molecules, and for protection. These cells are characterized and named according to their unique shapes, including cuboidal (cube-shaped), columnar (elongated), squamous (flattened), and ciliated. Epithelial tissue (known as an **epithelium**) may form from any type of epithelial cell. Epithelia may be arranged in single-cell-thick tissue, called a simple epithelium, or a thicker tissue consisting of numerous layers of cells, called a stratified epithelium. The type of epithelium that forms in a given region of the body reflects the function of that particular epithelium. For example, the epithelium that lines the inner surface of the main airway, the trachea, consists of ciliated epithelial cells (see Chapter 13). The beating of these cilia helps propel mucus up the trachea and into the mouth, which aids in preventing airborne particles and pollutants from reaching the sensitive lung tissue.

Epithelia are located at the surfaces that cover the body or individual organs, and they line the inner surfaces of the tubular and hollow structures within the body, such as the trachea just mentioned. Epithelial cells rest on an extracellular protein layer called the **basement membrane**, which (among other functions) anchors the tissue (**Figure 1.2**). The side of the cell anchored to the basement membrane is called the basolateral side; the opposite side, which typically faces the interior (called the lumen) of a structure such as the trachea or the tubules of the kidneys, is called the apical

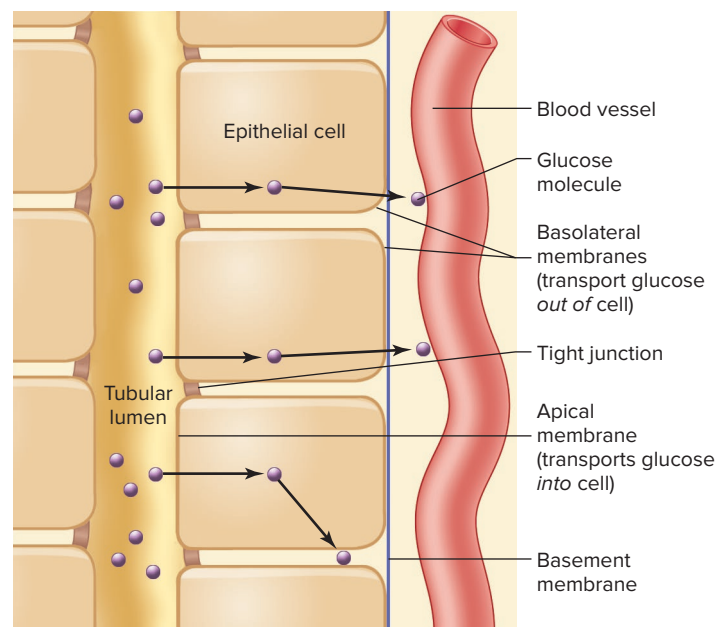


Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into the cell, and then directed out of the cell.

side. A defining feature of many epithelia is that the two sides of all the epithelial cells in the tissue may perform different physiological functions. In addition, the cells are held together along their lateral surfaces between the apical and basolateral membranes by extracellular barriers called tight junctions (look ahead to Figure 3.9, b and c, for a depiction of tight junctions). Tight junctions function as selective barriers regulating the exchange of molecules. For example, as shown in Figure 1.2 for the kidney tubules, the apical membranes transport useful solutes such as the sugar glucose from the tubule lumen into the epithelial cell; the basolateral sides of the cells transport glucose out of the cell and into the surrounding fluid where it can reach the bloodstream. The tight junctions prevent glucose from leaking “backward.”

Connective-Tissue Cells and Connective Tissue

Connective-tissue cells, as their name implies, connect, anchor, and support the structures of the body. Some connective-tissue cells are found in the loose meshwork of cells and fibers underlying most epithelial layers; this is called loose connective tissue. Another type called dense connective tissue includes the tough, rigid tissue that makes up tendons and ligaments. Other types of connective tissue include bone, cartilage, and adipose (fat-storing) tissue. Finally, blood is a type of fluid connective tissue. This is because the cells in the blood have the same embryonic origin as other connective tissue, and because the blood connects the various organs and tissues of the body through the delivery of nutrients, removal of wastes, and transport of chemical signals from one part of the body to another.

An important function of some connective tissue is to form the **extracellular matrix** (ECM) around cells. The ECM consists of a mixture of proteins; polysaccharides (chains of sugar molecules); and, in some cases, minerals, specific for any given tissue. The ECM serves two general functions: (1) It provides a scaffold for cellular attachments; and (2) it transmits information in the form of chemical messengers to the cells to help regulate their activity, migration, growth, and differentiation.

Some of the proteins of the ECM are known as **fibers**, insoluble proteins including ropelike **collagen fibers** and rubberband-like **elastin fibers**. Others are a mixture of nonfibrous proteins that contain carbohydrate. In some ways, the ECM is analogous to reinforced concrete. The fibers of the matrix, particularly collagen, which constitutes as much as one-third of all bodily proteins, are like the reinforcing iron mesh or rods in the concrete. The carbohydrate-containing protein molecules are analogous to the surrounding cement. However, these latter molecules are not merely inert packing material, as in concrete, but function as adhesion or recognition molecules between cells. Thus, they are links in the communication between extracellular messenger molecules and cells.

Organs and Organ Systems

Organs are composed of two or more of the four kinds of tissues arranged in various proportions and patterns, such as sheets, tubes, layers, bundles, and strips. For example, the kidneys consist of (1) a series of small tubes, each composed of a simple epithelium; (2) blood vessels, whose walls contain varying quantities of smooth muscle and connective tissue; (3) extensions from neurons that end near the muscle and epithelial cells; and (4) a loose network of connective-tissue elements that are interspersed

throughout the kidneys and include the protective capsule that surrounds the organ.

Many organs are organized into small, similar subunits often referred to as **functional units**, each performing the function of the organ. For example, the functional unit of the kidney, the nephron, contains the small tubes mentioned in the previous paragraph. The total production of urine by the kidneys is the sum of the amounts produced by the 2 million or so individual nephrons.

Finally, we have the organ system, a collection of organs that together perform an overall function (see Figure 1.1). For example, the urinary system consists of the kidneys; the urinary bladder; the ureters, the tubes leading from the kidneys to the bladder; and the urethra, the tube leading from the bladder to the exterior. **Table 1.1** lists the components and functions of the organ systems in the body. It is important to recognize, however, that organ systems do not function “in a vacuum.” That is, they function together to maintain a healthy body. As just one example, blood pressure is controlled by the circulatory, urinary, nervous, and endocrine systems working together.

1.3 Body Fluid Compartments

Another useful way to think about how the body is organized is to consider body fluid compartments. When we refer to “body fluid,” we are referring to a watery solution of dissolved substances such as oxygen, nutrients, and wastes. This solution is present within and around all cells of the body, and within blood vessels, and is known as the **internal environment**. Body fluids exist in two major compartments, intracellular fluid and extracellular fluid. **Intracellular fluid** is the fluid contained within all the cells of the body and accounts for about 67% of all the fluid in the body. Collectively, the fluid present in the blood and in the spaces surrounding cells is called **extracellular fluid**, that is, all the fluid that is outside of cells. Of this, only about 20%–25% is in the fluid portion of blood, which is called the **plasma**, in which the various blood cells are suspended. The remaining 75%–80% of the extracellular fluid, which lies around and between cells, is known as the **interstitial fluid**. The space containing interstitial fluid is called the **interstitium**. Therefore, the total volume of extracellular fluid is the sum of the plasma and interstitial fluid volumes. **Figure 1.3** summarizes the relative volumes of water in the different fluid compartments of the body. Water accounts for about 55%–60% of body weight in an adult.

As the blood flows through the smallest of blood vessels in all parts of the body, the plasma exchanges oxygen, nutrients, wastes, and other substances with the interstitial fluid. Because of these exchanges, concentrations of dissolved substances are virtually identical in the plasma and interstitial fluid, except for protein concentration (which, as you will learn in Chapter 12, remains higher in plasma than in interstitial fluid). With this major exception, the entire extracellular fluid may be considered to have a homogeneous solute composition. In contrast, the composition of the extracellular fluid is very different from that of the intracellular fluid. Maintaining differences in fluid composition across the cell membrane is an important way in which cells regulate their own activity. For example, intracellular fluid contains many different proteins that are important in regulating cellular events such as growth and metabolism. These proteins must be

TABLE 1.1**Organ Systems of the Body**

System	Major Organs or Tissues	Primary Functions
Circulatory	Heart, blood vessels, blood	Transport of blood throughout the body
Digestive	Mouth, salivary glands, pharynx, esophagus, stomach, small and large intestines, anus, pancreas, liver, gallbladder	Digestion and absorption of nutrients and water; elimination of wastes
Endocrine	All glands or organs secreting hormones: pancreas, testes, ovaries, hypothalamus, kidneys, pituitary, thyroid, parathyroids, adrenals, stomach, small intestine, liver, adipose tissue, heart, and pineal gland; and endocrine cells in other organs	Regulation and coordination of many activities in the body, including growth, metabolism, reproduction, blood pressure, water and electrolyte balance, and others
Immune	White blood cells and their organs of production	Defense against pathogens
Integumentary	Skin	Protection against injury and dehydration; defense against pathogens; regulation of body temperature
Lymphatic	Lymph vessels, lymph nodes	Collection of extracellular fluid for return to blood; participation in immune defenses; absorption of fats from digestive system
Musculoskeletal	Cartilage, bone, ligaments, tendons, joints, skeletal muscle	Support, protection, and movement of the body; production of blood cells
Nervous	Brain, spinal cord, peripheral nerves and ganglia, sense organs	Regulation and coordination of many activities in the body; detection of and response to changes in the internal and external environments; states of consciousness; learning; memory; emotion; others
Reproductive	Male: testes, penis, and associated ducts and glands Female: ovaries, fallopian tubes, uterus, vagina, mammary glands	Male: production of sperm; transfer of sperm to female Female: production of eggs; provision of a nutritive environment for the developing embryo and fetus; nutrition of the infant
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs	Exchange of carbon dioxide and oxygen; regulation of hydrogen ion concentration in the body fluids
Urinary	Kidneys, ureters, bladder, urethra	Regulation of plasma composition through controlled excretion of ions, water, and organic wastes

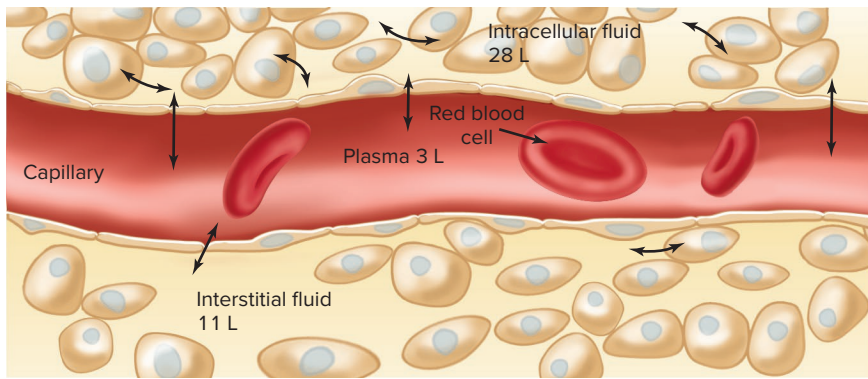
retained within the intracellular fluid and are not required in the extracellular fluid.

Compartmentalization is an important feature of physiology and is achieved by barriers between the compartments. The properties of the barriers determine which substances can move between compartments. These movements, in turn, account for the differences in composition of the different compartments. In the case of the body fluid compartments, plasma membranes that surround each cell separate the intracellular fluid from the extracellular fluid. Chapters 3 and 4 describe the properties of plasma membranes and how they account for the profound differences between intracellular and extracellular fluid. In contrast, the two components of extracellular fluid—the interstitial fluid and the plasma—are separated from each other by the walls of the blood vessels. Chapter 12 discusses how this barrier normally keeps most of the extracellular fluid in the interstitial compartment and restricts proteins mainly to the plasma.

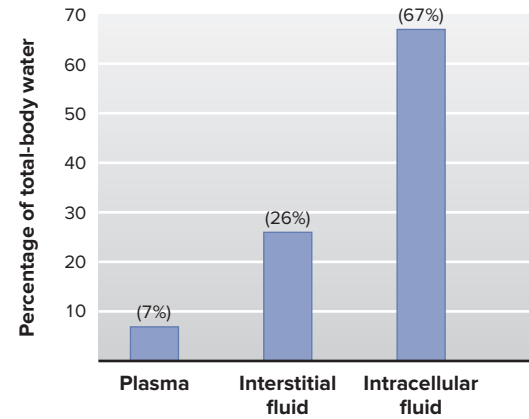
With this understanding of the structural organization of the body, we turn to a description of how balance is maintained in the internal environment of the body.

1.4 Homeostasis: A Defining Feature of Physiology

From the earliest days of physiology—at least as early as the time of Aristotle—physicians recognized that good health was somehow associated with a balance among the multiple life-sustaining forces (“humours”) in the body. It would take millennia, however, for scientists to determine what it was that was being balanced and how this balance was achieved. The advent of modern tools of science, including the ordinary microscope, led to the discovery that the human body is composed of trillions of cells, each of which can permit movement of certain substances—but not others—across the cell membrane. Over the course of the nineteenth and twentieth centuries, it became clear that most cells are in contact with the interstitial fluid. The interstitial fluid, in turn, was found to be in a state of flux, with water and solutes such as ions and gases moving back and forth through it between the cell interiors and the blood in nearby capillaries (see Figure 1.3a).



(a)



(b)

Figure 1.3 Fluid compartments of the body. Volumes are for a typical 70-kilogram (kg) (154-pound) person. (a) The bidirectional arrows indicate that fluid can move between any two adjacent compartments. Total-body water is about 42 liters (L), which makes up about 55%–60% of body weight. (b) The approximate percentage of total-body water normally found in each compartment.

PHYSIOLOGICAL INQUIRY

- What fraction of total-body water is extracellular? Assume that water constitutes 60% of a person's body weight. What fraction of a person's body weight is due to extracellular body water?

Answer can be found at end of chapter.

It was further determined by careful observation that most of the common physiological variables found in healthy organisms such as humans—blood pressure; body temperature; and blood-borne factors such as oxygen, glucose, and sodium ions, for example—are maintained within a predictable range. This is true despite external environmental conditions that may be far from constant. Thus was born the idea, first put forth by Claude Bernard, of a constant internal environment that is a prerequisite for good health, a concept later refined by the American physiologist Walter Cannon, who coined the term *homeostasis*.

Originally, **homeostasis** was defined as a state of reasonably stable balance between physiological variables such as those just described. However, this simple definition cannot give one a complete appreciation of what homeostasis entails. There probably is no such thing as a physiological variable that is constant over long periods of time. In fact, some variables undergo fairly dramatic swings around an average value during the course of a day, yet are still considered to be in balance. That is because homeostasis is a *dynamic*, not a static, process.

Consider swings in the concentration of glucose in the blood over the course of a day (**Figure 1.4**). After a typical meal, carbohydrates in food are broken down in the intestines into glucose molecules, which are then absorbed across the intestinal epithelium and released into the blood. As a consequence, the blood glucose concentration increases considerably within a short time after eating. Clearly, such a large change in the blood concentration of glucose is not consistent with the idea of a stable or static internal environment. What is important is that once the concentration of glucose in the blood increases, compensatory mechanisms restore it toward the concentration it was before the meal. These homeostatic compensatory mechanisms do not, however, overshoot to any significant degree in the opposite direction. That is, the blood glucose usually does not decrease below the premeal

concentration, or does so only slightly. In the case of glucose, the endocrine system is primarily responsible for this adjustment, but a wide variety of control systems may be initiated to regulate other homeostatic processes. In later chapters, we will see how every organ of the human body contributes to homeostasis, sometimes in multiple ways, and usually in concert with each other.

Homeostasis, therefore, does not imply that a given physiological function or variable is rigidly constant with respect to time but that it fluctuates within a predictable and often narrow range. When disturbed above or below the normal range, it is restored to normal.

What do we mean when we say that something varies within a normal range? This depends on just what we are monitoring. If the oxygen and carbon dioxide levels in the arterial blood of a healthy person are measured, they barely change over the course of time, even if the person exercises. Such a system is said to be

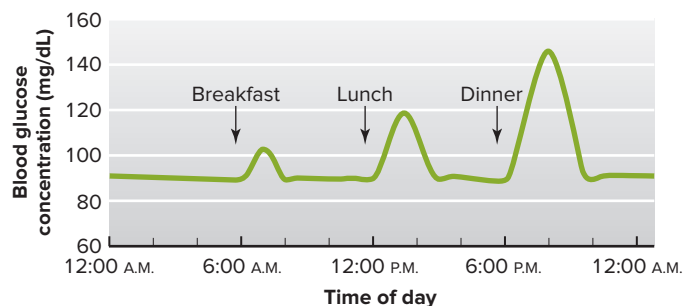


Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood glucose, even though concentrations of this sugar vary considerably throughout the day.

tightly controlled and to demonstrate very little variability or scatter around an average value. Blood glucose concentrations, as we have seen, may vary considerably over the course of a day. Yet, if the daily average glucose concentration was determined in the same person on many consecutive days, it would be much more predictable over days or even years than random, individual measurements of glucose over the course of a single day. In other words, there may be considerable variation in glucose values over short time periods, but less when they are averaged over long periods of time. This has led to the concept that homeostasis is a state of **dynamic constancy**. In such a state, a given variable like blood glucose may vary in the short term but is stable and predictable when averaged over the long term.

It is also important to realize that a person may be homeostatic for one variable but not homeostatic for another. Homeostasis must be described differently, therefore, for each variable. For example, as long as the concentration of sodium ions in the blood remains within its normal range, Na^+ homeostasis exists. However, a person whose Na^+ concentration is homeostatic may suffer from other disturbances, such as an abnormally low pH in the blood resulting from kidney disease, a condition that could be fatal. Just one nonhomeostatic variable, among the many that can be described, can have life-threatening consequences. Often, when one variable becomes significantly out of balance, other variables in the body become nonhomeostatic as a consequence. For example, when you exercise strenuously and begin to get warm, you perspire, which helps maintain body temperature homeostasis. This is important, because many cells (notably neurons) malfunction at elevated temperatures. However, the water that is lost in perspiration creates a situation in which total-body water is no longer in balance. In general, if all the major organ systems are operating in a homeostatic manner, a person is in good health. Certain kinds of disease, in fact, can be defined as the loss of homeostasis in one or more systems in the body. To elaborate on our earlier definition of *physiology*, therefore, when homeostasis is maintained, we refer to physiology; when it is not, we refer to pathophysiology (from the Greek *pathos*, meaning “suffering” or “disease”).

1.5 General Characteristics of Homeostatic Control Systems

The activities of cells, tissues, and organs must be regulated and integrated with each other so that any change in the extracellular fluid initiates a reaction to correct the change. The compensating mechanisms that mediate such responses are performed by **homeostatic control systems**.

Consider again an example of the regulation of body temperature. This time, our subject is a resting, lightly clad man in a room having a temperature of 20°C and moderate humidity. His internal body temperature is 37°C , and he is losing heat to the external environment because it is at a lower temperature. However, the chemical reactions occurring within the cells of his body are producing heat at a rate equal to the rate of heat loss. Under these conditions, the body undergoes no *net* gain or loss of heat, and the body temperature remains constant. The system is in a **steady state**, defined as a system in which a particular variable—temperature, in this case—is not changing but in which energy—in this case, heat—must be

added continuously to maintain a stable, homeostatic condition. (Steady state differs from **equilibrium**, in which a particular variable is not changing but no input of energy is required to maintain the constancy.) The steady-state temperature in our example is known as the **set point** of the thermoregulatory system.

This example illustrates a crucial generalization about homeostasis. Stability of an internal environmental variable is achieved by the balancing of inputs and outputs. In the previous example, the variable (body temperature) remains constant because metabolic heat production (input) equals heat loss from the body (output).

Now imagine that we rapidly decrease the temperature of the room, say to 5°C , and keep it there. This immediately increases the loss of heat from our subject’s warm skin, upsetting the balance between heat gain and loss. The body temperature therefore starts to decrease. Very rapidly, however, a variety of homeostatic responses occur to limit the decrease. **Figure 1.5** summarizes these responses. *The reader is urged to study Figure 1.5 and its legend carefully because the figure is typical of those used throughout the remainder of the book to illustrate homeostatic systems, and the legend emphasizes several conventions common to such figures.*

The first homeostatic response is that blood vessels to the skin become constricted (narrowed), reducing the amount of blood flowing through the skin. This decreases heat loss from the warm blood across the skin and out to the environment and helps maintain body

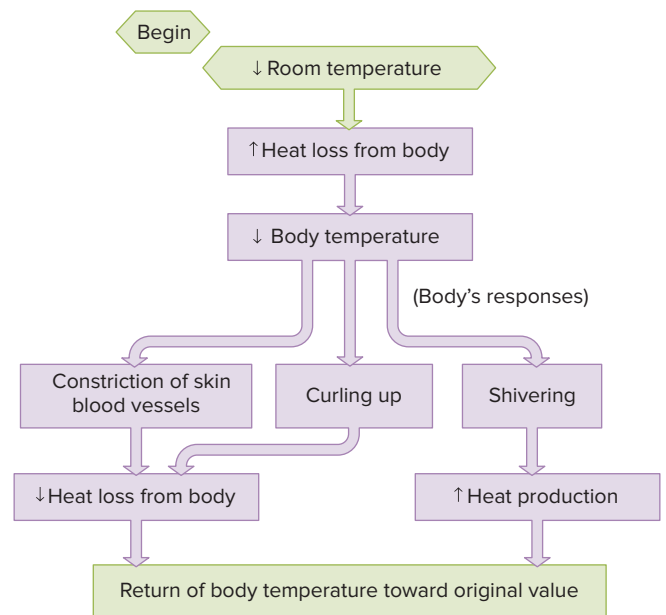


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The “Begin” sign indicates where to start. The arrows next to each term within the boxes denote increases or decreases. The arrows connecting any two boxes in the figure denote cause and effect; that is, an arrow can be read as “causes” or “leads to.” (For example, decreased room temperature “leads to” increased heat loss from the body.) In general, you should add the words “tends to” in thinking about these cause-and-effect relationships. For example, decreased room temperature tends to cause an increase in heat loss from the body, and curling up tends to cause a decrease in heat loss from the body. Qualifying the relationship in this way is necessary because variables like heat production and heat loss are under the influence of many factors, some of which oppose each other.

temperature. At a room temperature of 5°C, however, blood vessel constriction cannot by itself eliminate the extra heat loss from the body. Our subject hunches his shoulders and folds his arms in order to reduce the surface area of the skin available for heat loss. This helps somewhat, but heat loss still continues, and body temperature keeps decreasing, although at a slower rate. Clearly, then, if excessive heat loss (output) cannot be prevented, the only way of restoring the balance between heat input and output is to increase input, and this is precisely what occurs. Our subject begins to shiver, and the chemical reactions responsible for the skeletal muscle contractions that constitute shivering produce large quantities of heat.

Feedback Systems

The thermoregulatory system just described is an example of a **negative feedback** system, in which an increase or decrease in the variable being regulated brings about responses that tend to move the variable in the direction opposite (“negative” to) the direction of the original change. Thus, in our example, a decrease in body temperature led to responses that tended to increase the body temperature—that is, move it toward its original value.

Without negative feedback, oscillations like some of those described in this chapter would be much greater and, therefore, the variability in a given system would increase. Negative feedback also prevents the compensatory responses to a loss of homeostasis from continuing unabated. Details of the mechanisms and characteristics of negative feedback in different systems will be addressed in later chapters. For now, it is important to recognize that negative feedback has a vital part in the checks and balances on most physiological variables.

Negative feedback may occur at the organ, cellular, or molecular level. For instance, negative feedback regulates many enzymatic processes, as shown in schematic form in **Figure 1.6**. (An enzyme is a protein that catalyzes chemical reactions.)

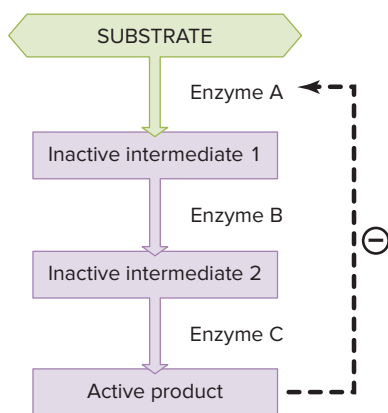


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its own formation.

PHYSIOLOGICAL INQUIRY

- What would be the effect on this pathway if negative feedback was removed?

Answer can be found at end of chapter.

In this example, the product formed from a substrate by an enzyme negatively feeds back to inhibit further action of the enzyme. This may occur by several processes, such as chemical modification of the enzyme by the product of the reaction. The production of adenosine triphosphate (ATP) within cells is a good example of a chemical process regulated by feedback. Normally, glucose molecules are enzymatically broken down inside cells to release some of the chemical energy that was contained in the bonds of the molecule. This energy is then stored in the bonds of ATP. The energy from ATP can later be tapped by cells to power such functions as muscle contraction, cellular secretions, and transport of molecules across cell membranes. As ATP accumulates in the cell, however, it inhibits the activity of some of the enzymes involved in the breakdown of glucose. Therefore, as ATP concentrations increase within a cell, further production of ATP slows down due to negative feedback. Conversely, if ATP concentrations decrease within a cell, negative feedback is removed and more glucose is broken down so that more ATP can be produced.

Not all forms of feedback are negative. In some cases, **positive feedback** accelerates a process, leading to an “explosive” system. This is counter to the general physiological principle of homeostasis, because positive feedback has no obvious means of stopping. Not surprisingly, therefore, positive feedback is much less common in nature than negative feedback. Nonetheless, there are examples in physiology in which positive feedback is very important. One well-described example, which you will learn about in detail in Chapter 12, is the process of blood clotting (**Figure 1.7**). When a blood vessel is ruptured, damaged cells in the vessel wall release chemicals into the blood that attract platelets to the injury site and activate them. Platelets are fragments of cells that stick together and form clots that seal a wound. Once activated, moreover, platelets themselves then release additional activating chemicals, which activate more platelets, and so on. The cycle finally stops once the wound is fully sealed with a clot.

Resetting of Set Points

As we have seen, changes in the external environment can displace a variable from its set point. In addition, the set points for many regulated variables can be physiologically reset to a new value. A common example is fever, the increase in body temperature that occurs in response to infection and that is somewhat analogous to raising the setting of a thermostat in a room. The homeostatic control systems regulating body temperature are still functioning during a fever, but they maintain the temperature at an increased value. This regulated increase in body temperature is adaptive for fighting the infection, because elevated temperature inhibits proliferation of some pathogens. In fact, this is why a fever is often preceded by chills and shivering. The set point for body temperature has been reset to a higher value, and the body responds by shivering to generate heat.

The example of fever may have left the impression that set points are reset only in response to external stimuli, such as the presence of pathogens, but this is not the case. Indeed, the set points for many regulated variables change on a rhythmic basis every day. For example, the set point for body temperature is higher during the day than at night.

Although the resetting of a set point is adaptive in some cases, in others it simply reflects the clashing demands of different regulatory systems. This brings us to one more generalization. It is not possible for everything to be held constant by homeostatic

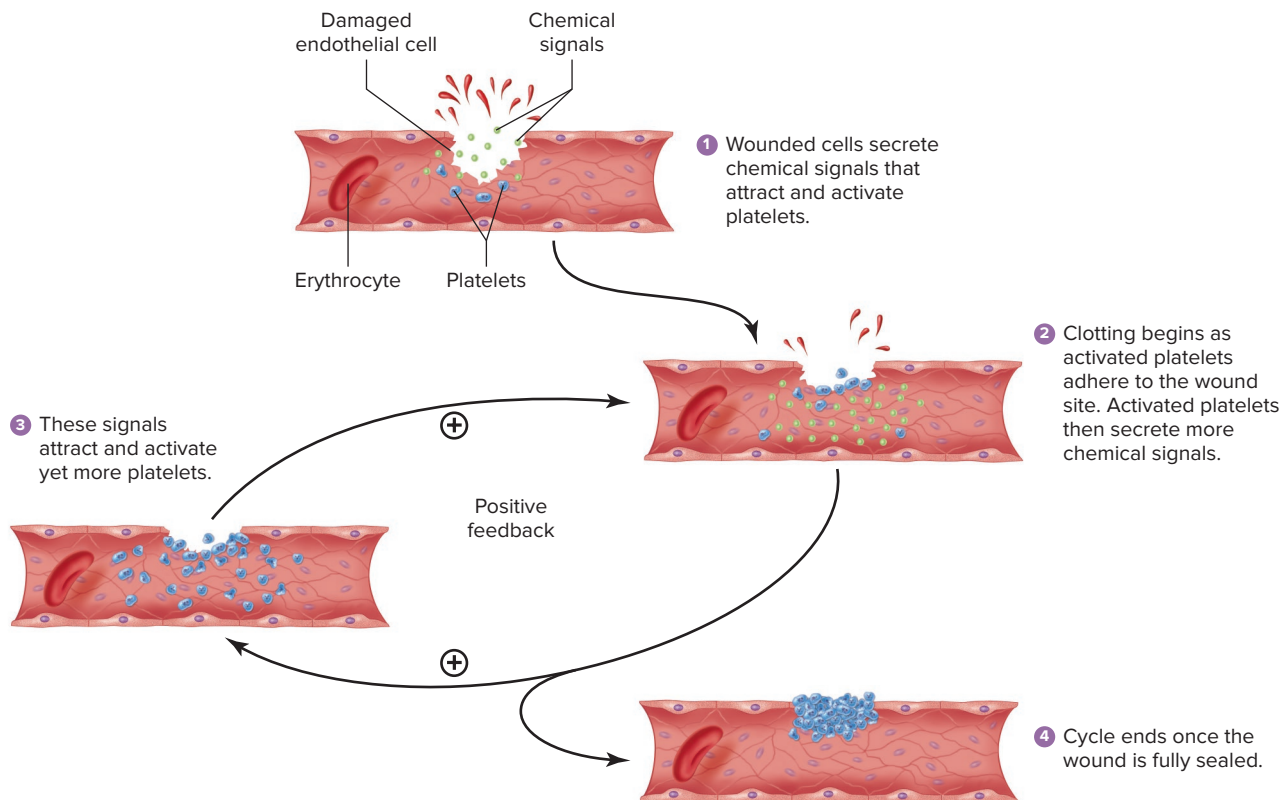


Figure 1.7 Positive feedback as illustrated by the clotting process in blood. Damaged endothelial cells (a type of epithelial cells) in the lining of a blood vessel secrete chemical signals that attract and activate platelets, tiny cell fragments that form clots. As clotting begins, the activated platelets produce chemical signals of their own, attracting and activating more platelets to the wound site, which then produce yet more chemical signals, and so on. The cycle ends when the wound is fully sealed. (Most details of the clotting process are omitted for clarity; you can look ahead to Figure 12.71 for details.)

control systems. In our earlier example, body temperature was maintained despite large swings in ambient temperature, but only because the homeostatic control system brought about large changes in skin blood flow and skeletal muscle contraction. Moreover, because so many properties of the internal environment are closely interrelated, it is often possible to keep one property relatively stable only by moving others away from their usual set point. This is what we mean by “clashing demands,” which explains the phenomenon mentioned earlier about the interplay between body temperature and water balance during exercise.

The generalizations we have given about homeostatic control systems are summarized in **Table 1.2**. One additional point is

that, as is illustrated by the regulation of body temperature, multiple systems usually control a single parameter. The adaptive value of such redundancy is that it provides much greater fine-tuning and also permits regulation to occur even when one of the systems is not functioning properly because of disease.

Feedforward Regulation

Another type of regulatory process often used in conjunction with feedback systems is **feedforward**, in which changes in regulated variables are anticipated and prepared for before they actually occur. Control of body temperature is a good example of a feedforward process. The temperature-sensitive neurons that trigger

TABLE 1.2 Some Important Generalizations About Homeostatic Control Systems

Stability of an internal environmental variable is achieved by balancing inputs and outputs. It is not the absolute magnitudes of the inputs and outputs that matter but the balance between them.

In negative feedback, a change in the variable being regulated brings about responses that tend to move the variable in the direction opposite the original change—that is, back toward the initial value (set point).

Homeostatic control systems cannot maintain complete constancy of any given feature of the internal environment. Therefore, any regulated variable will have a more or less narrow range of normal values depending on the external environmental conditions.

The set point of some variables regulated by homeostatic control systems can be reset—that is, physiologically raised or lowered.

It is not always possible for homeostatic control systems to maintain every variable within a narrow normal range in response to an environmental challenge. There is a hierarchy of importance, so that certain variables may be altered markedly to maintain others within their normal range.