

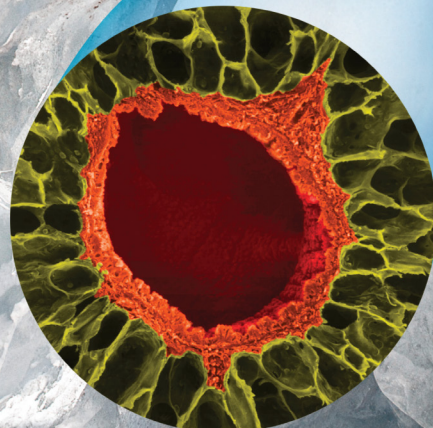
VANDER'S

Human Physiology

**THE MECHANISMS
OF BODY FUNCTION**

Eric P. Widmaier
Hershel Raff
Kevin T. Strang

FIFTEENTH EDITION



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FIFTEENTH EDITION

VANDER'S

Human Physiology

The Mechanisms of Body Function

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

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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

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©Kevin Strang

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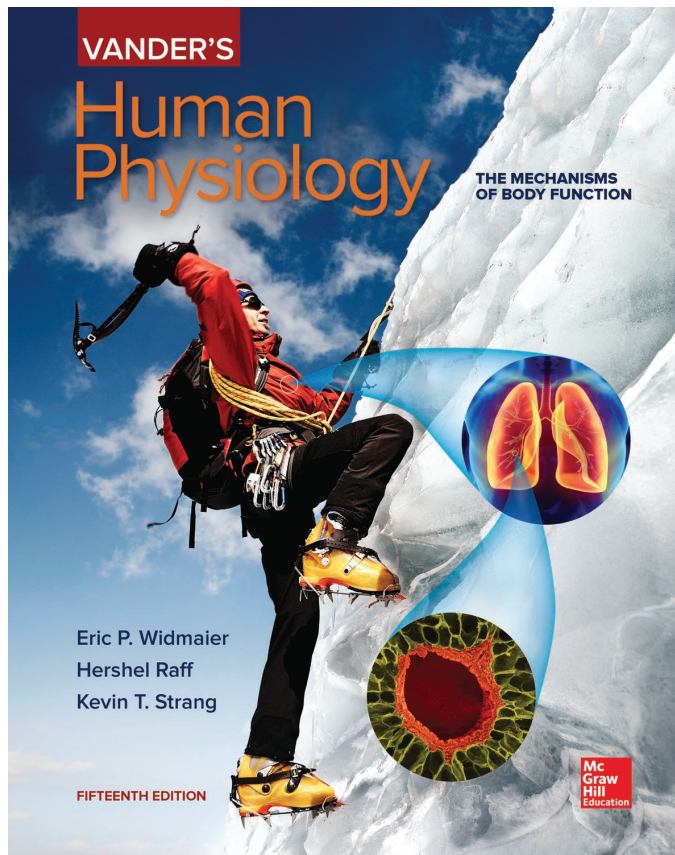
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TODD C. SHOEPE received his B.S. degree in Fitness Program Management in 1998 and his M.S. degree in Exercise Physiology in 2001 both from *Oregon State University*. In 2013 he received an Ed.D. degree in Learning Technologies from *Pepperdine University*. 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!

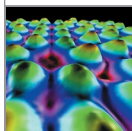
Table of Contents

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

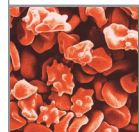
3.16 Essential Nutrients 89

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

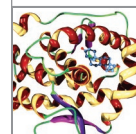
Exocytosis 111

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

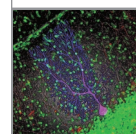
Other Messengers 129

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

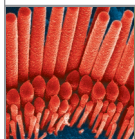
Meninges and Cerebrospinal Fluid 181

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

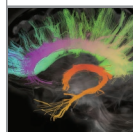
Gustation 224

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

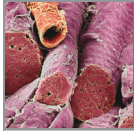
The Neural Basis of Learning and Memory 249

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 Ca^{2+} 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

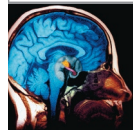
10.5 Maintenance of Upright Posture and Balance 313

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 Ca^{2+} Homeostasis 352

11.20 Effector Sites for Ca^{2+} 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

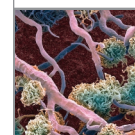
Why Do Ventilation–Perfusion Abnormalities Affect O_2 More Than CO_2 ? 479
Emphysema 479
Acclimatization to High Altitude 480

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

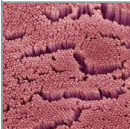
- 14.6 Total-Body Balance of Sodium and Water 503**
- 14.7 Basic Renal Processes for Sodium and Water 503**
Primary Active Na⁺ Reabsorption 503
Coupling of Water Reabsorption to Na⁺ Reabsorption 504
Urine Concentration: The Countercurrent Multiplier System 506
- 14.8 Renal Sodium Regulation 510**
Control 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

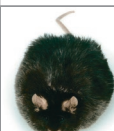
The Digestion and Absorption of Food 531

- 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

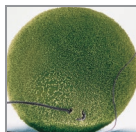
SECTION C Regulation of Body Temperature 593

- 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

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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

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

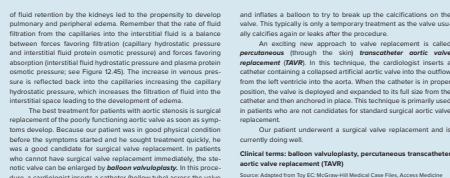
xvi

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.

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.

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, and 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. ■

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.

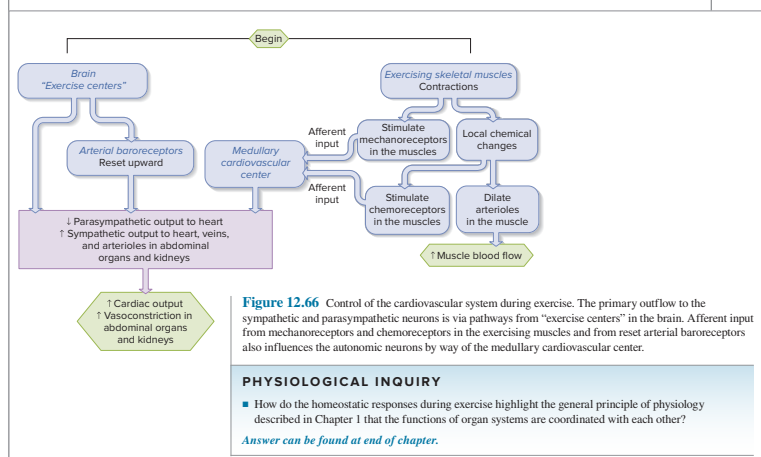


Summary Tables

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.

TABLE 12.3 The Circulatory System

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!

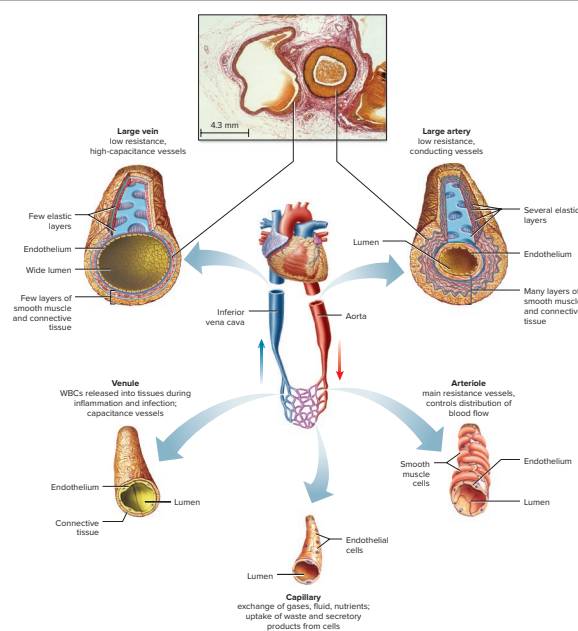
Anatomy and Physiology REVEALED® (APR) Icon

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.



APR Figure 12.31 Comparative features of blood vessels. Sizes are not drawn to scale. *Inset:* Light micrograph (enlarged four times) of a medium-sized artery near a vein. Note the difference between the two vessels in wall thickness and lumen diameter. Refer back to Table 12.3 for more details on function. ©Bridgeton Associates/Science Source

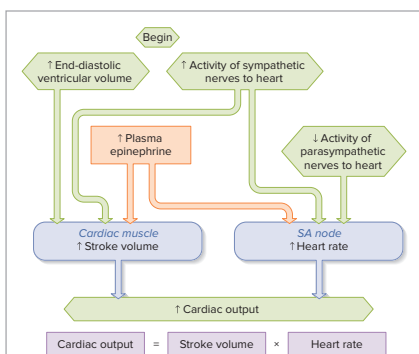


Figure 12.30 Major factors involved in increasing cardiac output. Reversal of all arrows in the boxes would illustrate how cardiac output can be decreased.

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.

- | | | |
|---|--------------------------------------|-------------------------|
| 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
blood vessels
cardiovascular system

12.1 Components of the Circulatory System

albumin
aorta
arteries
arterioles
atrium
basophils
bilirubin

circulatory system
heart
vascular system

bone marrow
bulk flow
capillaries
defensins
eosinophils
erythrocytes
erythropoiesis

12.2 Pressure, Flow, and Resistance

hemodynamics
hydrostatic pressure
Poiseuille's law

resistance (*R*)
viscosity

SECTION A CLINICAL TERMS

12.1 Components of the Circulatory System

anemia
hemochromatosis
iron deficiency
iron-deficiency anemia

malaria
pernicious anemia
polycythemia
sickle-cell disease

SECTION B

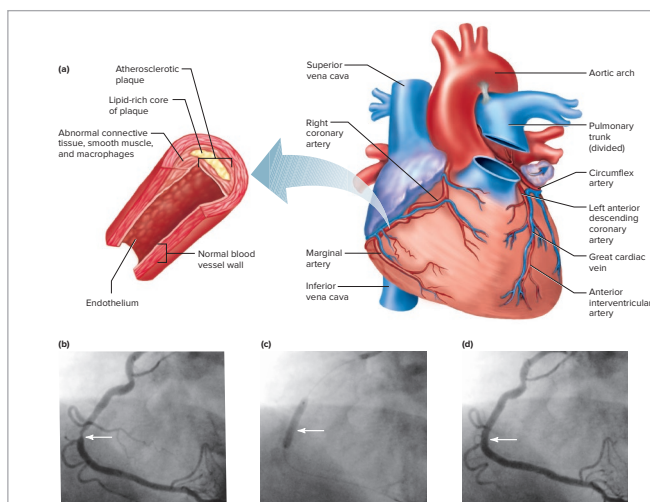
The Heart

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-



APR 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

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 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 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.
9. 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
10. 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
11. 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
12. 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.
13. Which correctly pairs an ECG phase with the cardiac event responsible?
 - a. P wave: depolarization of the ventricles
 - b. P wave: depolarization of the AV node
 - 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 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 ($1.5 / 4.5 \text{ L} = 0.33$, 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 in 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 →

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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 detail 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.

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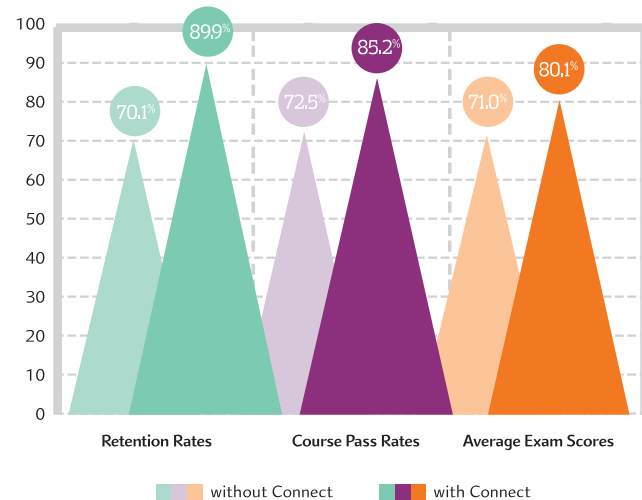
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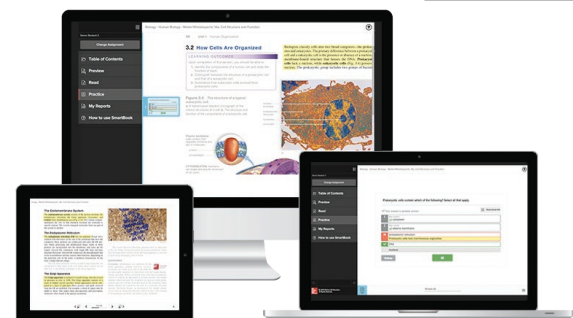
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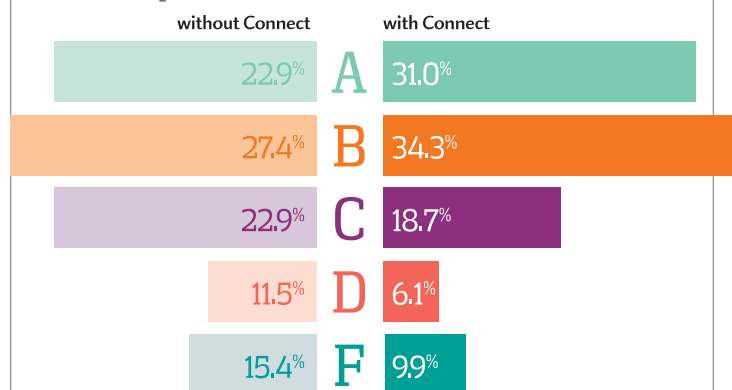
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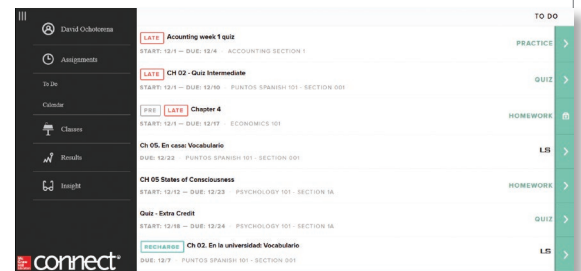


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In this fifteenth edition of *Vander's Human Physiology*, we are very excited to have been able to use real student data points derived from thousands of users to help guide our revision path. We are also deeply thankful to the following individuals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

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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,

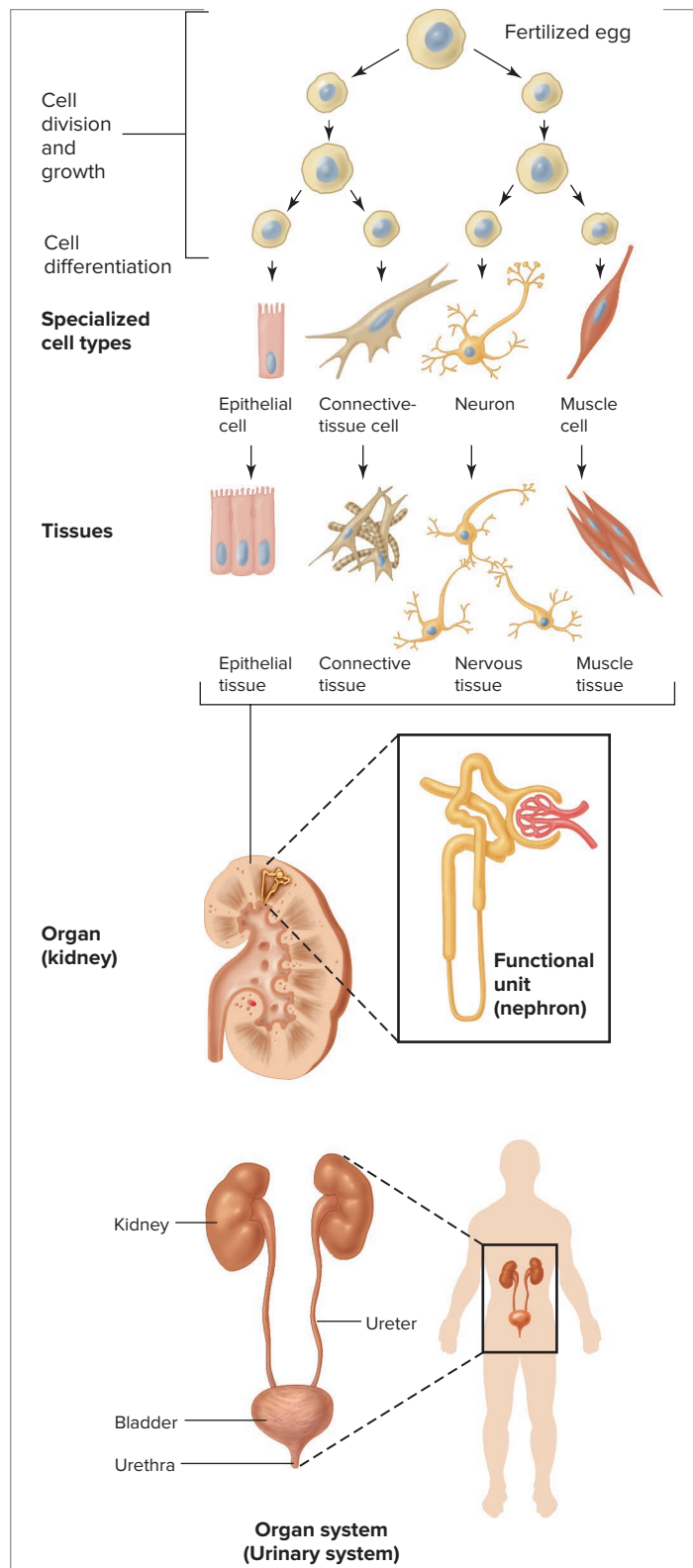


Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

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

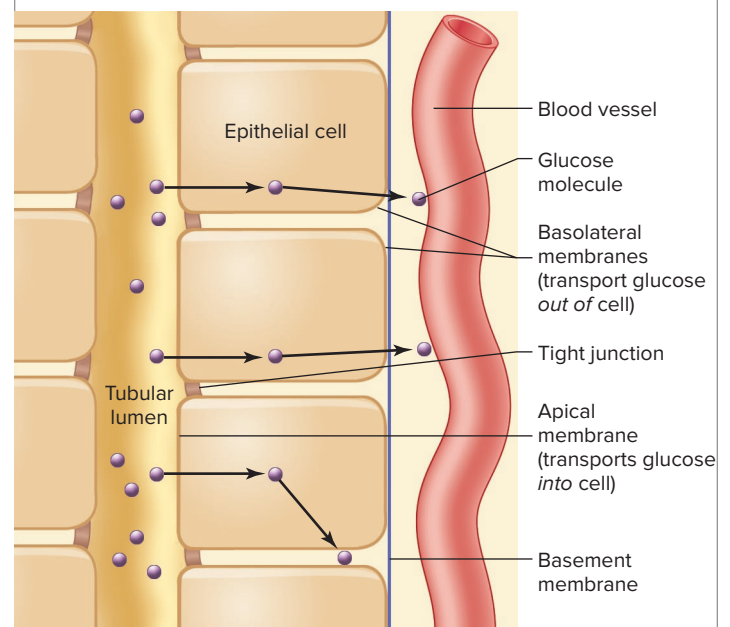


Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into 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	Male: production of sperm; transfer of sperm to female
	Female: ovaries, fallopian tubes, uterus, vagina, mammary glands	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

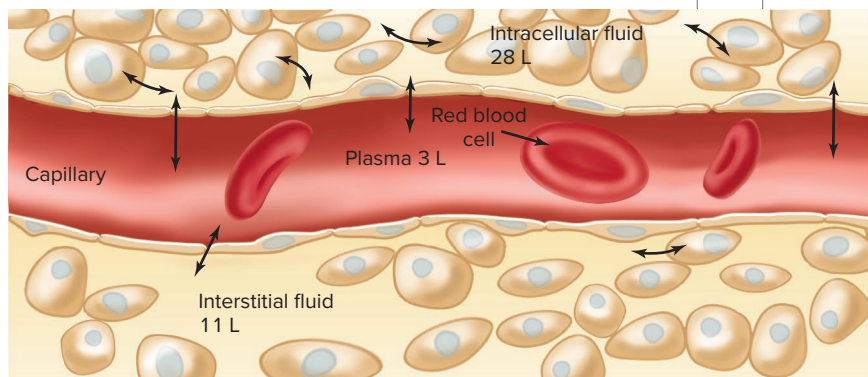
retained within the intracellular fluid and are not required in the extracellular fluid.

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.

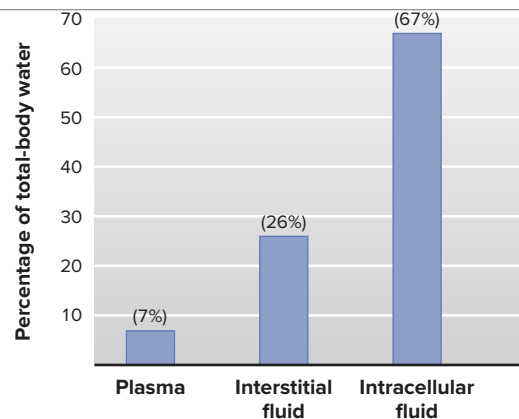
With this understanding of the structural organization of the body, we turn to a description of how balance is maintained in the internal environment of the body.

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

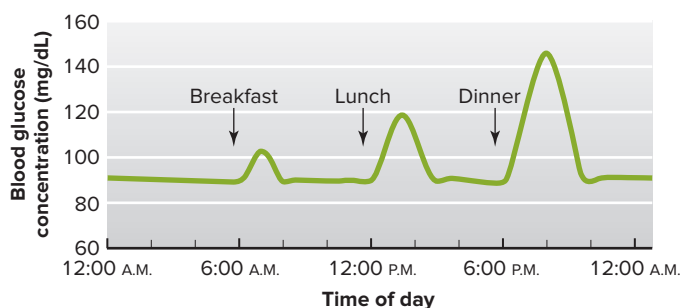


Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood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

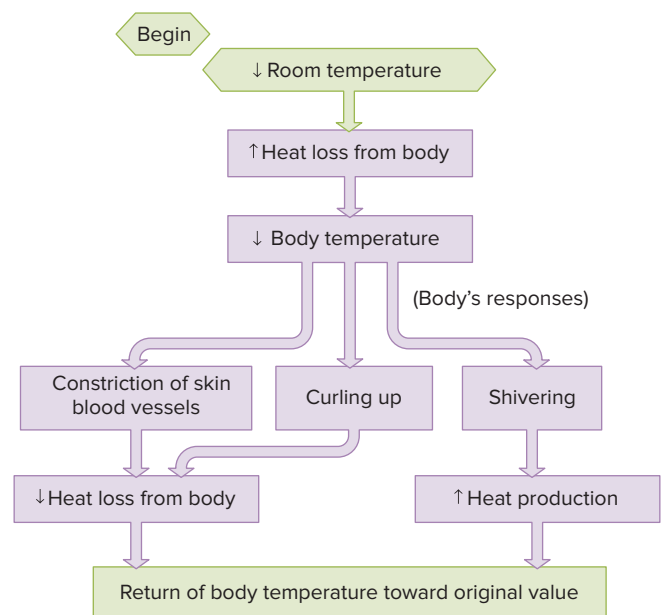


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The “Begin” sign indicates where to start. The arrows next to 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.)

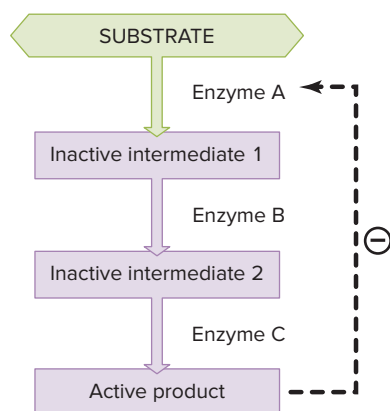


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its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

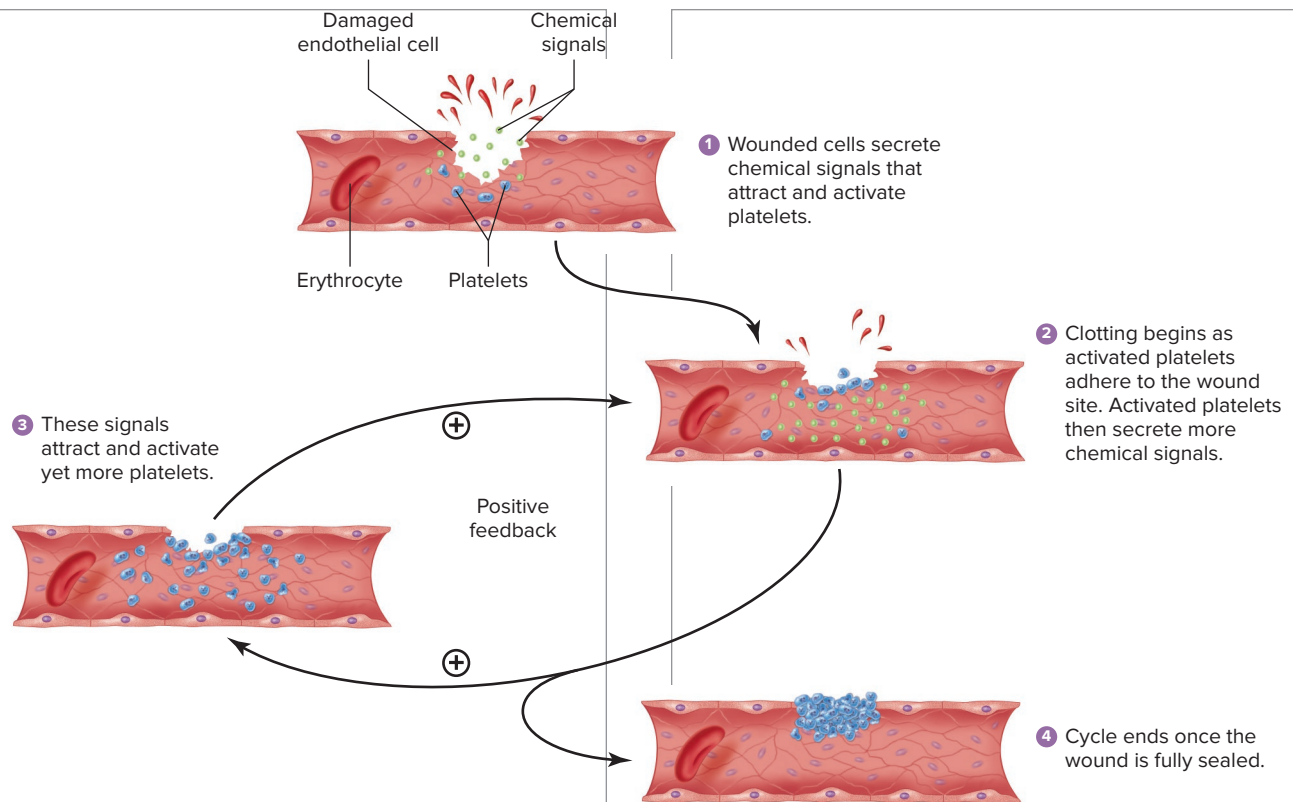


Figure 1.7 Positive feedback as illustrated by the clotting process in blood. Damaged endothelial cells (a type of epithelial cells) in the lining of a blood vessel secrete chemical signals that attract and activate platelets, tiny cell fragments that form clots. As clotting begins, the activated platelets 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.

negative feedback regulation of body temperature when it begins to decrease are located inside the body. In addition, there are temperature-sensitive neurons in the skin; these cells, in effect, monitor outside temperature. When outside temperature decreases, as in our example, these neurons immediately detect the change and relay this information to the brain. The brain then sends out signals to the blood vessels and muscles, resulting in heat conservation and increased heat production. In this manner, compensatory thermoregulatory responses are activated *before* the colder outside temperature can cause the internal body temperature to decrease. In another familiar example, the smell of food triggers nerve responses from odor receptors in the nose to the cells of the digestive system. The effect is to prepare the digestive system for the arrival of food before we even consume it, for example, by inducing saliva to be secreted in the mouth and causing the stomach to churn and produce acid. Thus, feedforward regulation improves the speed of the body's homeostatic responses and minimizes fluctuations in the level of the variable being regulated—that is, it reduces the amount of deviation from the set point.

In our examples, feedforward regulation utilizes a set of external or internal environmental detectors. It is likely, however, that many examples of feedforward regulation are the result of a different phenomenon—learning. The first times they occur, early in life, perturbations in the external environment probably cause relatively large changes in regulated internal environmental factors, and in responding to these changes the central nervous system learns to anticipate them and resist them more effectively. A familiar form of this is the increased heart rate that occurs in an athlete just before a competition begins.

1.6 Components of Homeostatic Control Systems

Reflexes

The thermoregulatory system we used as an example in the previous section and many of the other homeostatic control systems belong to the general category of stimulus–response sequences known as *reflexes*. Although in some reflexes we are aware of the stimulus and/or the response, many reflexes regulating the internal environment occur without our conscious awareness.

In the narrowest sense of the word, a **reflex** is a specific, involuntary, unpremeditated, “built-in” response to a particular stimulus. Examples of such reflexes include pulling your hand away from a hot object or shutting your eyes as an object rapidly approaches your face. Many responses, however, appear automatic and stereotyped but are actually the result of learning and practice. For example, an experienced driver performs many complicated acts in operating a car. To the driver, these motions are, in large part, automatic, stereotyped, and unpremeditated, but they occur only because a great deal of conscious effort was spent learning them. We term such reflexes **learned** or **acquired reflexes**. In general, most reflexes, no matter how simple they may appear to be, are subject to alteration by learning.

The pathway mediating a reflex is known as the **reflex arc**, and its components are shown in **Figure 1.8**. A **stimulus** is defined as a detectable change in the internal or external environment, such as a change in temperature, plasma potassium concentration, or blood pressure. A **receptor** detects the environmental change. A

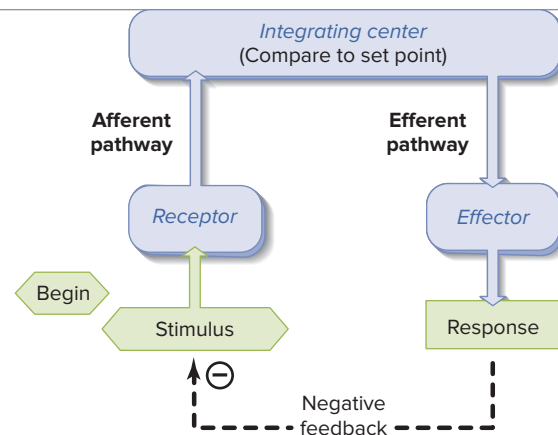


Figure 1.8 General components of a reflex arc that functions as a negative feedback control system. The response of the system has the effect of counteracting or eliminating the stimulus.

stimulus acts upon a receptor to produce a signal that is relayed to an **integrating center**. The signal travels between the receptor and the integrating center along the **afferent pathway** (the general term *afferent* means “to carry to,” in this case, to the integrating center).

An integrating center often receives signals from many receptors, some of which may respond to quite different types of stimuli. Thus, the output of an integrating center reflects the net effect of the total afferent input; that is, it represents an integration of numerous bits of information.

The output of an integrating center is sent to the last component of the system, whose change in activity constitutes the overall response of the system. This component is known as an **effector**. The information going from an integrating center to an effector is like a command directing the effector to alter its activity. This information travels along the **efferent pathway** (the general term *efferent* means “to carry away from,” in this case, away from the integrating center).

Thus far, we have described the reflex arc as the sequence of events linking a stimulus to a response. If the response produced by the effector causes a decrease in the magnitude of the stimulus that triggered the sequence of events, then the reflex leads to negative feedback and we have a typical homeostatic control system. Not all reflexes are associated with such feedback. For example, the smell of food stimulates the stomach to secrete molecules that are important for digestion, but these molecules do not eliminate our perception of the smell of food (the stimulus).

Figure 1.9 demonstrates the components of a negative feedback homeostatic reflex arc in the process of thermoregulation. The temperature receptors are the endings of certain neurons in various parts of the body. They generate electrical signals in the neurons at a rate determined by the temperature. These electrical signals are conducted by nerves containing processes from the neurons—the afferent pathway—to the brain, where the integrating center for temperature regulation is located. The integrating center, in turn, sends signals out along neurons in other nerves that cause skeletal muscles and the muscles in skin blood vessels to contract. The nerves to the muscles are the efferent pathway, and the muscles are the effectors. The dashed arrow and the negative sign indicate the negative feedback nature of the reflex.

Almost all body cells can act as effectors in homeostatic reflexes. Muscles and glands, however, are the major effectors of

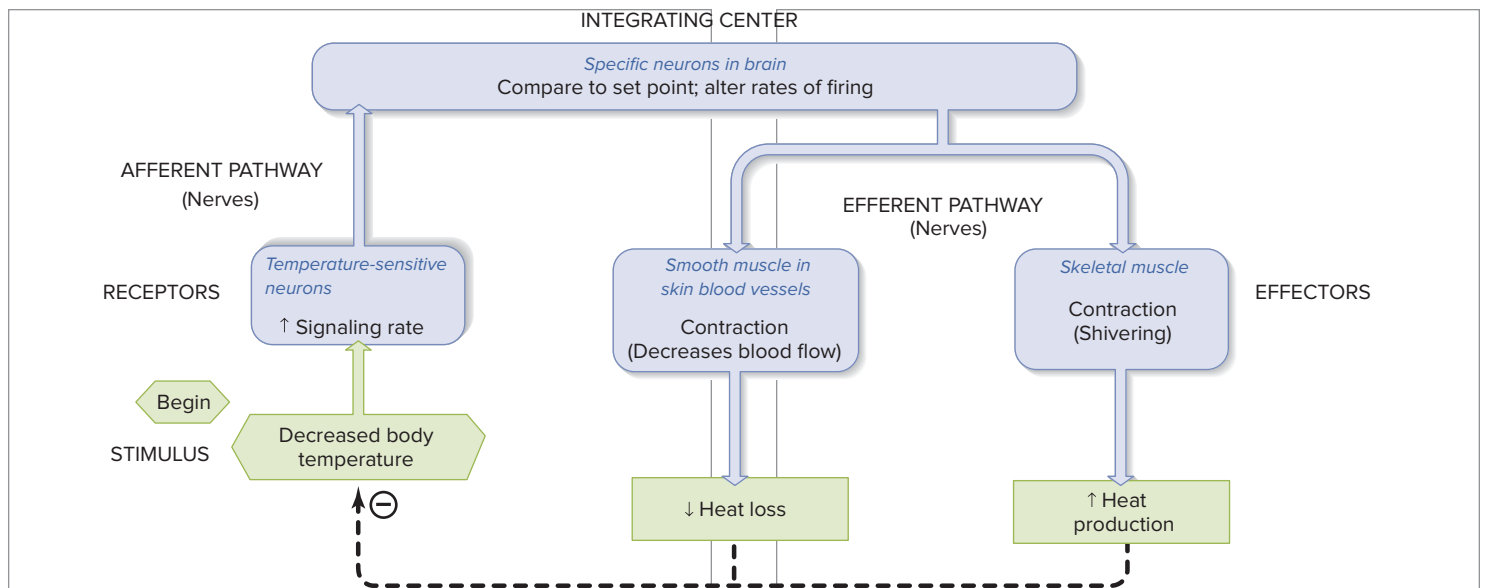


Figure 1.9 Reflex for minimizing the decrease in body temperature that occurs on exposure to a reduced external environmental temperature. This figure provides the internal components for the reflex shown in Figure 1.5. The dashed arrow and the $\ominus$ indicate the negative feedback nature of the reflex, denoting that the reflex responses cause the decreased body temperature to return toward normal. An additional flow-diagram convention is shown in this figure: Blue boxes always denote events that are occurring in anatomical structures (labeled in blue italic type in the upper portion of the box).

PHYSIOLOGICAL INQUIRY

- What might happen to the efferent pathway in this control system if body temperature *increased* above normal?

Answer can be found at end of chapter.

biological control systems. In the case of glands, for example, the effector may be a hormone secreted into the blood. As will be described in detail in Chapter 11, a **hormone** is a type of chemical messenger secreted into the blood by cells of the endocrine system (see Table 1.1). Hormones may act on many different cells simultaneously because they circulate throughout the body.

Traditionally, the term *reflex* was restricted to situations in which the receptors, afferent pathway, integrating center, and efferent pathway were all parts of the nervous system, as in the thermoregulatory reflex. However, the principles are essentially the same when a blood-borne chemical messenger, rather than a nerve, serves as the efferent pathway, or when a hormone-secreting gland serves as the integrating center.

In our use of the term *reflex*, therefore, we include hormones as reflex components. Moreover, depending on the specific nature of the reflex, the integrating center may reside either in the nervous system or in a gland. In addition, a gland may act in more than one way in a reflex. For example, when the glucose concentration in the blood is increased, this is detected by gland cells in the pancreas (receptor). These same cells then release the hormone insulin (effector) into the blood, which decreases the blood glucose concentration.

Local Homeostatic Responses

In addition to reflexes, another group of biological responses, called **local homeostatic responses**, is of great importance for homeostasis. These responses are initiated by a change in the external or internal environment (that is, a stimulus), and they induce an alteration of cell activity with the net effect of counteracting the

stimulus. Like a reflex, therefore, a local response is the result of a sequence of events proceeding from a stimulus. Unlike a reflex, however, the entire sequence occurs only in the area of the stimulus. For example, when cells of a tissue become very metabolically active, they secrete substances into the interstitial fluid that dilate (widen) local blood vessels. The resulting increased blood flow increases the rate at which nutrients and oxygen are delivered to that area, and the rate at which wastes are removed. The significance of local responses is that they provide individual areas of the body with mechanisms for local self-regulation.

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

Essential to reflexes and local homeostatic responses—and therefore to homeostasis—is the ability of cells to communicate with one another. In this way, cells in the brain, for example, can be made aware of the status of activities of structures outside the brain, such as the heart, and help regulate those activities to meet new homeostatic challenges. In the majority of cases, intercellular communication is performed by chemical messengers. There are four categories of such messengers: hormones, neurotransmitters, paracrine, and autocrine substances (Figure 1.10).

As noted earlier, a hormone is a chemical messenger that enables the hormone-secreting cell to communicate with other cells with the blood acting as the delivery system. The cells on which hormones act are called the hormone's **target cells**. Hormones are produced in and secreted from **endocrine glands** or in scattered cells

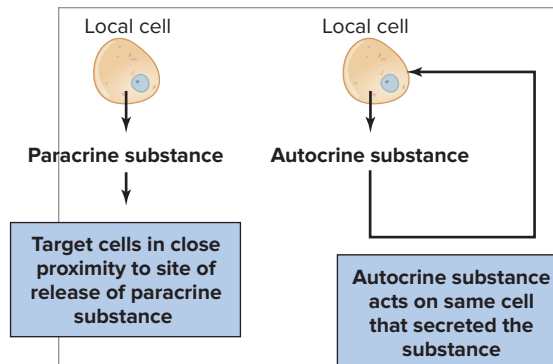
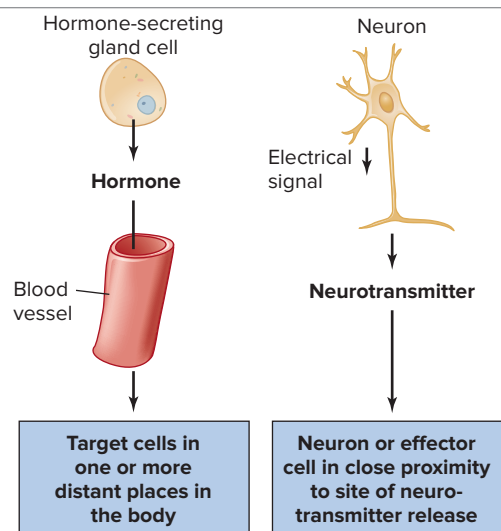


Figure 1.10 Categories of chemical messengers. With the exception of autocrine messengers, all messengers act between cells—that is, *intercellularly*.

that are distributed throughout an organ. They have important functions in essentially all physiological processes, including growth, reproduction, metabolism, mineral balance, and blood pressure, and several of them are produced whenever homeostasis is threatened.

In contrast to hormones, **neurotransmitters** are chemical messengers that are released from the endings of neurons onto other neurons, muscle cells, or gland cells. A neurotransmitter diffuses through the extracellular fluid separating the neuron and its target cell; it is not released into the blood like a hormone. Neurotransmitters and their functions in neuronal signaling and brain function will be covered in Chapter 6. In the context of homeostasis, they form the signaling basis of many reflexes, as well as having a vital role in the compensatory responses to a wide variety of challenges, such as the requirement for increased heart and lung function during exercise.

Chemical messengers participate not only in reflexes but also in local responses. Chemical messengers involved in local communication between cells are known as **paracrine substances** (or agents). Paracrine substances are synthesized by cells and released, once given the appropriate stimulus, into the extracellular fluid. They then diffuse to neighboring cells, some of which are their target cells. Given this broad definition, neurotransmitters could be classified as a subgroup of paracrine substances, but by convention they are not. Once they have performed their functions, paracrine substances are generally inactivated by locally existing enzymes and therefore they do not enter the bloodstream in large quantities. Paracrine substances are produced throughout the body; an example of their key role in homeostasis that you will learn about in Chapter 15 is their ability to fine-tune the amount of acid produced by cells of the stomach in response to eating food.

There is one category of local chemical messengers that are not *intercellular* messengers—that is, they do not communicate *between* cells. Rather, the chemical is secreted by a cell into the extracellular fluid and then acts upon the very cell that secreted it. Such messengers are called **autocrine substances** (or agents) (see Figure 1.10). Frequently, a messenger may serve both paracrine and autocrine functions simultaneously—that is, molecules of the messenger released by a cell may act locally on adjacent cells as well as on the same cell that released the messenger. This type of signaling is commonly found in cells of the immune system (Chapter 18).

A point of great importance must be emphasized here to avoid later confusion. A neuron, endocrine gland cell, and other cell type

may all secrete the same chemical messenger. In some cases, a particular messenger may sometimes function as a neurotransmitter, a hormone, or a paracrine or autocrine substance. Norepinephrine, for example, is not only a neurotransmitter in the brain; it is also produced as a hormone by cells of the adrenal glands.

All types of intercellular communication described thus far in this section involve secretion of a chemical messenger into the extracellular fluid. However, there are two important types of chemical communication between cells that do not require such secretion. The first type occurs via gap junctions, which are physical linkages connecting the cytosol between two cells (see Chapter 3). Molecules can move directly from one cell to an adjacent cell through gap junctions without entering the extracellular fluid. In the second type, the chemical messenger is not actually released from the cell producing it but rather is located in the plasma membrane of that cell. For example, the messenger may be a plasma membrane protein with part of its structure extending into the extracellular space. When the cell encounters another cell type capable of responding to the message, the two cells link up via the membrane-bound protein. This type of signaling, sometimes termed *juxtacrine*, is of particular importance in the growth and differentiation of tissues as well as in the functioning of cells that protect the body against pathogens (Chapter 18). It is one way in which similar types of cells “recognize” each other and form tissues.

1.8 Processes Related to Homeostasis

Adaptation and Acclimatization

The term **adaptation** denotes a characteristic that favors survival in specific environments. Common examples in humans include the ability of certain individuals to digest lactose in milk, and the protection against the dangerous effects of ultraviolet light conferred by dark skin. Homeostatic control systems are also inherited biological adaptations and allow an individual to adapt to encountered environmental changes. In addition, in some cases the effectiveness of such systems can be enhanced by prolonged exposure to an environmental change. This type of adaptation—the improved functioning of an already existing homeostatic system—is known as **acclimatization**.

Let us take sweating in response to heat exposure as an example of an adaptation and perform a simple experiment. On day 1, we expose a person for 30 minutes (min) to an elevated

temperature and ask her to do a standardized exercise test. Body temperature increases, and sweating begins after a certain period of time. The sweating provides a mechanism for increasing heat loss from the body and therefore tends to minimize the increase in body temperature in a hot environment. The volume of sweat produced under these conditions is measured. Then, for a week, our subject enters the heat chamber for 1 or 2 hours (h) per day and exercises. On day 8, her body temperature and sweating rate are again measured during the same exercise test performed on day 1. The striking finding is that the subject begins to sweat sooner and much more profusely than she did on day 1. As a consequence, her body temperature does not increase to nearly the same degree. The subject has become acclimatized to the heat. She has undergone a beneficial change induced by repeated exposure to the heat and is now better able to respond to heat exposure.

Acclimatizations are usually reversible. If, in the example just described, the daily exposures to heat are discontinued, our subject's sweating rate will revert to the preacclimatized value within a relatively short time.

The precise anatomical and physiological changes that bring about increased capacity to withstand change during acclimatization are highly varied. Typically, they involve an increase in the number, size, or sensitivity of one or more of the cell types in the homeostatic control system that mediates the basic response.

Biological Rhythms

As noted earlier, a striking characteristic of many body functions is the rhythmic changes they manifest. The most common type is the **circadian rhythm**, which cycles approximately once every 24 h. Waking and sleeping, body temperature, hormone concentrations in the blood, the excretion of ions into the urine, and many other functions undergo circadian variation; an example of one type of rhythm is shown in **Figure 1.11**.

What do biological rhythms have to do with homeostasis? They add an anticipatory component to homeostatic control systems, in effect, a feedforward system operating without detectors. The negative feedback homeostatic responses we described earlier in this chapter are *corrective* responses. They are initiated *after* the steady state of the individual has been perturbed. In contrast, biological rhythms enable homeostatic mechanisms to be utilized immediately and automatically by activating them at times when a challenge is *likely* to occur but before it actually does occur. For example, body

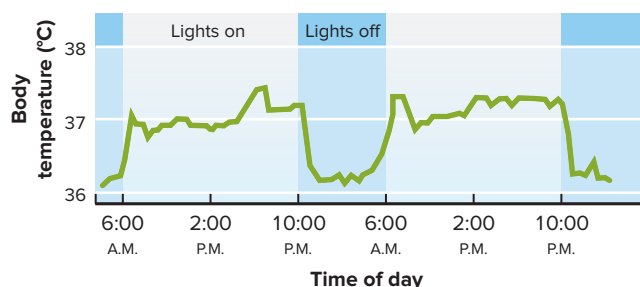


Figure 1.11 Circadian rhythm of body temperature in a human subject with room lights on (open bars at top) for 16 h, and off (blue bars at top) for 8 h. Note the increase in body temperature that occurs just prior to lights on, in anticipation of the increased activity and metabolism that occur during waking hours. Source: Moore-Ede, Martin C., Sulzman, Frank M., and Fuller, Charles A., *The Clocks that Time Us*. Harvard University Press, 1982.

temperature increases prior to waking in a person on a typical sleep–wake cycle. This allows the metabolic machinery of the body to operate most efficiently immediately upon waking, because metabolism (chemical reactions) is to some extent temperature dependent. During sleep, metabolism is slower than during the active hours, and therefore body temperature decreases at that time. A crucial point concerning most body rhythms is that they are internally driven. Environmental factors do not drive the rhythm but rather provide the timing cues important for **entrainment**, or setting of the actual hours of the rhythm. A classic experiment will clarify this distinction.

Subjects were put in experimental chambers that completely isolated them from their usual external environment, including knowledge of the time of day. For the first few days, they were exposed to a 24 h rest–activity cycle in which the room lights were turned on and off at the same times each day. Under these conditions, their sleep–wake cycles were 24 h long. Then, all environmental time cues were eliminated, and the subjects were allowed to control the lights themselves. Immediately, their sleep–wake patterns began to change. On average, bedtime began about 30 min later each day, and so did wake-up time. Thus, a sleep–wake cycle persisted in the complete absence of environmental cues. Such a rhythm is called a **free-running rhythm**. In this case, it was approximately 24.5 h rather than 24. This indicates that cues are required to entrain or set a circadian rhythm to 24 h.

The light–dark cycle is the most important environmental time cue in our lives—but not the only one. Others include external environmental temperature, meal timing, and many social cues. Thus, if several people were undergoing the experiment just described in isolation from each other, their free-running rhythms would be somewhat different, but if they were all in the same room, social cues would entrain all of them to the same rhythm.

Environmental time cues also function to **phase-shift** rhythms—in other words, to reset the internal clock. Thus, if you fly west or east to a different time zone, your sleep–wake cycle and other circadian rhythms slowly shift to the new light–dark cycle. These shifts take time, however, and the disparity between external time and internal time is one of the causes of the symptoms of jet lag—a disruption of homeostasis that leads to gastrointestinal disturbances, decreased vigilance and attention span, sleep problems, and a general feeling of malaise.

Similar symptoms occur in workers on permanent or rotating night shifts. These people generally do not adapt to their schedules even after several years because they are exposed to the usual outdoor light–dark cycle (normal indoor lighting is too dim to function as a good entrainer). In recent experiments, night-shift workers were exposed to extremely bright indoor lighting while they worked and they were exposed to 8 h of total darkness during the day when they slept. This schedule produced total adaptation to night-shift work within 5 days.

What is the neural basis of body rhythms? In the part of the brain called the hypothalamus, a specific collection of neurons (the suprachiasmatic nucleus) functions as the principal **pacemaker**, or time clock, for circadian rhythms. How it keeps time independent of any external environmental cues is not fully understood, but it appears to involve the rhythmic turning on and off of critical genes in the pacemaker cells.

The pacemaker receives input from the eyes and many other parts of the nervous system, and these inputs mediate the entrainment effects exerted by the external environment. In turn, the pacemaker

sends out neural signals to other parts of the brain, which then influence the various body systems, activating some and inhibiting others. One output of the pacemaker goes to the **pineal gland**, a gland within the brain that secretes the hormone **melatonin**. These neural signals from the pacemaker cause the pineal gland to secrete melatonin during darkness but not during daylight. It has been hypothesized, therefore, that melatonin may act as an important mediator to influence other organs either directly or by altering the activity of the parts of the brain that control these organs.

Balance of Chemical Substances in the Body

Many homeostatic systems regulate the balance between addition and removal of a chemical substance from the body. **Figure 1.12** is a generalized schema of the possible pathways involved in maintaining such balance. The **pool** occupies a position of central importance in the balance sheet. It is the body's readily available quantity of the substance and is often identical to the amount present in the extracellular fluid. The pool receives substances and redistributes them to all the pathways.

The pathways on the left of Figure 1.12 are sources of net gain to the body. A substance may enter the body through the gastrointestinal (GI) tract or the lungs. Alternatively, a substance may be synthesized within the body from other materials.

The pathways on the right of the figure are causes of net loss from the body. A substance may be lost in the urine, feces, expired air, or menstrual fluid, as well as from the surface of the body as skin, hair, nails, sweat, or tears. The substance may also be chemically altered by enzymes and thus removed by metabolism.

The central portion of the figure illustrates the distribution of the substance within the body. The substance may be taken from the pool and accumulated in storage depots—such as the accumulation of fat in adipose tissue. Conversely, it may leave the storage depots to reenter the pool. Finally, the substance may be incorporated reversibly into some other molecular structure, such as fatty acids into plasma membranes. Incorporation is reversible because the substance is liberated again whenever the more complex structure is broken down. This pathway is distinguished from storage in that the incorporation of the substance into other molecules produces new molecules with specific functions.

Substances do not necessarily follow all pathways of this generalized schema. For example, minerals such as Na^+ cannot be synthesized, do not normally enter through the lungs, and cannot be removed by metabolism.

The orientation of Figure 1.12 illustrates two important generalizations concerning the balance concept: (1) During any period of time, total-body balance depends upon the relative rates of net gain and net loss to the body; and (2) the pool concentration depends not only upon the total amount of the substance in the body but also upon exchanges of the substance *within* the body.

For any substance, three states of total-body balance are possible: (1) Loss exceeds gain, so that the total amount of the substance in the body is decreasing, and the person is in **negative balance**; (2) gain exceeds loss, so that the total amount of the substance in the body is increasing, and the person is in **positive**

balance; and (3) gain equals loss, and the person is in **stable balance**.

Clearly, a stable balance can be upset by a change in the amount being gained or lost in any single pathway in the schema. For example, increased sweating can cause severe negative water balance. Conversely, stable balance can be restored by homeostatic control of water intake and output.

Let us take the balance of calcium ions (Ca^{2+}) as another example. The concentration of Ca^{2+} in the extracellular fluid is critical for normal cellular functioning, notably muscle cells and neurons, but also for the formation and maintenance of the skeleton. The vast majority of the body's Ca^{2+} is present in bone. The control systems for Ca^{2+} balance target the intestines and kidneys such that the amount of Ca^{2+} absorbed from the diet is balanced with the amount excreted in the urine. During infancy and childhood, however, the net balance of Ca^{2+} is positive, and Ca^{2+} is deposited in growing bone. In later life, especially in women after menopause (see Chapter 17), Ca^{2+} is released from bones faster than it can be deposited, and that extra Ca^{2+} is lost in the urine. Consequently, the bone pool of Ca^{2+} becomes smaller, the rate of Ca^{2+} loss from the body exceeds the rate of intake, and Ca^{2+} balance is negative.

In summary, homeostasis is a complex, dynamic process that regulates the adaptive responses of the body to changes in the external and internal environments. To work properly, homeostatic systems require a sensor to detect the environmental change, and a means to produce a compensatory response. Because compensatory responses require muscle activity, behavioral changes, or synthesis of chemical messengers such as hormones, homeostasis is achieved by the expenditure of energy. The nutrients that provide this energy, as well as the cellular structures and chemical reactions that release the energy stored in the chemical bonds of the nutrients, are described in the following two chapters.

1.9 General Principles of Physiology

When you undertake a detailed study of the functions of the human body, several fundamental, general principles of physiology are repeatedly observed. Recognizing these principles and how they manifest in the different organ systems can provide a deeper understanding of the integrated function of the human body. To help you gain this insight, beginning with Chapter 2, the introduction to each chapter will highlight the general principles demonstrated in that chapter. Your understanding of how to apply the following general principles of physiology to a given chapter's content will

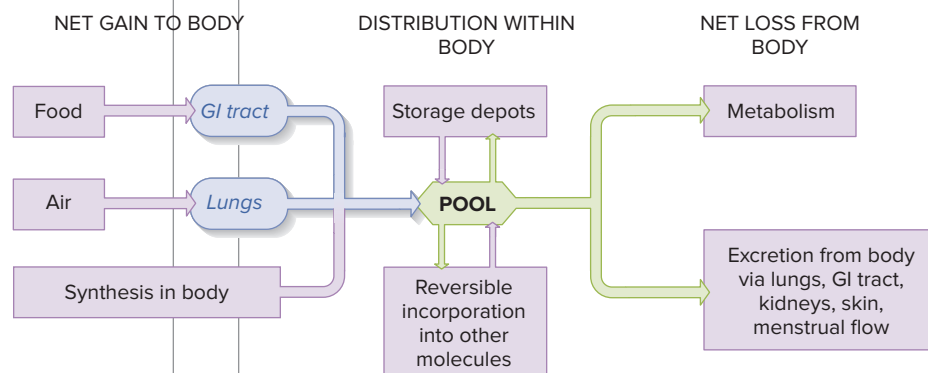


Figure 1.12 Balance diagram for a chemical substance.

then be tested with assessments at the end of the chapter and in Physiological Inquiry questions associated with certain figures.

1. **Homeostasis is essential for health and survival.** The ability to maintain physiological variables such as body temperature and blood sugar concentrations within normal ranges is the underlying principle upon which all physiology is based. Keys to this principle are the processes of feedback and feedforward. Challenges to homeostasis may result from disease or from environmental factors such as famine or exposure to extremes of temperature.
2. **The functions of organ systems are coordinated with each other.** Physiological mechanisms operate and interact at the levels of cells, tissues, organs, and organ systems. Furthermore, the different organ systems in the human body do not function independently of each other. Each system typically interacts with one or more others to control a homeostatic variable. A good example that you will learn about in Chapters 12 and 14 is the coordinated activity of the circulatory and urinary systems in regulating blood pressure. This type of coordination is often referred to as “integration” in physiological contexts.
3. **Most physiological functions are controlled by multiple regulatory systems, often working in opposition.** Typically, control systems in the human body operate such that a given variable, such as heart rate, receives both stimulatory and inhibitory signals. As you will learn in detail in Chapter 6, for example, the nervous system sends both types of signals to the heart; adjusting the ratio of stimulatory to inhibitory signals allows for fine-tuning of the heart rate under changing conditions such as rest or exercise.
4. **Information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes.** Cells can communicate with nearby cells via locally secreted chemical signals; a good example of this is the signaling between cells of the stomach that results in acid production, a key feature of the digestion of proteins (see Chapter 15). Cells in one structure can also communicate long distances using electrical signals or chemical messengers such as hormones. Electrical and hormonal signaling will be discussed throughout the textbook and particularly in Chapters 6, 7, and 11.
5. **Controlled exchange of materials occurs between compartments and across cellular membranes.** The movement of water and solutes—such as ions, sugars, and other molecules—between the extracellular and intracellular fluid is critical for the survival of all cells, tissues, and organs. In this way, important biological molecules are delivered to cells and wastes are removed and eliminated from the body. In addition, regulation of ion movements creates the electrical properties that are crucial to the function of many cell types. These exchanges occur via several different mechanisms, which are introduced in Chapter 4 and are reinforced where appropriate for each organ system throughout the book.
6. **Physiological processes are dictated by the laws of chemistry and physics.** Throughout this textbook, you will encounter some simple chemical reactions, such as the reversible binding of oxygen to the protein hemoglobin in red blood cells (Chapter 13). The basic mechanisms

that regulate such reactions are reviewed in Chapter 3. Physical laws, too, such as gravity, electromagnetism, and the relation between the diameter of a tube and the flow of liquid through the tube, help explain things like why we may feel light-headed upon standing too suddenly (Chapter 12, but also see the Clinical Case Study that follows in this chapter), how our eyes detect light (Chapter 7), and how we inflate our lungs with air (Chapter 13).

7. **Physiological processes require the transfer and balance of matter and energy.** Growth and the maintenance of homeostasis require regulation of the movement and transformation of energy-yielding nutrients and molecular building blocks between the body and the environment and between different regions of the body. Nutrients are ingested (Chapter 15), stored in various forms (Chapter 16), and ultimately metabolized to provide energy that can be stored in the bonds of ATP (Chapters 3 and 16). The concentrations of many inorganic molecules must also be regulated to maintain body structure and function, for example, the Ca^{2+} found in bones (Chapter 11). One of the most important functions of the body is to respond to changing demands, such as the increased requirement for nutrients and oxygen in exercising muscle. This requires a coordinated allocation of resources to regions that most require them at a particular time. The mechanisms by which the organ systems of the body recognize and respond to changing demands is a theme you will encounter repeatedly in Chapters 6 through 19.
8. **Structure is a determinant of—and has coevolved with—function.** The form and composition of cells, tissues, organs, and organ systems determine how they interact with each other and with the physical world. Throughout the text, you will see examples of how different body parts converge in their structure to accomplish similar functions. For example, enormous elaborations of surface areas to facilitate membrane transport and diffusion can be observed in the circulatory (Chapter 12), respiratory (Chapter 13), urinary (Chapter 14), digestive (Chapter 15), and reproductive (Chapter 17) systems. ■

SUMMARY

The Scope of Human Physiology

- I. Physiology is the study of how living organisms work.
Physiologists are interested in the regulation of body function.
- II. The study of disease states is pathophysiology.

How Is the Body Organized?

- I. Cells are the simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life.
- II. Cell differentiation results in the formation of four general categories of specialized cells:
 - a. Muscle cells generate the mechanical activities that produce force and movement.
 - b. Neurons initiate and conduct electrical signals.
 - c. Epithelial cells form barriers and selectively secrete and absorb ions and organic molecules.
 - d. Connective-tissue cells connect, anchor, and support the structures of the body.

- III. Specialized cells associate with similar cells to form tissues: muscle tissue, nervous tissue, epithelial tissue, and connective tissue.
- IV. Organs are composed of two or more of the four kinds of tissues arranged in various proportions and patterns. Many organs contain multiple, small, similar functional units.
- V. An organ system is a collection of organs that together perform an overall function.

Body Fluid Compartments

- I. The body fluids are enclosed in compartments.
 - a. The extracellular fluid is composed of the interstitial fluid (the fluid between cells) and the blood plasma. Of the extracellular fluid, 75%–80% is interstitial fluid, and 20%–25% is plasma.
 - b. Interstitial fluid and plasma have essentially the same composition except that plasma contains a much greater concentration of protein.
 - c. Extracellular fluid differs markedly in composition from the fluid inside cells—the intracellular fluid.
 - d. Approximately one-third of body water is in the extracellular compartment, and two-thirds is intracellular.
- II. The differing compositions of the compartments reflect the activities of the barriers separating them.

Homeostasis: A Defining Feature of Physiology

- I. The body's internal environment is the extracellular fluid.
- II. The function of organ systems is to maintain a stable internal environment—this is called homeostasis.
- III. Numerous variables within the body must be maintained homeostatically. When homeostasis is lost for one variable, it may trigger a series of changes in other variables.

General Characteristics of Homeostatic Control Systems

- I. Homeostasis denotes the stable condition of the internal environment that results from the operation of compensatory homeostatic control systems.
 - a. In a negative feedback control system, a change in the variable being regulated brings about responses that tend to push the variable in the direction opposite to the original change. Negative feedback minimizes changes from the set point of the system, leading to stability.
 - b. Homeostatic control systems minimize changes in the internal environment but cannot maintain complete constancy.
 - c. Feedforward regulation anticipates changes in a regulated variable, improves the speed of the body's homeostatic responses, and minimizes fluctuations in the level of the variable being regulated.

Components of Homeostatic Control Systems

- I. The components of a reflex arc are the receptor, afferent pathway, integrating center, efferent pathway, and effector. The pathways may be neural or hormonal.
- II. Local homeostatic responses are also stimulus–response sequences, but they occur only in the area of the stimulus, with neither nerves nor hormones involved.

The Role of Intercellular Chemical Messengers in Homeostasis

- I. Intercellular communication is essential to reflexes and local responses and is achieved by neurotransmitters, hormones, and paracrine or autocrine substances. Less common is intercellular communication through either gap junctions or cell-bound messengers.

Processes Related to Homeostasis

- I. Acclimatization is an improved ability to respond to an environmental stress. The improvement is induced by prolonged exposure to the stress with no change in genetic endowment.

- II. Biological rhythms provide a feedforward component to homeostatic control systems.
 - a. The rhythms are internally driven by brain pacemakers but are entrained by environmental cues, such as light, which also serve to phase-shift (reset) the rhythms when necessary.
 - b. In the absence of cues, rhythms free-run.
- III. The balance of substances in the body is achieved by matching inputs and outputs. Total-body balance of a substance may be negative, positive, or stable.

General Principles of Physiology

- I. Several fundamental, general principles of physiology are important in understanding how the human body functions at all levels of structure, from cells to organ systems. These include, among others, such things as homeostasis, information flow, coordination between the function of different organ systems, and the balance of matter and energy.

REVIEW QUESTIONS

1. Describe the levels of cellular organization and state the four major types of cells and tissues.
2. List the organ systems of the body and give one-sentence descriptions of their functions.
3. Name the two fluids that constitute the extracellular fluid. What are their relative proportions in the body?
4. What is one way in which the composition of intracellular and extracellular fluids differ?
5. Describe several important generalizations about homeostatic control systems, including the difference between steady state and equilibrium.
6. Contrast feedforward, positive feedback, and negative feedback.
7. List the components of a reflex arc.
8. What is the basic difference between a local homeostatic response and a reflex?
9. List the general categories of intercellular messengers and briefly describe how they differ.
10. Describe the conditions under which acclimatization occurs. Are acclimatizations passed on to a person's offspring?
11. Define *circadian rhythm*. Under what conditions do circadian rhythms become free running?
12. How do phase shifts occur?
13. What is the most important environmental cue for entrainment of circadian rhythms?
14. Draw a figure illustrating the balance concept in homeostasis.
15. Make and keep a list of the general principles of physiology. See if you can explain what is meant by each principle. To really see how well you've learned physiology at the end of your course, remember to return to the list you've made and try this exercise again at that time giving as many examples of each principle as you can.

KEY TERMS

1.1 The Scope of Human Physiology

pathophysiology

physiology

1.2 How Is the Body Organized?

basement membrane

epithelial cells

cell differentiation

epithelial tissue

cells

epithelium

collagen fibers

extracellular matrix

connective tissue

fibers

connective-tissue cells

functional units

elastin fibers

muscle cells

muscle tissue	organ systems
nerve	organs
nervous tissue	tissues
neuron	
1.3 Body Fluid Compartments	
extracellular fluid	interstitium
internal environment	intracellular fluid
interstitial fluid	plasma
1.4 Homeostasis: A Defining Feature of Physiology	
dynamic constancy	homeostasis
1.5 General Characteristics of Homeostatic Control Systems	
equilibrium	positive feedback
feedforward	set point
homeostatic control systems	steady state
negative feedback	
1.6 Components of Homeostatic Control Systems	
acquired reflexes	effector
afferent pathway	efferent pathway

hormone	receptor
integrating center	reflex
learned reflexes	reflex arc
local homeostatic responses	stimulus
1.7 The Role of Intercellular Chemical Messengers in Homeostasis	
autocrine substances	paracrine substances
endocrine glands	target cells
neurotransmitters	
1.8 Processes Related to Homeostasis	
acclimatization	pacemaker
adaptation	phase-shift
circadian rhythm	pineal gland
entrainment	pool
free-running rhythm	positive balance
melatonin	stable balance
negative balance	

CHAPTER 1

Clinical Case Study: Loss of Consciousness in a 64-Year-Old Man While Gardening on a Hot Day



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Throughout this text, you will find a feature at the end of each chapter called the “Clinical Case Study.” These segments reinforce what you have learned in that chapter by applying it to real-life examples of different medical conditions. The clinical case studies will increase in complexity as you progress through the text and will enable you to integrate recent material from a given chapter with information learned in previous chapters. In this first clinical case study, we examine a serious and potentially life-threatening condition that can occur in individuals in whom body temperature homeostasis is disrupted. All of the material presented in this clinical case study will be explored in depth in subsequent chapters, as you learn the mechanisms that underlie the pathologies and compensatory responses illustrated here in brief. Notice as you read that the first two general principles of physiology described earlier are particularly relevant to this case. *It is highly recommended that you return to this case study as a benchmark at the end of your semester; we are certain that you will be amazed at how your understanding of physiology has grown in that time.*

A 64-year-old, fair-skinned man in good overall health spent a very hot, humid summer day gardening in his backyard. After several hours in the sun, he began to feel light-headed and confused as he knelt over his vegetable garden. Although earlier he had been perspiring profusely and appeared flushed, his sweating had eventually stopped. Because he also felt confused and disoriented, he could not recall for how long he had not been perspiring, or even how long it had been since he had taken a drink of water. He called to his wife, who was alarmed to see that his skin had since turned a pale-blue color. She asked her husband to come indoors, but he

fainted as soon as he tried to stand. The wife called for an ambulance, and the man was taken to a hospital and diagnosed with a condition called heatstroke. What happened to this man that would explain his condition? How does it relate to homeostasis?

Reflect and Review #1

- Review the homeostatic control of body temperature in Figure 1.5. Based on that, what would you expect to occur to skin blood vessels when a person first starts feeling warm?

As you learned in this chapter, body temperature is a physiological function that is under homeostatic control. If body temperature decreases, heat production increases and heat loss decreases, as illustrated in Figures 1.5 and 1.9. Conversely, as in our example here, if body temperature increases, heat production decreases and heat loss increases. When our patient began gardening on a hot, humid day, his body temperature began to increase. At first, the blood vessels in his skin dilated, making him appear flushed and helping him dissipate heat across his skin. In addition, he perspired heavily. As you will learn in Chapter 16, perspiration is an important mechanism by which the body loses heat; it takes considerable heat to evaporate water from the surface of the skin, and the source of that heat is from the body. However, as you likely know from personal experience, evaporation of water from the body is less effective in humid environments, which makes it more dangerous to exercise when it is not only hot but also humid.

The sources of perspiration are the sweat glands, which are located beneath the skin and which secrete a salty solution through ducts to the surface of the skin. The fluid in sweat comes from the extracellular fluid compartment, which, as you have learned, consists of the plasma and interstitial fluid compartments (see Figure 1.3). Consequently, the profuse sweating that initially

—Continued next page

—Continued

occurred in this man caused his extracellular fluid levels to decrease. In fact, the fluid levels decreased so severely that the amount of blood available to be pumped out of his heart with each heartbeat also decreased. The relationship between fluid volume and blood pressure is an important one that you will learn about in detail in Chapter 12. Generally speaking, if extracellular fluid levels decrease, blood pressure decreases as a consequence. This explains why our subject felt light-headed, particularly when he tried to stand up too quickly. As his blood pressure decreased, the ability of his heart to pump sufficient blood against gravity up to his brain also decreased; when brain cells are deprived of blood flow, they begin to malfunction. Suddenly standing only made matters worse. Perhaps you have occasionally experienced a little of this light-headed feeling when you have jumped out of a chair or bed and stood up too quickly. Normally, your nervous system quickly compensates for the effects of gravity on blood flowing up to the brain, as will be described in Chapters 6 and 12. In a person with decreased blood volume and pressure, however, this compensation may not happen and the person can lose consciousness. After fainting and falling, the man's head and heart were at the same horizontal level; consequently, blood could more easily reach his brain.

Another concern is that the salt (ion) concentrations in the body fluids changed. If you have ever tasted the sweat on your upper lip on a hot day, you know that it is somewhat salty. That is because sweat is derived from extracellular fluid, which as you have learned is a watery solution of ions (derived from salts, such as NaCl) and other substances. Sweat, however, is slightly more dilute than extracellular fluid because more water than ions is secreted from sweat glands. Consequently, the more heavily one perspires, the more concentrated the extracellular fluid becomes. In other words, the total amount of water and ions in the extracellular fluid decreases with perspiration, but the remaining fluid is "saltier." Heavy perspiration, therefore, not only disrupts fluid balance and blood pressure homeostasis but also has an impact on the balance of the ions in the body fluids, notably Na^+ , K^+ , and Cl^- . A homeostatic balance of ion concentrations in the body fluids is absolutely essential for normal heart and brain function, as you will learn in Chapters 4 and 6. As the man's ion concentrations changed, therefore, the change affected the activity of the cells of his brain.

Reflect and Review #2

- Refer to Figure 1.12. Was the man in a positive or negative balance for total-body Na^+ ?

Why did the man stop perspiring and why did his skin turn pale? To understand this, we must consider that several homeostatic variables were disrupted by his activities. His body temperature increased, which initially resulted in heavy sweating. As the sweating continued, it resulted in decreased fluid levels and a negative balance of key ion concentrations in his body; this contributed to a decrease in mental function, and he became confused. As his body fluid levels continued to decrease, his blood pressure also decreased, further endangering brain function. At this point, the homeostatic control systems were essentially in competition. Though it is potentially life threatening for body temperature to

increase too much, it is also life threatening for blood pressure to decrease too much. Eventually, many of the blood vessels in regions of the body that are not immediately required for survival, such as the skin, began to constrict, or close off. By doing so, the more vital organs of the body—such as the brain—could receive sufficient blood. This is why the man's skin turned a pale blue, because the amount of oxygen-rich blood flowing to the surface of his skin was decreased. Unfortunately, although this compensatory mechanism helped protect the man's brain and other vital organs by providing the necessary blood flow to them, the reduction in blood flow to the skin made it increasingly more difficult to dissipate heat from the body to the environment. It also made it more difficult for sweat glands in the skin to obtain the fluid required to produce sweat. The man gradually decreased perspiring and eventually stopped sweating altogether. At that point, his body temperature spiraled out of control and he was hospitalized (**Figure 1.13**).

This case illustrates a critical feature of homeostasis that you will encounter throughout this textbook and that was emphasized in this chapter. Often, when one physiological variable such as body temperature is disrupted, the compensatory responses initiated to correct that disruption cause, in turn, imbalances in other variables. These secondary imbalances must also be compensated for, and the significance of each imbalance must be "weighed" against the others. In this example, the man was treated with intravenous fluids made up of a salt solution to restore his fluid levels and concentrations, and he was immersed in a cool bath and given cool compresses to help reduce his body temperature. Although he recovered, many people do not survive heatstroke because of its profound impact on homeostasis.

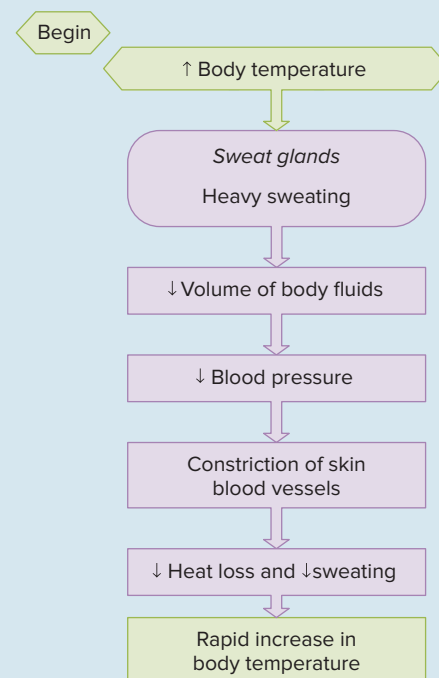


Figure 1.13 Sequence of events that occurred in the man described in this case study.

See Chapter 19 for complete, integrative case studies.

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.

- Which of the following is one of the four basic cell types in the body?
 - respiratory
 - epithelial
 - endocrine
 - integumentary
 - immune
- Which of the following is incorrect?
 - Equilibrium requires a constant input of energy.
 - Positive feedback is less common in nature than negative feedback.
 - Homeostasis does not imply that a given variable is unchanging.
 - Fever is an example of resetting a set point.
 - Efferent pathways carry information away from the integrating center of a reflex arc.
- In a reflex arc initiated by touching a hand to a hot stove, the effector belongs to which class of tissue?
 - nervous
 - connective
 - muscle
 - epithelial
- In the absence of any environmental cues, a circadian rhythm is said to be
 - entrained.
 - in phase.
 - free running.
 - phase-shifted.
 - no longer present.
- Most of the water in the human body is found in
 - the interstitial fluid compartment.
 - the intracellular fluid compartment.
 - the plasma compartment.
 - the total extracellular fluid compartment.
- The type of tissue involved in many types of transport processes, and which often lines the inner surfaces of tubular structures, is called _____.
- All the fluid found outside cells is collectively called _____ fluid, and consists of _____ and _____ fluid.
- Physiological changes that occur in anticipation of a future change to a homeostatic variable are called _____ processes.
- A _____ is a chemical factor released by cells that acts on neighboring cells without having to first enter the blood.
- When loss of a substance from the body exceeds its gain, a person is said to be in _____ balance for that substance.

CHAPTER 1 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.

- The Inuit of Alaska and Canada have a remarkable ability to work in the cold without gloves and not suffer decreased skin blood flow. Does this prove that there is a genetic difference between the Inuit and other people with regard to this characteristic? *Hint:* Refer back to “Adaptation and Acclimatization” in Section 1.8.
- Explain how an imbalance in any given physiological variable may produce a change in one or more *other* variables. *Hint:* For help, see Section 1.4 and Figure 1.13 (in the Clinical Case Study in this chapter).

CHAPTER 1 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 1.3 Approximately one-third of total-body water is in the extracellular compartments. If water makes up 60% of a person’s body weight, then the water in extracellular fluid makes up approximately 20% of body weight (because $0.33 \times 0.60 = 0.20$).

Figure 1.6 Removing negative feedback in this example would result in an increase in the amount of active product formed, and eventually the amount of available substrate would be greatly depleted.

Figure 1.9 If body temperature were to increase, the efferent pathway shown in this diagram would either turn off or become reversed. For example, shivering would not occur (muscles may even become more relaxed than usual), and blood vessels in the skin would not constrict. Indeed, in such a scenario, skin blood vessels would dilate to bring warm blood to the skin surface, where the heat could leave the body across the skin. Heat loss, therefore, would be increased.

ONLINE STUDY TOOLS



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

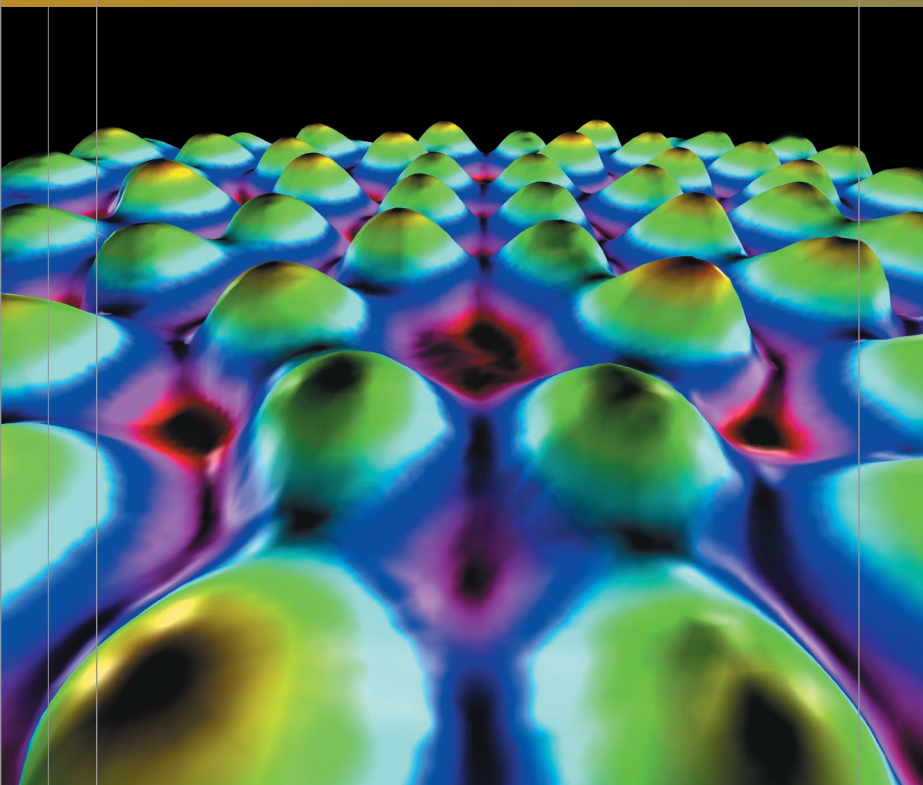


Do you have trouble accessing and retaining key concepts when reading a textbook? This personalized adaptive learning tool serves as a guide to your reading by helping you discover which aspects of homeostasis you have mastered, and which will require more attention.



A fascinating view inside real human bodies that also incorporates animations to help you understand homeostasis, the central idea of physiology.

Chemical Composition of the Body and Its Relation to Physiology



Scanning tunneling micrograph of individual silicon atoms on a silicon chip. ©Andrew Dunn/Alamy Stock Photo

In Chapter 1, you were introduced to the concept of homeostasis, in which variables such as the concentrations of many chemicals in the blood are maintained within a normal range. To fully appreciate the mechanisms by which homeostasis is achieved, we must first understand the basic chemistry of the human body, including the key features of atoms and molecules that contribute to their ability to interact with one another. Such interactions form the basis for processes as diverse as maintaining a healthy pH of the body fluids, determining which molecules will bind to or otherwise influence the function of other molecules, forming functional proteins that mediate numerous physiological processes, and maintaining energy homeostasis.

In this chapter, we also describe the distinguishing characteristics of some of the major organic molecules in the human body. The specific functions of these molecules in physiology will be introduced here and discussed more fully in subsequent chapters where appropriate. This chapter will provide you with the knowledge required to best appreciate the significance of one of the general principles of physiology introduced in Chapter 1, namely that physiological processes are dictated by the laws of chemistry and physics. ■

2.1 Atoms

Components of Atoms

Atomic Number

Atomic Mass

Ions

Atomic Composition of the Body

2.2 Molecules

Covalent Chemical Bonds

Ionic Bonds

Hydrogen Bonds

Molecular Shape

Ionic Molecules

Free Radicals

2.3 Solutions

Water

Molecular Solubility

Concentration

Hydrogen Ions and Acidity

2.4 Classes of Organic Molecules

Carbohydrates

Lipids

Proteins

Nucleic Acids

Chapter 2 Clinical Case Study

2.1 Atoms

The units of matter that form all chemical substances are called **atoms**. Each type of atom—carbon, hydrogen, oxygen, and so on—is called a **chemical element**. A one- or two-letter symbol is used as an abbreviated identification for each element. Although more than 100 elements occur naturally or have been synthesized in the laboratory, only 24 (**Table 2.1**) have been clearly identified as essential for the function of the human body and are therefore of particular interest to physiologists.

Components of Atoms

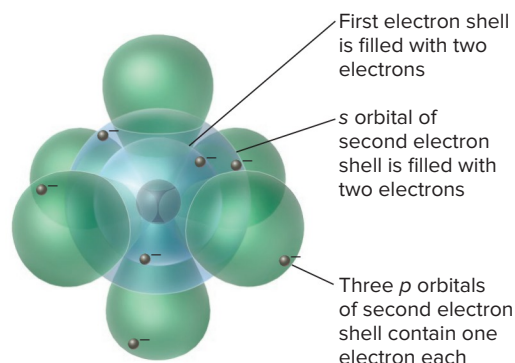
The chemical properties of atoms can be described in terms of three subatomic particles—**protons**, **neutrons**, and **electrons**. The protons and neutrons are confined to a very small volume at the center of

TABLE 2.1

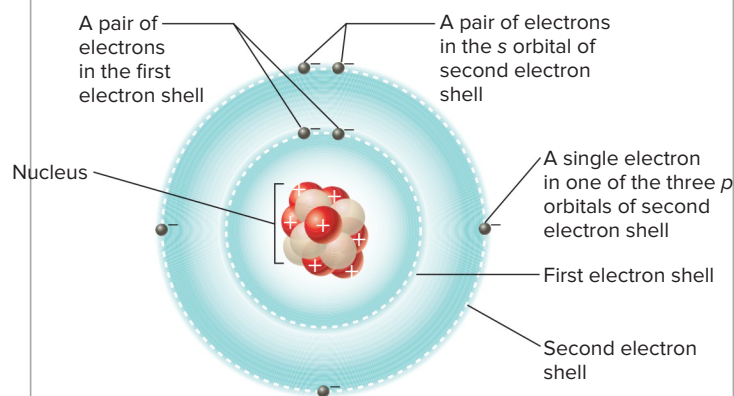
Essential Chemical Elements in the Body
(Neo-Latin Terms in *Italics*)

Element	Symbol
<i>Major Elements: 99.3% of Total Atoms in the Body</i>	
Hydrogen	H (63%)
Oxygen	O (26%)
Carbon	C (9%)
Nitrogen	N (1%)
<i>Mineral Elements: 0.7% of Total Atoms in the Body</i>	
Calcium	Ca
Phosphorus	P
Potassium	K (<i>kalium</i>)
Sulfur	S
Sodium	Na (<i>natrium</i>)
Chlorine	Cl
Magnesium	Mg
<i>Trace Elements: Less than 0.01% of Total Atoms in the Body</i>	
Iron	Fe (<i>ferrum</i>)
Iodine	I
Copper	Cu (<i>cuprum</i>)
Zinc	Zn
Manganese	Mn
Cobalt	Co
Chromium	Cr
Selenium	Se
Molybdenum	Mo
Fluorine	F
Tin	Sn (<i>stannum</i>)
Silicon	Si
Vanadium	V

an atom called the **atomic nucleus**. The electrons revolve in orbitals at various distances from the nucleus. Each orbital can hold up to two electrons and no more. The larger the atom, the more electrons it contains, and therefore the more orbitals that exist around the nucleus. Orbitals are found in regions known as electron shells; additional shells exist at greater and greater distances from the nucleus as atoms get bigger. An atom such as carbon has more shells than does hydrogen with its lone electron, but fewer than an atom such as iron, which has a greater number of electrons. The first, innermost shell of any atom can hold up to two electrons in a single, spherical (“s”) orbital (**Figure 2.1a**). Once the lone orbital of the innermost shell is filled, electrons begin to fill the second shell. The second shell can hold up to eight electrons; the first two electrons fill a spherical orbital, and subsequent electrons fill three additional, propeller-shaped (“p”) orbitals. Additional shells can accommodate further orbitals; this will happen once the inner shells are filled. For simplicity, we will ignore the distinction between *s* and *p* orbitals and represent the shells of an atom in two dimensions as shown in **Figure 2.1b** for nitrogen.



(a) Nitrogen atom showing electrons in orbitals



(b) Simplified depiction of a nitrogen atom (seven electrons; two electrons in first electron shell, five in second electron shell)

AP|R Figure 2.1 Arrangement of subatomic particles in an atom, shown here for nitrogen. (a) Negatively charged electrons orbit around a nucleus consisting of positively charged protons and (except for hydrogen) uncharged neutrons. Up to two electrons may occupy an orbital, shown here as regions in which an electron is likely to be found. The orbitals exist within electron shells at progressively greater distances from the nucleus as atoms get bigger. The first electron shell contains only a single orbital; progressively distant shells may contain a different number of orbitals. (b) Simplified, two-dimensional depiction of a nitrogen atom, showing a full complement of two electrons in its innermost shell and five electrons in its second, outermost shell. Orbitals are not depicted using this simplified means of illustrating an atom.

An atom is most stable when all of the orbitals in its outermost shell are filled with two electrons each. If one or more orbitals do not have their capacity of electrons, the atom can react with other atoms and form molecules, as described later. For many of the atoms that are most important for physiology, the outer shell requires eight electrons in its orbitals in order to be filled to capacity.

Each of the subatomic particles has a different electrical charge. Protons have one unit of positive charge, electrons have one unit of negative charge, and neutrons are electrically neutral. Because the protons are located in the atomic nucleus, the nucleus has a net positive charge equal to the number of protons it contains. One of the fundamental principles of physics is that opposite electrical charges attract each other and like charges repel each other. It is the attraction between the positively charged protons and the negatively charged electrons that serves as a major force that forms an atom. The entire atom has no net electrical charge, however, because the number of negatively charged electrons orbiting the nucleus equals the number of positively charged protons in the nucleus.

Atomic Number

Each chemical element contains a unique and specific number of protons, and it is this number, known as the **atomic number**, that distinguishes one type of atom from another. For example, hydrogen, the simplest atom, has an atomic number of 1, corresponding to its single proton. As another example, calcium has an atomic number of 20, corresponding to its 20 protons. Because an atom is electrically neutral, the atomic number is also equal to the number of electrons in the atom.

Atomic Mass

Atoms have very little mass. A single hydrogen atom, for example, has a mass of only 1.67×10^{-24} g. The **atomic mass** scale indicates an atom's mass relative to the mass of other atoms. By convention, this scale is based upon assigning the carbon atom a mass of exactly 12. On this scale, a hydrogen atom has an atomic mass of approximately 1, indicating that it has one-twelfth the mass of a carbon atom. A magnesium atom, with an atomic mass of 24, has twice the mass of a carbon atom. The unit of atomic mass is known as a dalton. One dalton (d) equals one-twelfth the mass of a carbon atom.

Although the number of neutrons in the nucleus of an atom is often equal to the number of protons, many chemical elements can exist in multiple forms, called **isotopes**, which have identical numbers of protons but which differ in the number of neutrons they contain. For example, the most abundant form of the carbon atom, ^{12}C , contains six protons and six neutrons and therefore has an atomic number of 6. Protons and neutrons are approximately equal in mass, and so ^{12}C has an atomic mass of 12. The radioactive carbon isotope ^{14}C contains six protons and eight neutrons, giving it an atomic number of 6 but an atomic mass of 14. The value of atomic mass given in the standard Periodic Table of the Elements is actually an average mass that reflects the relative abundance in nature of the different isotopes of a given element.

Many isotopes are unstable; they will spontaneously emit energy or even release components of the atom itself, such as part of the nucleus. This process is known as radiation, and such isotopes are called **radioisotopes**. The special qualities of radioisotopes

are of great practical benefit in the practice of medicine and the study of physiology. In one example, high-energy radiation can be focused onto cancerous areas of the body to kill cancer cells. Radioisotopes may also be useful in making diagnoses. In one common method, the sugar glucose can be chemically modified so that it contains a radioactive isotope of fluorine. When injected into the blood, the cells of all of the organs of the body take up the radioactive glucose just as they would ordinary glucose. Special imaging techniques such as **PET (positron emission tomography) scans** can then be used to detect how much of the radioactive glucose appears in different organs (**Figure 2.2**); because glucose is a key source of energy used by all cells, this information can be used to determine if a given organ is functioning normally or at an increased or decreased rate. For example, a PET scan that revealed decreased uptake of radioactive glucose into the heart might indicate that the blood vessels of the heart were diseased, thereby depriving the heart of nutrients. PET scans can also reveal the presence of cancer—a disease characterized by uncontrolled cell growth and increased glucose uptake.

The **gram atomic mass** of a chemical element is the amount of the element, in grams, equal to the numerical value of its atomic mass. Thus, 12 g of carbon (assuming it is all ^{12}C) is 1 gram

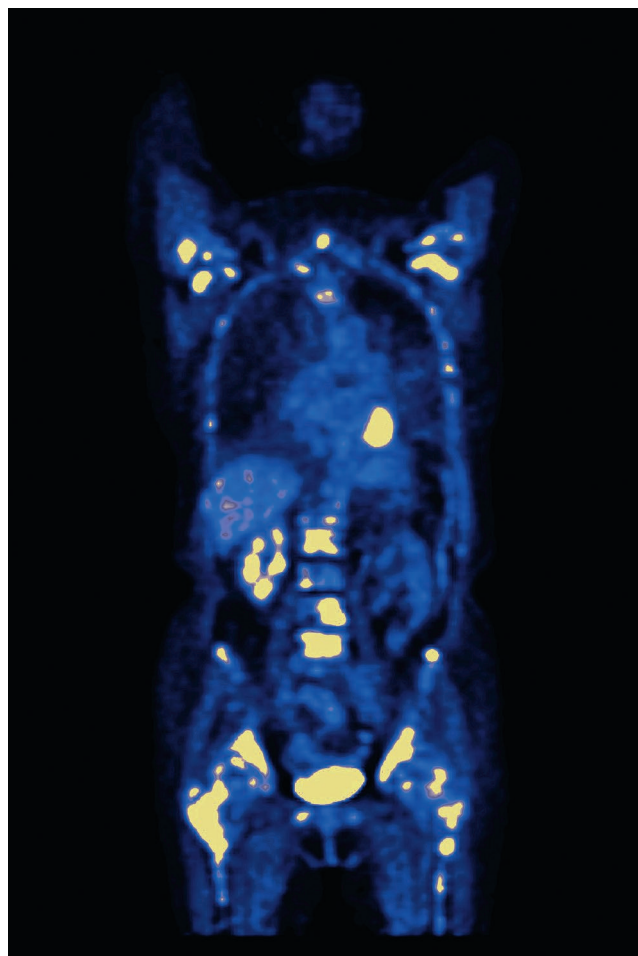


Figure 2.2 Positron emission tomography (PET) scan of a human body. In this image, radioactive glucose that has been taken up by the body's organs appears as a false color; the greater the uptake, the more intense the color. The brightest regions were found to be areas of cancer in this particular individual. ©Living Art Enterprises/Science Source

atomic mass of carbon, and 1 g of hydrogen is 1 gram atomic mass of hydrogen. *One gram atomic mass of any element contains the same number of atoms.* For example, 1 g of hydrogen contains 6×10^{23} atoms; likewise, 12 g of carbon, whose atoms have 12 times the mass of a hydrogen atom, also has 6×10^{23} atoms (this value is often called Avogadro's constant, or Avogadro's number, after the nineteenth-century Italian scientist Amedeo Avogadro).

Ions

As mentioned earlier, a single atom is electrically neutral because it contains equal numbers of negative electrons and positive protons. There are instances, however, in which certain atoms may gain or lose one or more electrons; in such cases, they will then acquire a net electrical charge and become an **ion**. This may happen, for example, if an atom has an outer shell that contains only one or a few electrons; losing those electrons would mean that the next innermost shell would then become the outermost shell. This shell is complete with a full capacity of electrons and is therefore very stable (recall that each successive shell does not begin to acquire electrons until all the preceding inner shells are filled). For example, when a sodium atom (Na), which has 11 electrons, loses one electron, it becomes a sodium ion (Na^+) with a net positive charge; it still has 11 protons, but it now has only 10 electrons, two in its first shell and a full complement of eight in its second, outer shell. On the other hand, a chlorine atom (Cl), which has 17 electrons, is one electron shy of a full outer shell. It can gain an electron and become a chloride ion (Cl^-) with a net negative charge—it now has 18 electrons but only 17 protons. Some atoms can gain or lose more than one electron to become ions with two or even three units of net electrical charge (for example, the calcium ion Ca^{2+}).

Hydrogen and many other atoms readily form ions. **Table 2.2** lists the ionic forms of some of these elements that are found in the body. Ions that have a net positive charge are called **cations**, and those that have a net negative charge are called **anions**. Because of their charge, ions are able to conduct electricity when dissolved in water; consequently, the ionic forms of mineral elements are collectively referred to as **electrolytes**. This is extremely important in physiology, because electrolytes are used to carry electrical charge across cell membranes; in this way, they serve as the source of electrical current in certain cells. You will learn in Chapters 6, 9, and 12 that such currents are critical to the ability of muscle cells and neurons to function in their characteristic ways.

Atomic Composition of the Body

Just four of the body's essential elements (see Table 2.1)—hydrogen, oxygen, carbon, and nitrogen—account for over 99% of the atoms in the body.

The seven essential **mineral elements** are the most abundant substances dissolved in the extracellular and intracellular fluids. Most of the body's calcium and phosphorus atoms, however, make up the solid matrix of bone tissue.

The 13 essential **trace elements**, so-called because they are present in extremely small quantities, are required for normal growth and function. For example, iron has a critical function in the blood's transport of oxygen, and iodine is required for the production of thyroid hormone.

Many other elements, in addition to the 24 listed in Table 2.1, may be detected in the body. These elements enter in the foods we eat and the air we breathe but are not essential for normal body function and may even interfere with normal body chemistry. For example, ingested arsenic has poisonous effects.

2.2 Molecules

Two or more atoms bonded together make up a **molecule**. A molecule made up of two or more different elements is called a compound, but the two terms are often used interchangeably. For example, a molecule of oxygen gas consists of two atoms of oxygen bonded together. By contrast, water is a compound that contains two hydrogen atoms and one oxygen atom. For simplicity, we will simply use the term *molecule* in this textbook. Molecules can be represented by their component atoms. In the two examples just given, a molecule of oxygen can be represented as O_2 and water as H_2O . The atomic composition of glucose, a sugar, is $\text{C}_6\text{H}_{12}\text{O}_6$, indicating that the molecule contains 6 carbon atoms, 12 hydrogen atoms, and 6 oxygen atoms. Such formulas, however, do not indicate how the atoms are linked together in the molecule. This occurs by means of chemical bonds, as described next.

Covalent Chemical Bonds

Chemical bonds between atoms in a molecule form when electrons transfer from the outer electron shell of one atom to that of another, or when two atoms with partially unfilled electron orbitals share electrons. The strongest chemical bond between two atoms is called a **covalent bond**, which forms when one or more electrons in the outer electron orbitals of each atom are shared

TABLE 2.2 Ionic Forms of Elements Most Frequently Encountered in the Body

Chemical Atom	Symbol	Ion	Chemical Symbol	Electrons Gained or Lost
Hydrogen	H	Hydrogen ion	H^+	1 lost
Sodium	Na	Sodium ion	Na^+	1 lost
Potassium	K	Potassium ion	K^+	1 lost
Chlorine	Cl	Chloride ion	Cl^-	1 gained
Magnesium	Mg	Magnesium ion	Mg^{2+}	2 lost
Calcium	Ca	Calcium ion	Ca^{2+}	2 lost