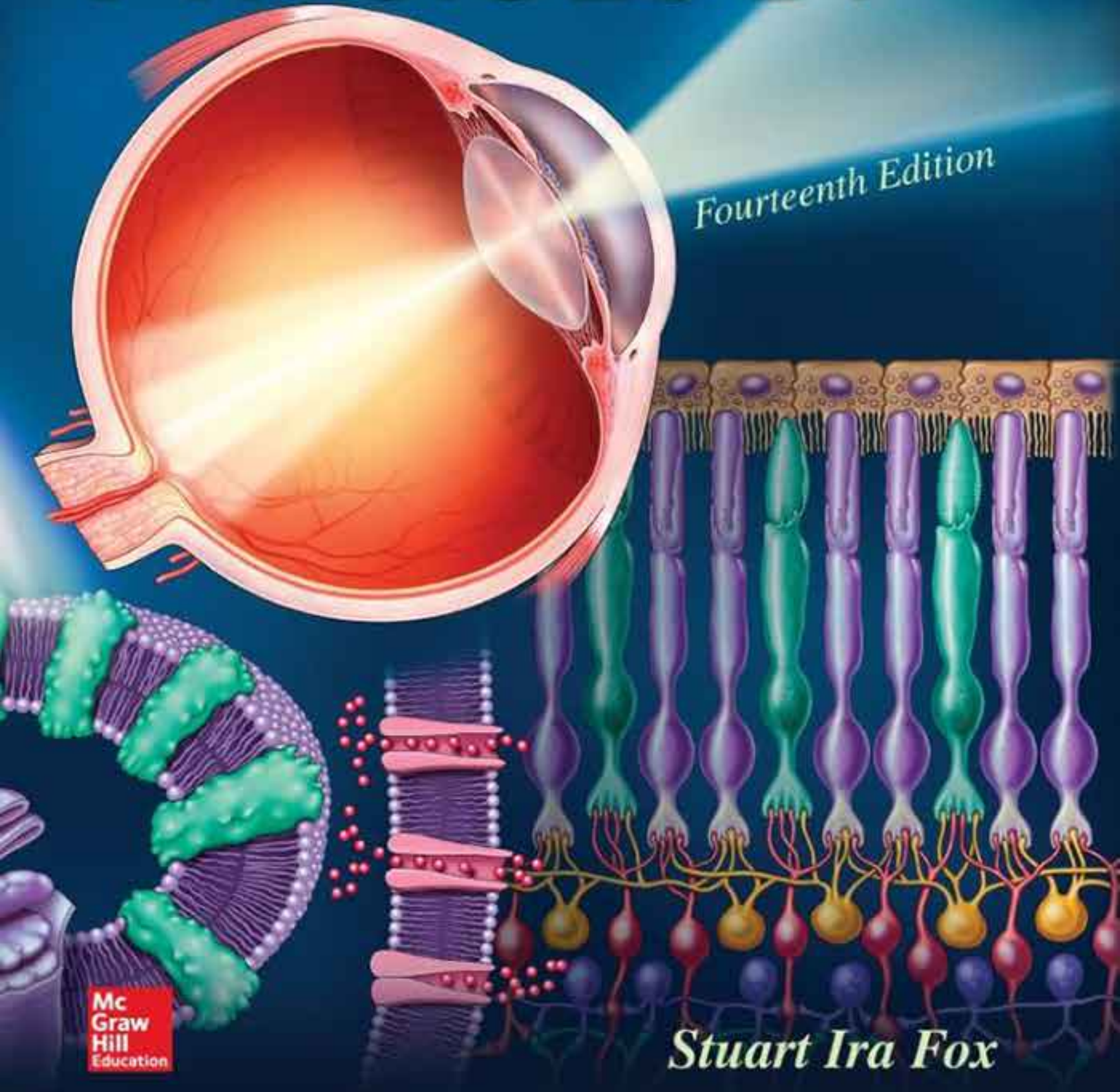
Human PHYSIOLOGY

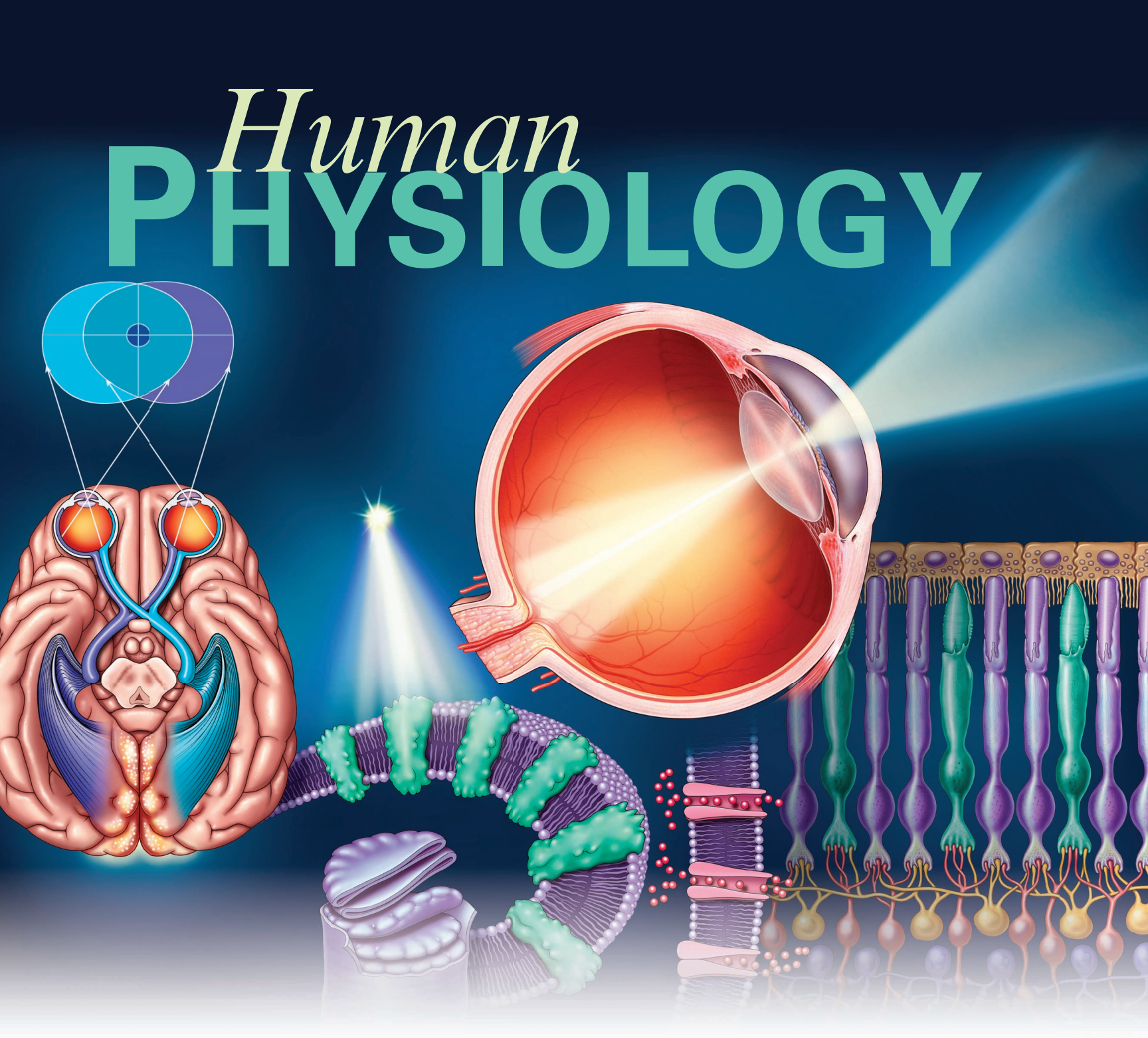
Fourteenth Edition



Mc Graw Hill Education

Stuart Ira Fox

Human PHYSIOLOGY



Stuart Ira Fox
Pierce College

Mc Graw Hill Education

HUMAN PHYSIOLOGY, FOURTEENTH EDITION

This book is printed on acid-free paper.

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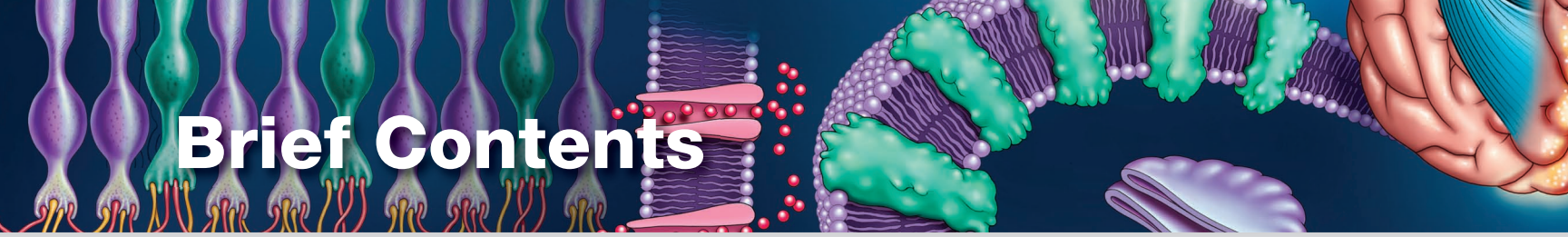


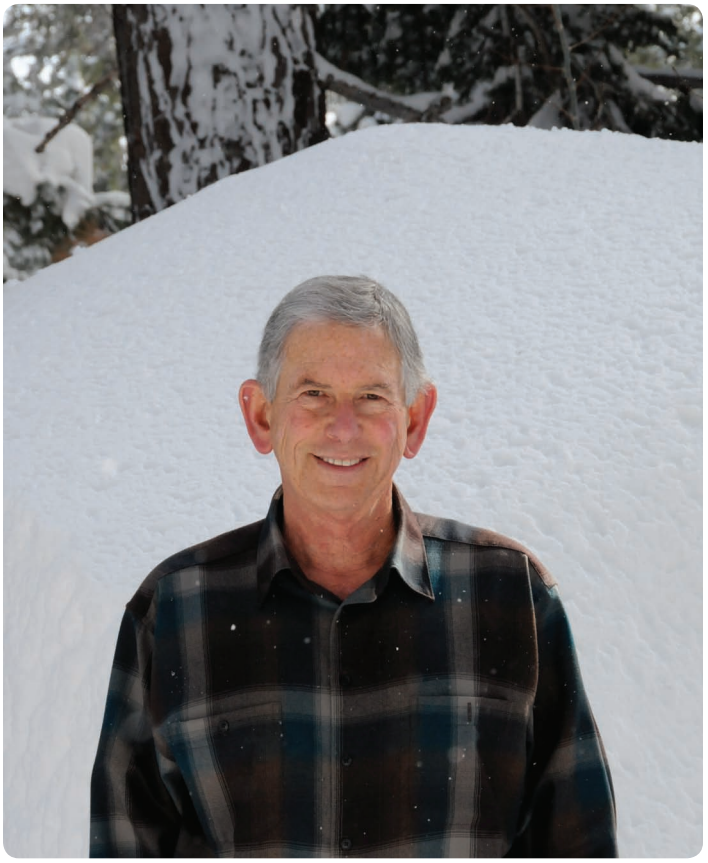
Brief Contents

About the Author

Stuart Ira Fox earned a Ph.D. in human physiology from the Department of Physiology, School of Medicine, at the University of Southern California, after earning degrees at the University of California at Los Angeles (UCLA); California State University, Los Angeles; and UC Santa Barbara. He has spent most of his professional life teaching at Los Angeles City College; California State University, Northridge; and Pierce College, where he has won numerous teaching awards, including several Golden Apples. Stuart has authored thirty-nine editions of seven textbooks, which are used worldwide and have been translated into several languages, and two novels. When not engaged in professional activities, he likes to hike, fly fish, and cross-country ski in the Eastern Sierra Nevada Mountains.

I wrote the first edition of *Human Physiology* to provide my students with a readable textbook to support the lecture material and help them understand physiology concepts they would need later in their health curricula and professions. This approach turned out to have wide appeal, which afforded me the opportunity to refine and update the text with each new edition. Writing new editions is a challenging educational experience, and an activity I find immensely enjoyable. Although changes have occurred in the scientific understanding and applications of physiological concepts, the students using this fourteenth edition have the same needs as those who used the first, and so my writing goals have remained the same. I am thankful for the privilege of being able to serve students and their instructors through these fourteen editions of *Human Physiology.*

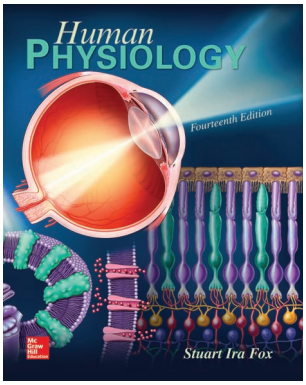
—Stuart Ira Fox



To my wife, Ellen;
and to Laura, Eric, Kayleigh, and Jacob Van Gilder; for all the important reasons.

Preface

The Cover



William B. Westwood's cover illustration of the eye and the structures and processes required for vision encompasses the study of physiology at multiple levels. The physiology of vision entails the biophysical processes of light becoming focused onto and interacting with photoreceptors, the molecular and cellular constituents of these receptors that enable them to respond to light, and neural interactions needed for the brain to meaningfully interpret this stimulation.

Photoreceptors are located in the part of the eye and brain called the retina, which is a neural layer at the back of the eye. The front cover shows light entering the eye and becoming focused by the lens onto the retina. The outer segments of photoreceptors contain stacks of membranes, shown as purple at the bottom of the book's spine, which contain the photoreceptor pigment rhodopsin (the green structures within the membranes at the bottom left of the front cover).

The bottom middle of the front cover illustrates a plasma membrane of a photoreceptor neuron containing ion channels (pink). In the dark, these channels allow Na^+ ions (pink spheres) to enter the photoreceptor. Light induces a change in the rhodopsin that initiates a signaling pathway (not shown), which leads to the closing of these channels (shown by the bottom channel). This indirectly causes the photoreceptors to stimulate other neurons in the retina (bipolar cells, depicted in red near the bottom of the front cover), which then stimulate another layer of neurons (ganglion cells, depicted green at the bottom of the front cover.).

The axons (nerve fibers) of the ganglion cells gather together to form the optic nerves, which leave the eye to carry visual information to the brain, as shown on the back cover. The visual fields illustrated as blue and purple circles on the back cover stimulate different regions of the retina. Because many of the axons in the optic nerves cross to the opposite side, aspects of the right visual field are conveyed to the left cerebral cortex and vice versa, as illustrated by the blue and purple colors of the nerve tracts. Physiological processes continue within the brain, allowing it to create images that our mind interprets as the reality of the external world.

What Sets This Book Apart?

The study of human physiology provides the scientific foundation for the field of medicine and all other professions related to human health and physical performance. The scope of topics included in a human physiology course is therefore wide-ranging, yet each topic must be covered in sufficient detail to provide a firm basis for future expansion and application.

Human Physiology, fourteenth edition, is written for the undergraduate introductory human physiology course. Based on the author's extensive experience with teaching this course, the framework of the textbook is designed to provide basic biology and chemistry (chapters 2–5) before delving into more complex physiological processes. This approach is appreciated by both instructors and students; specific references in later chapters direct readers back to the foundational material as needed, presenting a self-contained study of human physiology.

In addition to not presupposing student's preparedness, this popular textbook is known for its clear and approachable writing style, detailed realistic art, and unsurpassed clinical information.

Acknowledgments

Reviewers

Patti Allen, Dixie State College
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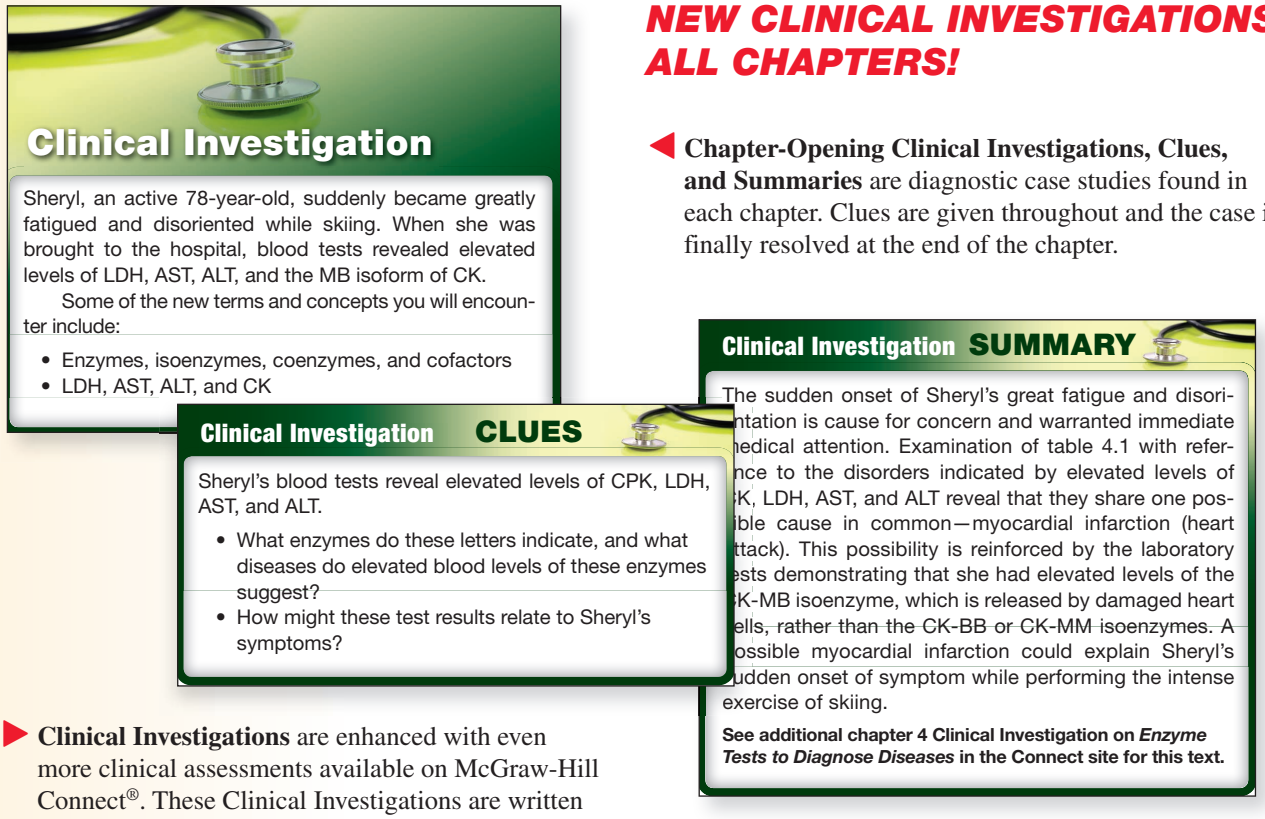
GUIDED TOUR

WHAT MAKES THIS TEXT A MARKET LEADER?

Clinical Applications—No Other Human Physiology Text Has More!

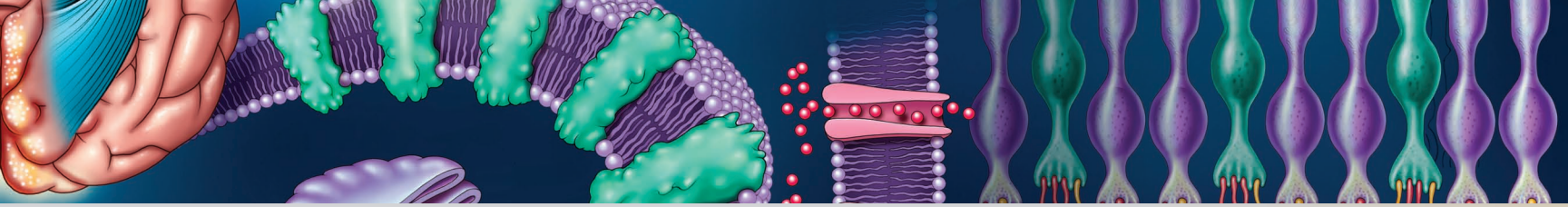
The framework of this textbook is based on integrating clinically germane information with knowledge of the body's physiological processes. Examples of this abound throughout the book. For example, in a clinical setting we record electrical activity from the body: this includes action potentials (chapter 7, section 7.2); EEG (chapter 8, section 8.2); and ECG (chapter 13, section 13.5). We also record mechanical force in muscle contractions (chapter 12, section 12.3). We note blood plasma measurements of many chemicals to assess internal body conditions. These include measurements of blood glucose (chapter 1, section 1.2) and the oral glucose tolerance test (chapter 19, section 19.4); and measurements of the blood cholesterol profile (chapter 13, section 13.7). These are just a few of many examples the author includes that focus on the connections between the study of physiology and our health industry.



NEW CLINICAL INVESTIGATIONS IN ALL CHAPTERS!

◀ **Chapter-Opening Clinical Investigations, Clues, and Summaries** are diagnostic case studies found in each chapter. Clues are given throughout and the case is finally resolved at the end of the chapter.

▶ **Clinical Investigations** are enhanced with even more clinical assessments available on McGraw-Hill Connect®. These Clinical Investigations are written by the author and are specific to each chapter. They will offer the students great insight into that specific chapter.



ALL APPLICATION BOXES ARE NEW OR UPDATED!

Clinical Application Boxes are in-depth boxed essays that explore relevant topics of clinical interest and are placed at key points in the chapter to support the surrounding material. Subjects covered include pathologies, current research, pharmacology, and a variety of clinical diseases.

CLINICAL APPLICATION

When diseases damage tissues, some cells die and release their enzymes into the blood. The activity of these enzymes, reflecting their concentrations in the blood plasma, can be measured in a test tube by adding their specific substrates. Because an increase in certain enzymes in the blood can indicate damage to specific organs, such tests may aid the diagnosis of diseases. An increase in a man's blood levels of the acid, phosphatase, for example, may result from disease of the prostate (table 4.1).

FITNESS APPLICATION

Metabolic syndrome is a combination of abnormal measurements—including central obesity (excess abdominal fat), hypertension (high blood pressure), insulin resistance (prediabetes), type 2 diabetes mellitus, high plasma triglycerides, and high LDL cholesterol—that greatly increase the risk of coronary heart disease, stroke, diabetes mellitus, and other conditions. The incidence of metabolic syndrome has increased alarmingly in recent years because of the increase in obesity. Eating excessive calories, particularly in the form of sugars (including high fructose corn syrup), stimulates insulin secretion. Insulin then promotes the uptake of blood glucose into adipose cells, where (through lipogenesis) it is converted into stored triglycerides (see figs. 5.12 and 5.13). Conversely, the lowering of insulin secretion, by diets that prevent the plasma glucose from rising sharply, promotes lipolysis (the breakdown of fat) and weight loss.

Fitness Application Boxes are readings that explore physiological principles as applied to well-being, sports medicine, exercise physiology, and aging. They are also placed at relevant points in the text to highlight concepts just covered in the chapter.

Learning Outcomes are numbered for easy referencing in digital material!

LEARNING OUTCOMES

After studying this section, you should be able to:

2. Describe the aerobic cell respiration of glucose through the citric acid cycle.

3. Describe the electron transport system and oxidative phosphorylation, explaining the role of oxygen in this process.

Learning Outcome numbers are tied directly to **Checkpoint numbers!**

CHECKPOINT

2a. Compare the fate of pyruvate in aerobic and anaerobic cell respiration.

2b. Draw a simplified citric acid cycle and indicate the high-energy products.

3a. Explain how NADH and $FADH_2$ contribute to oxidative phosphorylation.

3b. Explain how ATP is produced in oxidative phosphorylation.

GUIDED TOUR

WHAT MAKES THIS TEXT A MARKET LEADER?

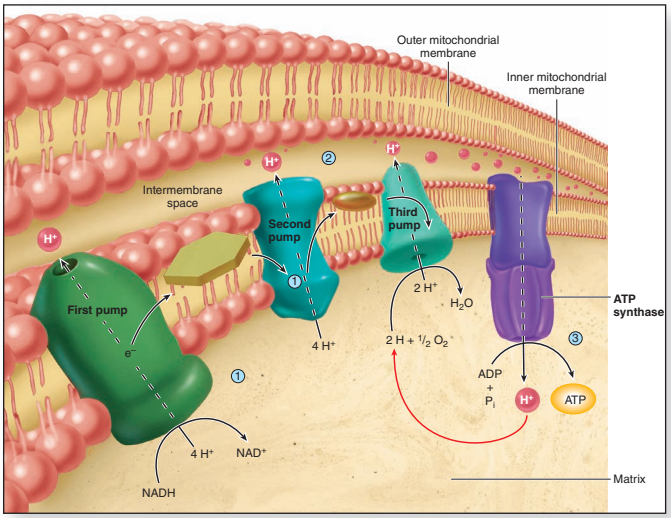
Writing Style—Easygoing, Logical, and Concise

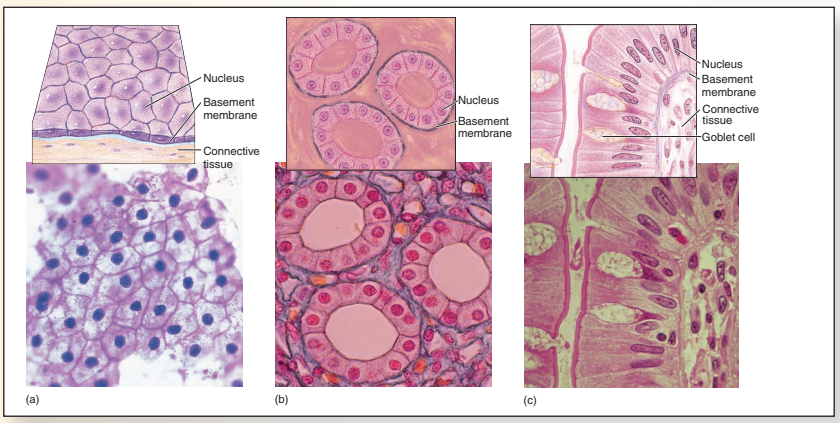
The words in *Human Physiology,* fourteenth edition, read as if the author is explaining concepts to you in a one-on-one conversation, pausing now and then to check and make sure you understand what he is saying. Each major section begins with a short overview of the information to follow. Numerous **comparisons** ("Unlike the life of an organism, which can be viewed as a linear progression from birth to death, the life of a cell follows a cyclical pattern"), **examples** ("A callus on the hand, for example, involves thickening of the skin by hyperplasia due to frequent abrasion"), **reminders** ("Recall that each member of a homologous pair came from a different parent"), and **analogies** ("In addition to this 'shuffling of the deck' of chromosomes . . ."') lend the author's style a comfortable grace that enables readers to easily flow from one topic to the next.

Exceptional Art—Designed from the Student's Point of View

What better way to support such unparalleled writing than with high-quality art? Large, bright illustrations demonstrate the physiological processes of the human body beautifully in a variety of ways.

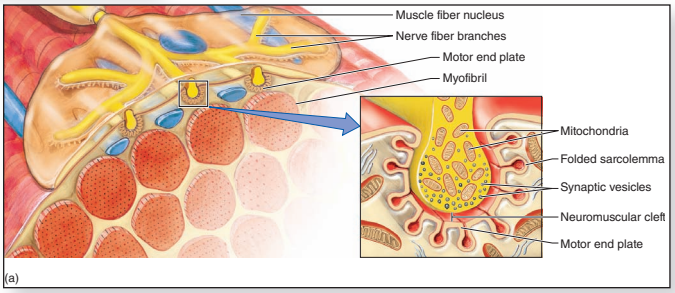
Stepped-out art clearly depicts various stages or movements with numbered explanations.

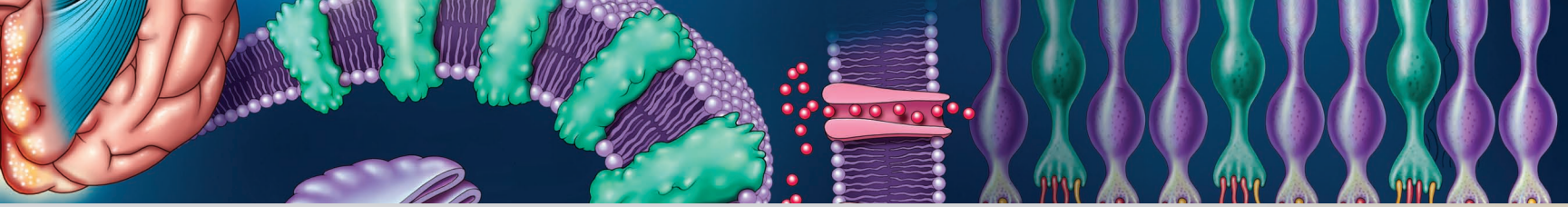




Labeled photos placed side by side with illustrations allow diagrammatic detail and realistic application.

Macro-to-micro art helps students put context around detailed concepts.





FOURTEENTH EDITION CHANGES

What's New?

Human Physiology, fourteenth edition, incorporates a number of new and recently modified physiological concepts. This may surprise people who are unfamiliar with the subject; indeed, the author sometimes is asked if the field really changes much from one edition to the next. It does; that's one of the reasons physiology is so much fun to study. Stuart has tried to impart this sense of excitement and fun in the book by indicating, in a manner appropriate for this level of student, where knowledge is new and where gaps in our knowledge remain.

The list that follows indicates only the larger areas of text and figure revisions and updates. It doesn't indicate instances where passages were rewritten to improve the clarity or accuracy of the existing material, or smaller changes made in response to information from recently published journals and from the reviewers of the previous edition.

GLOBAL CHANGES:

- Each Clinical Investigation in every chapter of the textbook is new.
- Each of the Clinical Investigation Clues, in every chapter, is new.
- The Clinical Investigation Summaries at the ends of all chapters are new.
- Every Clinical Application box, in each and every chapter, has been rewritten and updated.
- Every Fitness Application box, in each and every chapter, has been rewritten and updated.

MAJOR CHANGES IN CHAPTERS

These are specific changes made in the individual chapters in addition to the global changes described above.

Chapter 1: The Study of Body Function

- Discussions of exfoliative cytology and Pap smear added.
- Discussions of embryonic stem cells, totipotency, and pluripotency added.

Chapter 3: Cell Structure and Genetic Control

- New figures 3.3, 3.4, 3.7, 3.9*a,* and 3.18.
- Descriptions of microtubules and autophagosomes updated.
- Updated discussion of mitochondria, including hereditary mitochondrial diseases.
- Updated and expanded discussion of the agranular endoplasmic reticulum and drug tolerance.
- Updated and expanded discussion of genes, including new description of retrotransposons.
- Updated discussion of microRNA and new description of circular RNA.
- Updated discussion of the medical uses of RNA interference.
- Updated discussion of epigenetic regulation and its significance.

Chapter 5: Cell Respiration and Metabolism

- Updated description of the respiratory assemblies and their functions.
- New discussion of inherited mitochondrial diseases.
- Updated discussion of metabolic syndrome.
- Updated and expanded discussion of brown fat.

Chapter 6: Interactions Between Cells and the Extracellular Environment

- New figure 6.22*b*.
- Updated discussion of dialysis and hemodialysis.

Chapter 7: The Nervous System: Neurons and Synapses

- Updated and expanded discussions of microglia, axon regeneration, neurotrophins, astrocytes, and of microglia.
- Discussion of the structure and function of gap junctions updated and expanded.
- Figure 7.23 updated and revised.
- Explanation of synaptic vesicle docking and exocytosis updated and expanded.
- Expanded Table 7.4.
- New discussion of different subtypes of muscarinic ACh receptors.
- Updated and expanded discussion of dopamine receptors and new discussion of atypical antipsychotic drugs.
- Updated discussion of inhibitory neurotransmitters.
- Expanded discussion of endocannabinoid neurotransmitters.
- New discussion of hydrogen sulfide as a neurotransmitter.

Chapter 8: The Central Nervous System

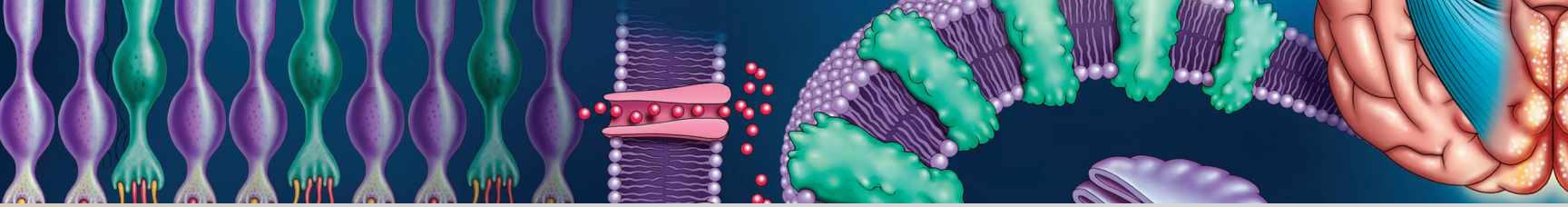
- New photos in figures 8.9, 8.17, and 8.18.
- Updated and expanded discussion of CSF formation and circulation.
- Updated discussion of neurogenesis in the adult brain.
- Updated discussion of the origin of the electroencephalogram.
- New discussion of transient ischemic attack and stroke.
- Updated description of brain areas involved in memory storage.
- Updated and expanded discussion of Alzheimer's disease.
- Updated and expanded discussion of the molecular mechanisms involved in memory formation.
- Updated and expanded discussion of the roles of dendritic spines and neurogenesis in memory formation.
- Updated discussion of the regulation of circadian rhythms.
- Updated discussion of the role of the nucleus accumbens in the reward pathway.
- Updated discussion of orexin and new discussion of hypnotic drugs.

Chapter 9: The Autonomic Nervous System

- New discussion of β_3-adrenergic receptors added.

Chapter 10: Sensory Physiology

- New figures 10.10 and 10.14*a.*
- Updated and expanded discussions of nociceptors, afferent fiber categories, and spinal cord lamina.
- Discussion of salty taste updated.



- Updated and expanded discussion of olfactory processing.
- Discussion of the structure and function of the cochlea updated and expanded.
- New discussion of the role of microsaccades in vision.
- New discussion of direction sensitive ganglion cells in vision.

Chapter 11: Endocrine Glands: Secretion and Action of Hormones

- New photos in figures 11.24 and 11.26.
- Updated and expanded discussion of the different drugs used to treat breast cancer.
- Updated and expanded discussion of insulin receptor structure and function.
- Revised rendering of insulin receptor in figure 11.11.
- Updated and expanded discussion of anterior pituitary cells and the hormones they produce.
- Updated and expanded discussion of stress and glucocorticoid effects.
- Updated discussions of calcitonin and the pancreatic islets.
- New discussion of adipokines and myokines.

Chapter 12: Muscle: Mechanisms of Contraction and Neural Control

- Expanded discussion of motor end plates and new explanation of end plate potential.
- New figure 12.9*a*.
- New discussion of the SERCA pumps in muscle contraction and relaxation.
- New discussion of muscle glycogen and exercise.
- Updated discussion of muscle metabolism of fat during exercise.
- New discussion of myokines and irisin.
- Updated and expanded discussion of satellite cells in muscle regeneration and sarcopenia.
- Updated and expanded discussion of calcium-induced calcium release in cardiac muscle.
- New discussion of calcium puffs and sparks in smooth muscle contraction.
- New discussion of myosin light-chain phosphatase in smooth muscle relaxation.

Chapter 13: Blood, Heart, and Circulation

- New discussion of the dietary need for iron in erythropoiesis.
- Updated discussions of hepcidin and the intrinsic clotting pathway.
- Updated discussion of the role of platelets in blood clotting and the use of warfarin to inhibit blood clotting.
- Updated and expanded discussion of the origin of the pacemaker potential.
- New discussion of sinoatrial conduction pathways and ectopic foci.
- Updated discussion of calcium pumping in the regulation of the heartbeat.
- New figure 13.31.
- Updated discussion of atherosclerosis.
- Updated discussion of myocardial infarction and diet.
- Updated and expanded discussion of blood tests to detect myocardial infarction.
- New discussion of interstitial fluid and the extracellular matrix.

Chapter 14: Cardiac Output, Blood Flow, and Blood Pressure

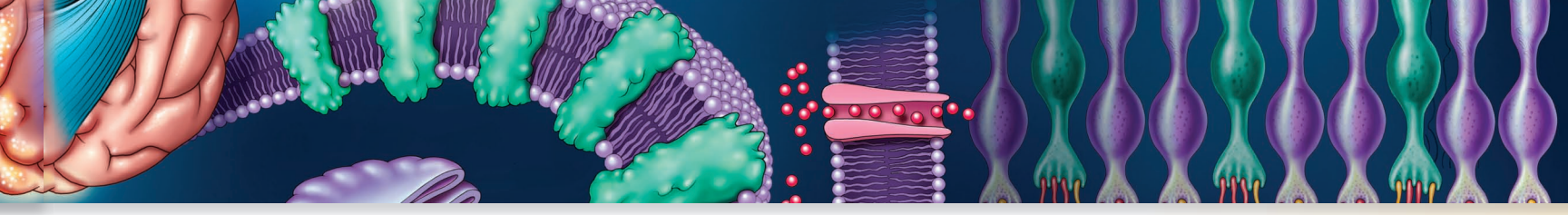
- New comparison of the pulmonary and systemic circulations.
- Updated discussion of the effects of sympathetic and parasympathetic nerves on the cardiac rate.
- Expanded discussion on the resting cardiac rate.
- New discussion of the Anrep effect.
- New discussion of neurovascular coupling and functional hyperemia.
- New goals for the treatment of hypertension discussed.
- Updated discussion of the mechanisms responsible for hypertension.
- Updated discussion of the role of dietary salt in hypertension.

Chapter 15: The Immune System

- Updated and expanded discussion of epithelial membranes and immunity.
- New discussion of NOD-like receptors and immunity.
- Updated and expanded discussion of opsonization and phagocytosis.
- Updated discussions of interferons and of secondary lymphoid organs.
- Updated discussion of the effects of mast cell cytokines in local inflammation.
- Updated discussion of the roles of resident macrophages and neutrophils in an inflammation.
- New figure 15.9.
- Updated discussions of helper and regulatory T cells and antigen-presenting cells.
- Updated discussion of MHC class-1 and class-2 molecules.
- Updated discussion of immune response to viral infections.
- Figures 15.15, 15.17, and 15.18 revised.
- Updated and expanded discussions of memory T cells and of adjuvants.
- New discussion of intravenous immunoglobulin.
- New discussion of humanized monoclonal antibodies and adoptive cell transfer.
- New discussion of natural killer T cells.
- Updated discussion of autoimmune and allergic reactions.
- Updated and expanded discussion of contact dermatitis.

Chapter 16: Respiratory Physiology

- Updated description of alveoli structure and function.
- New figures 16.3 and 16.5.
- Revised discussion of surfactant and respiratory distress syndrome.
- Updated and expanded discussion of the function of the diaphragm in ventilation.
- Updated discussions of asthma and of the pulmonary capillaries.
- Updated and expanded discussion of the mechanisms of ventilation/perfusion matching.
- Revised discussion of pulmonary hypertension and cor pulmonale.
- Updated and expanded discussion of the central regulation of breathing.



- Updated and expanded discussions of the carotid bodies and the central chemoreceptors.
- Updated discussion of the role of nitric oxide in acclimatization to high altitude.

Chapter 17: Physiology of the Kidneys

- Updated discussion of glomerular structure and function.
- New figure 17.9.
- Updated discussion of the renal tubule transport of sodium and chloride.
- Revised discussion of the countercurrent multiplier system.
- Updated discussion of urea transporters and aquaporin channels in the vasa recta.
- Updated discussion of countercurrent exchange in the renal medulla.
- Updated and expanded discussion of the role of urea in concentrating the urine.
- New discussion of arginine vasopressin as the antidiuretic hormone, and updated discussion of its secretion.
- Revised organization of the sections on renal plasma clearance.
- Updated discussion of renal tubule potassium secretion.
- Updated discussion of the roles of kidney-generated angiotensin II.
- New discussion of B-type natriuretic peptide.
- Updated discussion of ammonia produced by the renal tubules.

Chapter 18: The Digestive System

- Revised figure 18.7 and new fig. 18.11.
- Updated discussion of the lower esophageal sphincter.
- New discussion of parietal cells and potassium recycling.
- Updated discussion of Paneth cells and intestinal stem cells.
- Updated and expanded discussion of the enteric nervous system.
- Updated discussion of intestinal slow waves and action potentials.
- Updated and expanded discussion of the origin and function of the intestinal microbiota.
- Updated and expanded discussion of the antimicrobial properties of the intestinal mucosa.
- New discussion of the gut-associated lymphoid tissue.
- New discussions of Clostridium difficile infections and fecal microbiota transplantation.
- Updated discussions of liver fibrosis and cirrhosis.
- Updated and expanded discussion of transport processes in the pancreatic acini.
- New discussion of the function of somatostatin secreted by the D cells of the pancreatic islets.
- New discussion of incretins in the regulation of insulin secretion.
- Updated discussion of CCK in the regulation of pancreatic juice secretion.
- Updated discussion of secretin action.
- Updated discussions of fat transport and fatty acid uptake.

Chapter 19: Regulation of Metabolism

- New figures 19.17 and 19.20*a*.
- New discussion of hypothermia and hypothermic circulatory arrest.
- Updated discussion of the formation of the superoxide radical.
- Updated discussions of adipocyte turnover, and adipose tissue in starvation and obesity.
- Discussion of weight-loss medications updated.
- Updated and expanded discussion of hypothalamic neurons and neurotransmitters involved in the regulation of eating.
- Updated discussion of leptin and its regulation of appetite.
- New discussion of beige (or brite) adipocytes.
- Updated discussion of the mechanisms of beta cell insulin secretion.
- Updated discussion of how autonomic nerves and somatostatin regulate insulin secretion.
- Updated and expanded discussions of type 1 and type 2 diabetes and their treatments.
- New discussion on the roles of ectopic fat and visceral obesity in impaired glucose tolerance and type 2 diabetes.
- New discussion of soluble and insoluble fiber and its affect on insulin resistance.
- Updated discussion of dwarfism and new discussion of achondroplasia.
- Updated discussion of the regulation of osteoclast formation.
- New discussion of articular cartilage regeneration.
- Discussion of calcitonin updated.
- New discussion of osteocalcin and updated discussion of leptin actions on bone.
- Updated and expanded discussion of intestinal calcium absorption and the actions of vitamin D.
- Updated discussion of the actions of parathyroid hormone on renal phosphate excretion.

Chapter 20: Reproduction

- New figures 20.3, 20.40, and 20.42*c*.
- Updated discussion of X chromosome inactivation and SRY.
- New discussion of kisspeptins and the regulation of GnRH secretion.
- Updated discussion of DHT and estradiol in male physiology.
- Updated discussion of spermatogenesis and the blood-testis barrier.
- Updated and expanded discussions of the mechanisms of penile erection and of male contraception.
- Updated and expanded discussion of ovarian follicle hormone production and its regulation.
- Updated and expanded discussion of female contraception.
- Updated and expanded discussion of sperm capacitation and hyperactivation.
- New discussion of CatSper channels in sperm.
- Updated discussion of fertilization.
- Updated and expanded discussion of cloning and pluripotency.
- Updated discussion of stem cells in regenerative medicine.
- Updated discussion of adult stem cells and transdifferentiation.
- Updated and expanded discussion of the pituitary-like hormones secreted by the placenta.
- Table 20.7 updated and expanded.

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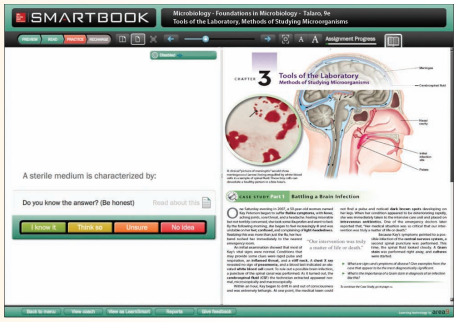

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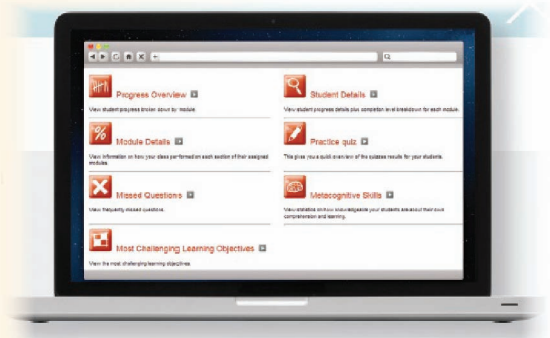

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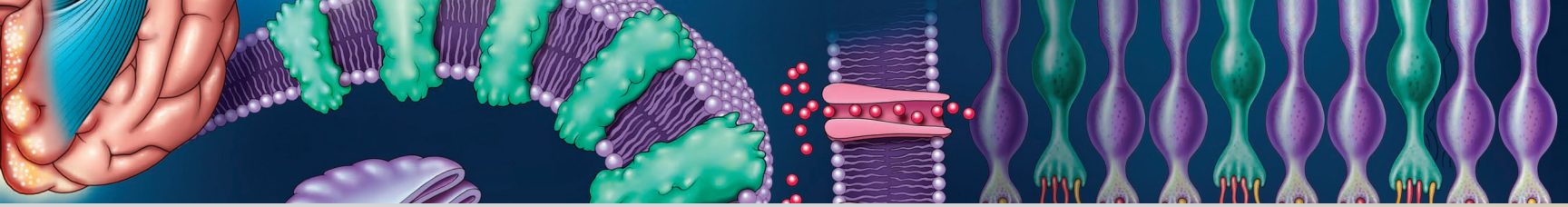

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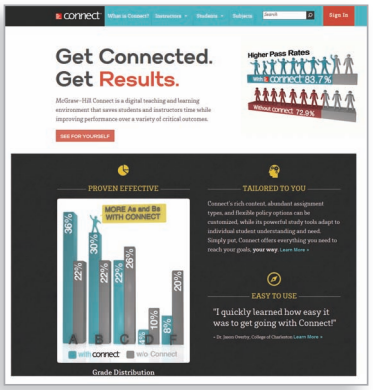

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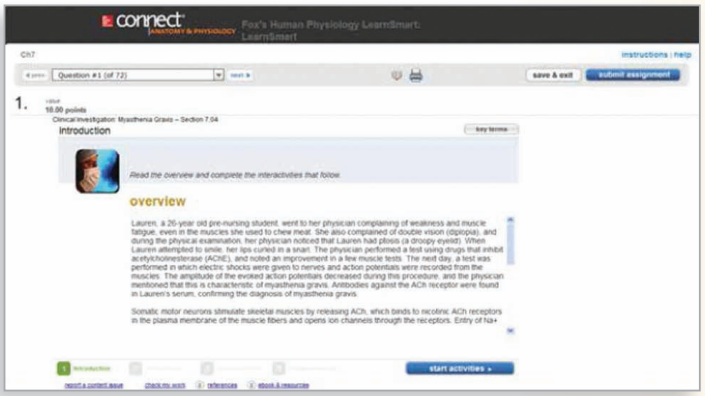

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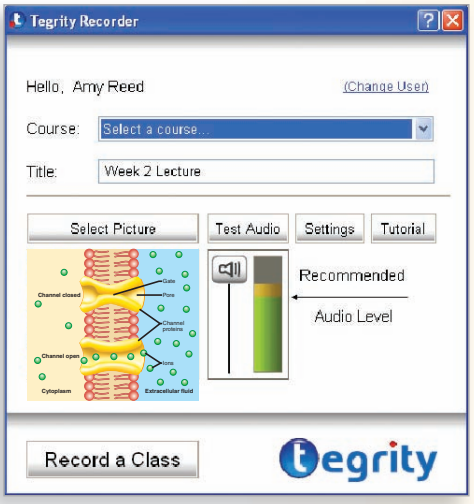

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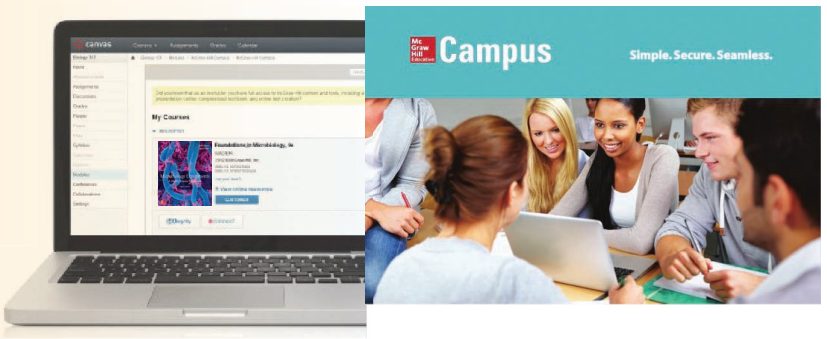

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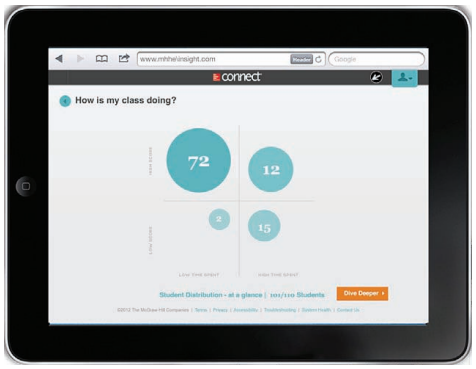
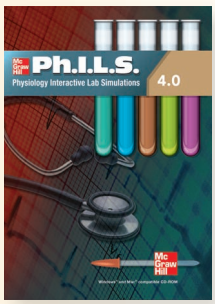
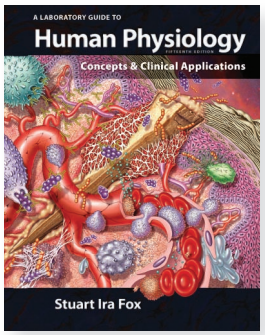
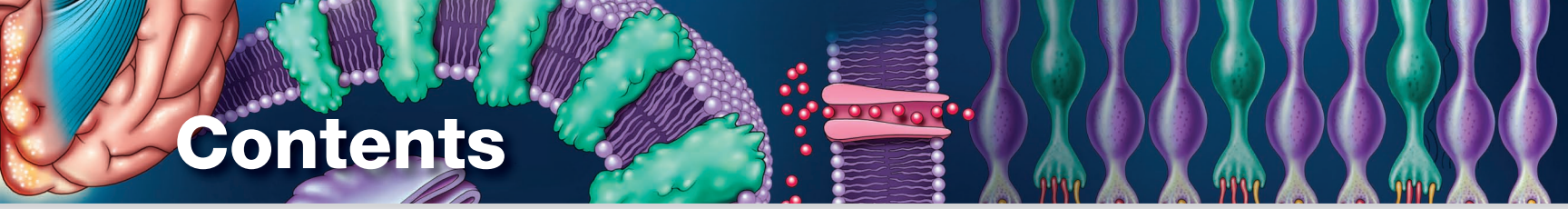




Ph.I.L.S. 4.0 has been updated! Users have requested and we are providing ***five new exercises*** (Respiratory Quotient, Weight & Contraction, Insulin and Glucose Tolerance, Blood Typing, and Anti-Diuretic Hormone). **Ph.I.L.S. 4.0** is the perfect way to reinforce key physiology concepts with powerful Jab experiments. Created by Dr. Phil Stephens at Villanova University, this program offers ***42 laboratory simulations*** that may be used to supplement or substitute for wet labs. All 42 labs are self-contained experiments—no lengthy instruction manual required. Users can adjust variables, view outcomes, make predictions, draw conclusions, and print lab reports. This easy-to-use software offers the flexibility to change the parameters of the lab experiment. There is no limit!

Fox's Laboratory Guide to Human Physiology: Concepts and Clinical Applications, **13th edition,** contains time- and student-tested laboratory exercises that support most of the subjects covered in a human physiology course. It functions as a standalone manual, but is particularly well suited far use with Fox's *Human Physiology,* textbook.





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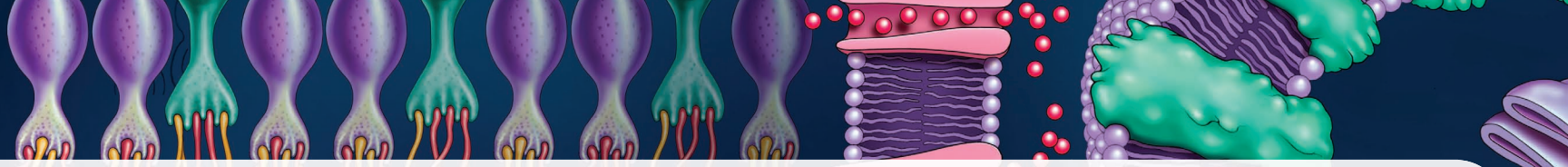

CHAPTER OUTLINE

CHAPTER 1

The Study of Body Function

Clinical Investigation

As you study the sections of chapter 1, you can see how your new knowledge can be applied to interesting health issues that may be important to know in your future career as a health professional. This can add zest to your studies and increase your motivation to truly understand physiological concepts, rather than to simply memorize facts for examinations. Each chapter begins with a medical mystery for you to solve, using information in the text of that chapter and "Clinical Investigation Clues" within the chapter.

For example, suppose Linda goes for a medical examination where her body temperature is measured, and she gives a fasting blood sample to test for glucose. Your first Clinical Investigation challenge is to determine the medical significance of these physiological tests.

1.1 INTRODUCTION TO PHYSIOLOGY

Human physiology is the study of how the human body functions, with emphasis on specific cause-and-effect mechanisms. Knowledge of these mechanisms has been obtained experimentally through applications of the scientific method.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. Describe the scientific study of human physiology.
2. Describe the characteristics of the scientific method.

Physiology (from the Greek *physis* = nature; *logos* = study) is the study of biological function—of how the body works, from molecular mechanisms within cells to the actions of tissues, organs, and systems, and how the organism as a whole accomplishes particular tasks essential for life. In the study of physiology, the emphasis is on mechanisms—with questions that begin with the word *how* and answers that involve cause-and-effect sequences. These sequences can be woven into larger and larger stories that include descriptions of the structures involved (anatomy) and that overlap with the sciences of chemistry and physics.

The separate facts and relationships of these cause-and-effect sequences are derived empirically from experimental evidence. Explanations that seem logical are not necessarily true; they are only as valid as the data on which they are based, and they can change as new techniques are developed and further experiments are performed. The ultimate objective of physiological research is to understand the normal functioning of cells, organs, and systems. A related science—*pathophysiology*—is concerned with how physiological processes are altered in disease or injury.

Pathophysiology and the study of normal physiology complement one another. For example, a standard technique for investigating the functioning of an organ is to observe what happens when the organ is surgically removed from an experimental animal or when its function is altered in a specific way. This study is often aided by "experiments of nature"—diseases—that involve specific damage to the functioning of an organ. The study of disease processes has thus aided our understanding of normal functioning, and the study of normal physiology has provided much of the scientific basis of modern medicine. This relationship is recognized by the Nobel Prize committee, whose members award prizes in the category "Physiology or Medicine."

The physiology of invertebrates and of different vertebrate groups is studied in the science of *comparative physiology.* Much of the knowledge gained from comparative physiology has benefited the study of human physiology. This is because animals, including humans, are more alike than they are different. This is especially true when comparing humans with other mammals. The small differences in physiology between humans and other mammals can be of crucial importance in the development of pharmaceutical drugs (discussed later in this section), but these differences are relatively slight in the overall study of physiology.

Scientific Method

All of the information in this text has been gained by people applying the **scientific method.** Although many different techniques are involved when people apply the scientific method, all share three attributes: (1) confidence that the natural world, including ourselves, is ultimately explainable in terms we can understand; (2) descriptions and explanations of the natural world that are honestly based on observations and that could be modified or refuted by other observations; and (3) humility, or the willingness to accept the fact that we could be wrong. If further study should yield conclusions that refuted all or part of an idea, the idea would have to be modified accordingly. In short, the scientific method is based on a confidence in our rational ability, honesty, and humility. Practicing scientists may not always display these attributes, but the validity of the large body of scientific knowledge that has been accumulated—as shown by the technological applications and the predictive value of scientific hypotheses—are ample testimony to the fact that the scientific method works.

The scientific method involves specific steps. After certain observations regarding the natural world are made, a **hypothesis** is formulated. In order for this hypothesis to be scientific, it must be capable of being refuted by experiments or other observations of the natural world. For example, one might hypothesize that people who exercise regularly have a lower resting pulse rate than other people. Experiments are conducted, or other observations are made, and the results are analyzed. Conclusions are then drawn as to whether the new

data either refute or support the hypothesis. If the hypothesis survives such testing, it might be incorporated into a more general **theory.** Scientific theories are thus not simply conjectures; they are statements about the natural world that incorporate a number of proven hypotheses. They serve as a logical framework by which these hypotheses can be interrelated and provide the basis for predictions that may as yet be untested.

The hypothesis in the preceding example is scientific because it is *testable;* the pulse rates of 100 athletes and 100 sedentary people could be measured, for example, to see if there were statistically significant differences. If there were, the statement that athletes, on the average, have lower resting pulse rates than other people would be justified *based on these data.* One must still be open to the fact that this conclusion could be wrong. Before the discovery could become generally accepted as fact, other scientists would have to consistently replicate the results. Scientific theories are based on *reproducible* data.

It is quite possible that when others attempt to replicate the experiment, their results will be slightly different. They may then construct scientific hypotheses that the differences in resting pulse rate also depend on other factors, such as the nature of the exercise performed. When scientists attempt to test these hypotheses, they will likely encounter new problems requiring new explanatory hypotheses, which then must be tested by additional experiments.

In this way, a large body of highly specialized information is gradually accumulated, and a more generalized explanation (a scientific theory) can be formulated. This explanation will almost always be different from preconceived notions. People who follow the scientific method will then appropriately modify their concepts, realizing that their new ideas will probably have to be changed again in the future as additional experiments are performed.

Use of Measurements, Controls, and Statistics

Suppose you wanted to test the hypothesis that a regular exercise program causes people to have a lower resting heart rate. First, you would have to decide on the nature of the exercise program. Then, you would have to decide how the heart rate (or pulse rate) would be measured. This is a typical problem in physiology research because the testing of most physiological hypotheses requires quantitative **measurements.**

The group that is subject to the testing condition—in this case, exercise—is called the **experimental group.** A measurement of the heart rate for this group would be meaningful only if it is compared to that of another group, known as the **control group.** How shall this control group be chosen? Perhaps the subjects could serve as their own controls—that is, a person's resting heart rate could be measured before and after the exercise regimen. If this isn't possible, a control group could be other people who do not follow the exercise program. The choice of control groups is often a controversial aspect of physiology studies. In this example, did the people in the control group really refrain from *any* exercise? Were they comparable to the people in the experimental group with regard to age, sex, ethnicity, body weight, health status, and so on? You can see how difficult it could be in practice to get a control group that could satisfy any potential criticism.

Another possible criticism could be bias in the way that the scientists perform the measurements. This bias could be completely unintentional; scientists are human, after all, and they may have invested months or years in this project. To prevent such bias, the person doing the measurements often does not know if a subject is part of the experimental or the control group. This is known as a *blind measurement.*

Now suppose the data are in and it looks like the experimental group indeed has a lower average resting heart rate than the control group. But there is overlap—some people in the control group have measurements that are lower than some people in the experimental group. Is the difference in the average measurements of the groups due to a real physiological difference, or is it due to chance variations in the measurements? Scientists attempt to test the *null hypothesis* (the hypothesis that the difference is due to chance) by employing the mathematical tools of **statistics.** If the statistical results so warrant, the null hypothesis can be rejected and the experimental hypothesis can be deemed to be supported by this study.

The statistical test chosen will depend upon the design of the experiment, and it can also be a source of contention among scientists in evaluating the validity of the results. Because of the nature of the scientific method, "proof" in science is always provisional. Some other researchers, employing the scientific method in a different way (with different measuring techniques, experimental procedures, choice of control groups, statistical tests, and so on), may later obtain different results. The scientific method is thus an ongoing enterprise.

The results of the scientific enterprise are written up as research articles, and these must be reviewed by other scientists who work in the same field before they can be published in **peer-reviewed journals.** More often than not, the reviewers will suggest that certain changes be made in the articles before they can be accepted for publication.

Examples of such peer-reviewed journals that publish articles in many scientific fields include *Science* (www. sciencemag .org/), *Nature* (www.nature.com/nature/), and *Proceedings of the National Academy of Sciences* (www.pnas.org/). Review articles on physiology can be found in *Annual Review of Physiology* (physiol .annualreviews.org/), *Physiological Reviews* (physrev.physiology .org/), and *Physiology* (physiologyonline. physiology.org). Medical research journals, such as the *New England Journal of Medicine* (content.nejm.org/) and *Nature Medicine* (www.nature.com/nm/), also publish articles of physiological interest. There are also many specialty journals in areas of physiology such as neurophysiology, endocrinology, and cardiovascular physiology.

Students who wish to look online for scientific articles published in peer-reviewed journals that relate to a particular

subject can do so at the National Library of Medicine website, *PubMed* (www.ncbi.nlm.nih.gov/entrez/query.fcgi).

Development of Pharmaceutical Drugs

The development of new pharmaceutical drugs can serve as an example of how the scientific method is used in physiology and its health applications. The process usually starts with basic physiological research, often at cellular and molecular levels. Perhaps a new family of drugs is developed using cells in tissue culture (*in vitro,* or outside the body). For example, cell physiologists studying membrane transport may discover that a particular family of compounds blocks membrane channels for calcium ions (Ca^{2+}). Because of their knowledge of physiology, other scientists may predict that a drug of this nature might be useful in the treatment of hypertension (high blood pressure). This drug may then be tried in animal experiments.

If a drug is effective at extremely low concentrations *in vitro* (in cells cultured outside of the body), there is a chance that it may work *in vivo* (in the body) at concentrations low enough not to be toxic (poisonous). This possibility must be thoroughly tested utilizing experimental animals, primarily rats and mice. More than 90% of drugs tested in experimental animals are too toxic for further development. Only in those rare cases when the toxicity is low enough may development progress to human/clinical trials.

Biomedical research is often aided by **animal models** of particular diseases. These are strains of laboratory rats and mice that are genetically susceptible to particular diseases that resemble human diseases. Research utilizing laboratory animals typically takes several years and always precedes human (clinical) trials of promising drugs. It should be noted that this length of time does not include all of the years of "basic" physiological research (involving laboratory animals) that provided the scientific foundation for the specific medical application.

In **phase I clinical trials,** the drug is tested on healthy human volunteers. This is done to test its toxicity in humans and to study how the drug is "handled" by the body: how it is metabolized, how rapidly it is removed from the blood by the liver and kidneys, how it can be most effectively administered, and so on. If significant toxic effects are not observed, the drug can proceed to the next stage. In **phase II clinical trials,** the drug is tested on the target human population (for example, those with hypertension). Only in those exceptional cases where the drug seems to be effective but has minimal toxicity does testing move to the next phase. **Phase III trials** occur in many research centers across the country to maximize the number of test participants. At this point, the test population must include a sufficient number of subjects of both sexes, as well as people of different ethnic groups. In addition, people are tested who have other health problems besides the one that the drug is intended to benefit. For example, those who have diabetes in addition to hypertension would be included in this phase. If the drug passes phase III trials, it goes to the Food and Drug Administration (FDA) for approval. **Phase IV trials** test other potential uses of the drug.

Less than 10% of the tested drugs make it all the way through clinical trials to eventually become approved and marketed. This low success rate does not count those that fail after approval because of unexpected toxicity, nor does it take into account the great amount of drugs that fail earlier in research before clinical trials begin. Notice the crucial role of basic research, using experimental animals, in this process. Virtually every prescription drug on the market owes its existence to such research.

CHECKPOINTS

1. How has the study of physiology aided, and been aided by, the study of diseases?

2a. Describe the steps involved in the scientific method. What would qualify a statement as unscientific?

2b. Describe the different types of trials a new drug must undergo before it is "ready for market."

1.2 HOMEOSTASIS AND FEEDBACK CONTROL

The regulatory mechanisms of the body can be understood in terms of a single shared function: that of maintaining constancy of the internal environment. A state of relative constancy of the internal environment is known as homeostasis, maintained by negative feedback loops.

LEARNING OUTCOMES

After studying this section, you should be able to:

3. Define homeostasis, and identify the components of negative feedback loops.
4. Explain the role of antagonistic effectors in maintaining homeostasis, and the nature of positive feedback loops.
5. Give examples of how negative feedback loops involving the nervous and endocrine systems help to maintain homeostasis.

History of Physiology

The Greek philosopher Aristotle (384–322 B.C.) speculated on the function of the human body, but another ancient Greek, Erasistratus (304–250? B.C.), is considered to be the first to study physiology because he attempted to apply physical laws to understand human function. Galen (A.D. 130–201) wrote widely on the subject and was considered the supreme authority until the Renaissance. Physiology became a fully experimental

science with the revolutionary work of the English physician William Harvey (1578–1657), who demonstrated that the heart pumps blood through a closed system of vessels.

However, the originator of modern physiology is the French physiologist Claude Bernard (1813–1878), who observed that the *milieu intérieur* (internal environment) remains remarkably constant despite changing conditions in the external environment. In a book entitled *The Wisdom of the Body,* published in 1932, the American physiologist Walter Cannon (1871–1945) coined the term **homeostasis** to describe this internal constancy. Cannon further suggested that the many mechanisms of physiological regulation have but one purpose—the maintenance of internal constancy.

Most of our present knowledge of human physiology has been gained in the twentieth century. However, new knowledge in the twenty-first century is being added at an ever more rapid pace, fueled in more recent decades by the revolutionary growth of molecular genetics and its associated biotechnologies, and by the availability of more powerful computers and other equipment. A very brief history of twentieth- and twenty-first-century physiology, limited by space to only two citations per decade, is provided in table 1.1.

Most of the citations in table 1.1 indicate the winners of Nobel prizes. The **Nobel Prize in Physiology or Medicine** (a single prize category) was first awarded in 1901 to Emil Adolf von Behring, a pioneer in immunology who coined the term

Table 1.1 | History of Twentieth- and Twenty-First-Century Physiology (two citations per decade)

1900	Karl Landsteiner discovers the A, B, and O blood groups.
1904	Ivan Pavlov wins the Nobel Prize for his work on the physiology of digestion.
1910	Sir Henry Dale describes properties of histamine.
1918	Earnest Starling describes how the force of the heart's contraction relates to the amount of blood in it.
1921	John Langley describes the functions of the autonomic nervous system.
1923	Sir Frederick Banting, Charles Best, and John Macleod win the Nobel Prize for the discovery of insulin.
1932	Sir Charles Sherrington and Lord Edgar Adrian win the Nobel Prize for discoveries related to the functions of neurons.
1936	Sir Henry Dale and Otto Loewi win the Nobel Prize for the discovery of acetylcholine in synaptic transmission.
1939–47	Albert von Szent-Györgyi explains the role of ATP and contributes to the understanding of actin and myosin in muscle contraction.
1949	Hans Selye discovers the common physiological responses to stress.
1953	Sir Hans Krebs wins the Nobel Prize for his discovery of the citric acid cycle.
1954	Hugh Huxley, Jean Hanson, R. Niedergerde, and Andrew Huxley propose the sliding filament theory of muscle contraction.
1962	Francis Crick, James Watson, and Maurice Wilkins win the Nobel Prize for determining the structure of DNA.
1963	Sir John Eccles, Sir Alan Hodgkin, and Sir Andrew Huxley win the Nobel Prize for their discoveries relating to the nerve impulse.
1971	Earl Sutherland wins the Nobel Prize for his discovery of the mechanism of hormone action.
1977	Roger Guillemin and Andrew Schally win the Nobel Prize for discoveries of the brain's production of peptide hormone.
1981	Roger Sperry wins the Nobel Prize for his discoveries regarding the specializations of the right and left cerebral hemispheres.
1986	Stanley Cohen and Rita Levi-Montalcini win the Nobel Prize for their discoveries of growth factors regulating the nervous system.
1994	Alfred Gilman and Martin Rodbell win the Nobel Prize for their discovery of the functions of G-proteins in signal transduction in cells.
1998	Robert Furchgott, Louis Ignarro, and Ferid Murad win the Nobel Prize for discovering the role of nitric oxide as a signaling molecule in the cardiovascular system.
2004	Linda B. Buck and Richard Axel win the Nobel Prize for their discoveries of odorant receptors and the organization of the olfactory system.
2006	Andrew Z. Fine and Craig C. Mello win the Noble Prize for their discovery of RNA interference by short, double-stranded RNA molecules.

antibody and whose many other discoveries included the use of serum (containing antibodies) to treat diphtheria. Many scientists who might deserve a Nobel Prize never receive one, and the prizes are given for particular achievements and not others (Einstein didn't win his Nobel Prize in Physics for relativity, for example) and are often awarded many years after the discoveries were made. Nevertheless, the awarding of the Nobel Prize in Physiology or Medicine each year is a celebrated event in the biomedical community, and the awards can be a useful yardstick for tracking the course of physiological research over time.

Negative Feedback Loops

The concept of homeostasis has been of immense value in the study of physiology because it allows diverse regulatory mechanisms to be understood in terms of their "why" as well as their "how." The concept of homeostasis also provides a major foundation for medical diagnostic procedures. When a particular measurement of the internal environment, such as a blood measurement (table 1.2), deviates significantly from the normal range of values, it can be concluded that homeostasis is not being maintained and that the person is sick. A number of such measurements, combined with clinical observations, may allow the particular defective mechanism to be identified.

In order for internal constancy to be maintained, changes in the body must stimulate **sensors** that can send information to an **integrating center.** This allows the integrating center to detect changes from a **set point.** The set point is analogous to the temperature set on a house thermostat. In a similar manner, there is a set point for body temperature, blood glucose concentration, the tension on a tendon, and so on. The integrating center is often a particular region of the brain or spinal cord, but it can also be a group of cells in an endocrine gland. A number of different sensors may send information to a particular integrating center, which can then integrate this information and direct the responses of **effectors**—generally muscles or glands. The integrating center may cause increases or decreases in effector action to counter the deviations from the set point and defend homeostasis.

The thermostat of a house can serve as a simple example. Suppose you set the thermostat at a set point of 70° F. If the temperature in the house rises sufficiently above the set point, a sensor connected to an integrating center within the thermostat will detect that deviation and turn on the air conditioner (the effector in this example). The air conditioner will turn off when the room temperature falls and the thermostat no longer detects a deviation from the set-point temperature. However, this simple example gives a wrong impression: the effectors in the body are generally increased or decreased in activity, *not* just turned on or off. Because of this, negative feedback control in the body works far more efficiently than does a house thermostat.

If the body temperature exceeds the set point of 37° C, sensors in a part of the brain detect this deviation and, acting via an integrating center (also in the brain), stimulate activities of effectors (including sweat glands) that lower the temperature. For another example, if the blood glucose concentration falls below normal, the effectors act to increase the blood glucose. One can think of the effectors as "defending" the set points against deviations. Because the activity of the effectors is influenced by the effects they produce, and because this regulation is in a negative, or reverse, direction, this type of control system is known as a **negative feedback loop** (fig. 1.1). (Notice that in figure 1.1 and in all subsequent figures, negative feedback is indicated by a dashed line and a negative sign.)

Table 1.2 | Approximate Normal Ranges for Measurements of Some Fasting Blood Values

Measurement	Normal Range
Arterial pH	7.35–7.45
Bicarbonate	24–28 mEq/L
Sodium	135–145 mEq/L
Calcium	4.5–5.5 mEq/L
Oxygen content	17.2–22.0 ml/100 ml
Urea	12–35 mg/100 ml
Amino acids	3.3–5.1 mg/100 ml
Protein	6.5–8.0 g/100 ml
Total lipids	400–800 mg/100 ml
Glucose	75–110 mg/100 ml

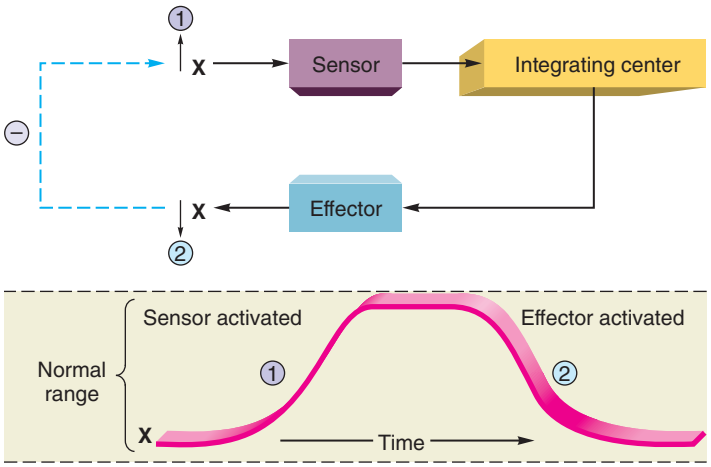

Figure 1.1 A rise in some factor of the internal environment (↑X) is detected by a sensor. This information is relayed to an integrating center, which causes an effector to produce a change (1) in the opposite direction (↓X). The initial deviation is thus reversed (2), completing a negative feedback loop (shown by the dashed arrow and negative sign). The numbers indicate the sequence of changes.

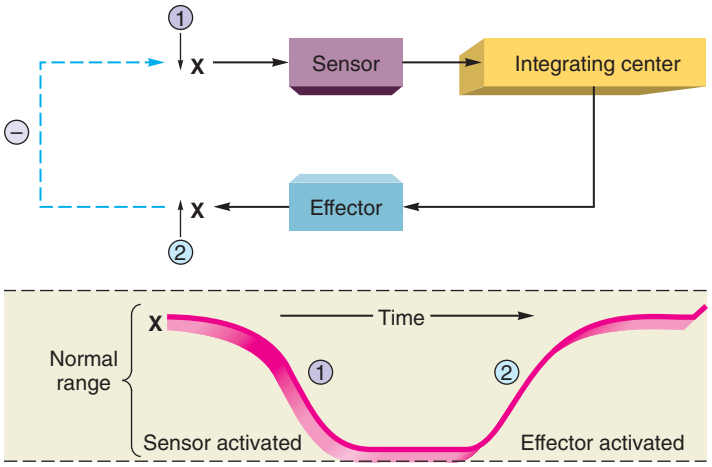

Figure 1.2 **A fall in some factor of the internal environment (↓X) is detected by a sensor.** (Compare this negative feedback loop with that shown in figure 1.1.)

The nature of the negative feedback loop can be understood by again referring to the analogy of the thermostat and air conditioner. After the air conditioner has been on for some time, the room temperature may fall significantly below the set point of the thermostat. When this occurs, the air conditioner will be turned off. The effector (air conditioner) is turned on by a high temperature and, when activated, produces a negative change (lowering of the temperature) that ultimately causes the effector to be turned off. In this way, constancy is maintained.

It is important to realize that these negative feedback loops are continuous, ongoing processes. Thus, a particular nerve fiber that is part of an effector mechanism may always display some activity, and a particular hormone that is part of another effector mechanism may always be present in the blood. The nerve activity and hormone concentration may decrease in response to deviations of the internal environment in one direction (fig. 1.1), or they may increase in response to deviations in the opposite direction (fig. 1.2). Changes from the normal range in either direction are thus compensated for by reverse changes in effector activity.

Because negative feedback loops respond after deviations from the set point have stimulated sensors, the internal environment is never absolutely constant. Homeostasis is best conceived as a state of **dynamic constancy** in which conditions are stabilized above and below the set point. These conditions can be measured quantitatively, in degrees Celsius for body temperature, for example, or in milligrams per deciliter (one-tenth of a liter) for blood glucose. The set point can be taken as the average value within the normal range of measurements (fig. 1.3).

Antagonistic Effectors

Most factors in the internal environment are controlled by several effectors, which often have antagonistic actions. Control by antagonistic effectors is sometimes described as "push-pull," where the increasing activity of one effector is

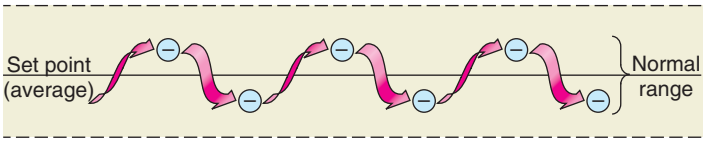

Figure 1.3 **Negative feedback loops maintain a state of dynamic constancy within the internal environment.** The completion of the negative feedback loop is indicated by negative signs.

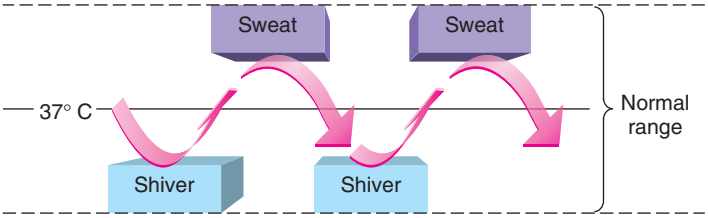

Figure 1.4 **How body temperature is maintained within the normal range.** The body temperature normally has a set point of 37° C. This is maintained, in part, by two antagonistic mechanisms—shivering and sweating. Shivering is induced when the body temperature falls too low, and it gradually subsides as the temperature rises. Sweating occurs when the body temperature is too high, and it diminishes as the temperature falls. Most aspects of the internal environment are regulated by the antagonistic actions of different effector mechanisms.

See the *Test Your Quantitative Ability* section of the Review Activities at the end of this chapter.

accompanied by decreasing activity of an antagonistic effector. This affords a finer degree of control than could be achieved by simply switching one effector on and off.

Room temperature can be maintained, for example, by simply turning an air conditioner on and off, or by just turning a heater on and off. A much more stable temperature, however, can be achieved if the air conditioner and heater are both controlled by a thermostat. Then the heater is turned on when the air conditioner is turned off, and vice versa. Normal body temperature is maintained about a set point of 37° C by the antagonistic effects of sweating, shivering, and other mechanisms (fig. 1.4).

The blood concentrations of glucose, calcium, and other substances are regulated by negative feedback loops involving hormones that promote opposite effects. Insulin, for example, lowers blood glucose, and other hormones raise the blood glucose concentration. The heart rate, similarly, is controlled by nerve fibers that produce opposite effects: stimulation of one group of nerve fibers increases heart rate; stimulation of another group slows the heart rate.

Quantitative Measurements

In order to study physiological mechanisms, scientists must measure specific values and mathematically determine such statistics as their normal range, their averages, and their

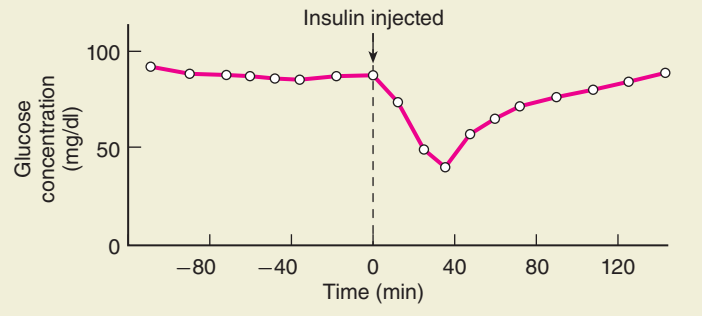

Figure 1.5 Homeostasis of the blood glucose concentration. Average blood glucose concentrations of five healthy individuals are graphed before and after a rapid intravenous injection of insulin. The "0" indicates the time of the injection. The blood glucose concentration is first lowered by the insulin injection, but is then raised back to the normal range (by hormones antagonistic to insulin that stimulate the liver to secrete glucose into the blood). Homeostasis of blood glucose is maintained by the antagonistic actions of insulin and several other hormones.

deviations from the average (which can represent the set point). For these and other reasons, quantitative measurements are basic to the science of physiology. One example of this, and of the actions of antagonistic mechanisms in maintaining homeostasis, is shown in figure 1.5. Blood glucose concentrations were measured in five healthy people before and after an injection of insulin, a hormone that acts to lower the blood glucose concentration. A graph of the data reveals that the blood glucose concentration decreased rapidly but was brought back up to normal levels within 80 minutes after the injection. This demonstrates that negative feedback mechanisms acted to restore homeostasis in this experiment. These mechanisms involve the action of hormones whose effects are antagonistic to that of insulin—that is, they promote the secretion of glucose from the liver (see chapter 19).

Positive Feedback

Constancy of the internal environment is maintained by effectors that act to compensate for the change that served as the stimulus for their activation; in short, by negative feedback loops. A thermostat, for example, maintains a constant temperature by increasing heat production when it is cold and decreasing heat production when it is warm. The opposite occurs during **positive feedback**—in this case, the action of effectors *amplifies* those changes that stimulated the effectors. A thermostat that works by positive feedback, for example, would increase heat production in response to a rise in temperature.

It is clear that homeostasis must ultimately be maintained by negative rather than by positive feedback mechanisms. The effectiveness of some negative feedback loops, however, is increased by positive feedback mechanisms that amplify the actions of a negative feedback response. Blood clotting, for example, occurs as a result of a sequential activation of clotting factors; the activation of one clotting factor results in activation of many in a positive feedback cascade. In this way, a single change is amplified to produce a blood clot. Formation of the clot, however, can prevent further loss of blood, and thus represents the completion of a negative feedback loop that restores homeostasis.

Two other examples of positive feedback in the body are both related to the female reproductive system. One of these examples occurs when estrogen, secreted by the ovaries, stimulates the women's pituitary gland to secrete LH (luteinizing hormone). This stimulatory, positive feedback effect creates an "LH surge" (very rapid rise in blood LH concentrations) that triggers ovulation. Interestingly, estrogen secretion after ovulation has an inhibitory, negative feedback, effect on LH secretion (this is the physiological basis for the birth control pill, discussed in chapter 20). Another example of positive feedback is contraction of the uterus during childbirth (parturition). Contraction of the uterus is stimulated by the pituitary hormone oxytocin, and the secretion of oxytocin is increased by sensory feedback from contractions of the uterus during labor. The strength of uterine contractions during labor is thus increased through positive feedback. The mechanisms involved in labor are discussed in more detail in chapter 20 (see fig. 20.50).

Neural and Endocrine Regulation

Homeostasis is maintained by two general categories of regulatory mechanisms: (1) those that are **intrinsic,** or "built into" the organs being regulated (such as molecules produced in the walls of blood vessels that cause vessel dilation or constriction); and (2) those that are **extrinsic,** as in regulation of an organ by the nervous and endocrine systems. The endocrine system functions closely with the nervous system in regulating and integrating body processes and maintaining homeostasis. The nervous system controls the secretion of many endocrine glands, and some hormones in turn affect the function of the nervous system. Together, the nervous and endocrine systems regulate the activities of most of the other systems of the body.

Regulation by the endocrine system is achieved by the secretion of chemical regulators called **hormones** into the blood, which carries the hormones to all organs in the body. Only specific organs can respond to a particular hormone, however; these are known as the **target organs** of that hormone.

Nerve fibers are said to *innervate* the organs that they regulate. When stimulated, these fibers produce electrochemical nerve impulses that are conducted from the origin of the fiber to its terminals in the target organ innervated by the fiber. These target organs can be muscles or glands that may function as effectors in the maintenance of homeostasis.

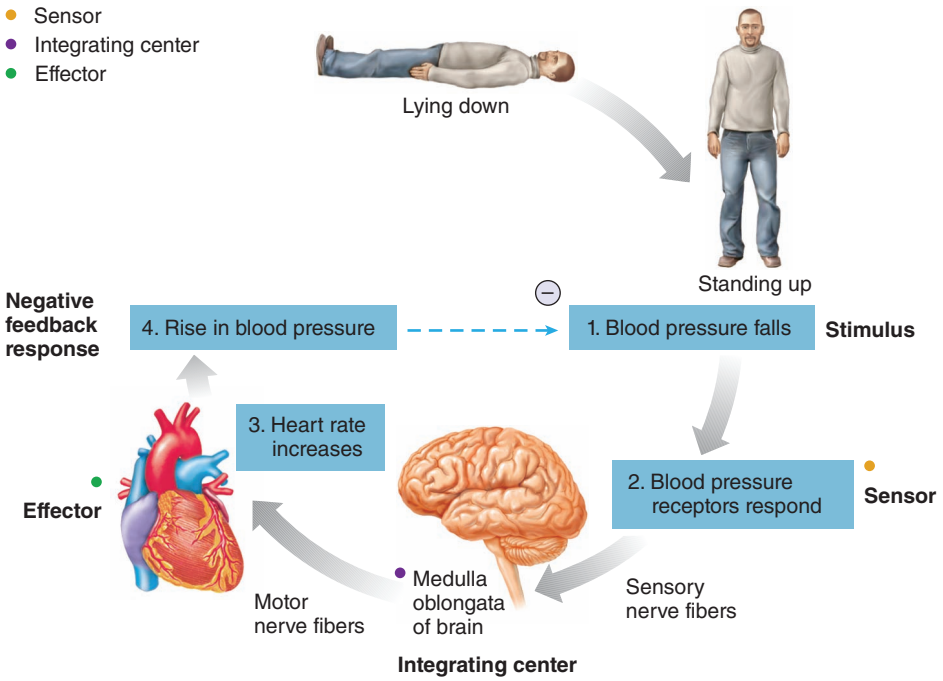

Figure 1.6 **Negative feedback control of blood pressure.** Blood pressure influences the activity of sensory neurons from the blood pressure receptors (sensors); a rise in pressure increases the firing rate, and a fall in pressure decreases the firing rate of nerve impulses. When a person stands up from a lying-down position, the blood pressure momentarily falls. The resulting decreased firing rate of nerve impulses in sensory neurons affects the medulla oblongata of the brain (the integrating center). This causes the motor nerves to the heart (effector) to increase the heart rate, helping to raise the blood pressure.

For example, we have negative feedback loops that help maintain homeostasis of arterial blood pressure, in part by adjusting the heart rate. If everything else is equal, blood pressure is lowered by a decreased heart rate and raised by an increased heart rate. This is accomplished by regulating the activity of the autonomic nervous system, as will be discussed in later chapters. Thus, a fall in blood pressure—produced daily as we go from a lying to a standing position—is compensated by a faster heart rate (fig. 1.6). As a consequence of this negative feedback loop, our heart rate varies as we go through our day, speeding up and slowing down, so that we can maintain homeostasis of blood pressure and keep it within normal limits.

Feedback Control of Hormone Secretion

The nature of the endocrine glands, the interaction of the nervous and endocrine systems, and the actions of hormones will be discussed in detail in later chapters. For now, it is sufficient to describe the regulation of hormone secretion very broadly, because it so superbly illustrates the principles of homeostasis and negative feedback regulation.

Hormones are secreted in response to specific chemical stimuli. A rise in the plasma glucose concentration, for example, stimulates insulin secretion from structures in the pancreas known as the *pancreatic islets,* or *islets of Langerhans.* Hormones are also secreted in response to nerve stimulation and stimulation by other hormones.

The secretion of a hormone can be inhibited by its own effects in a negative feedback manner. Insulin, as previously described, produces a lowering of blood glucose. Because a rise in blood glucose stimulates insulin secretion, a lowering of blood glucose caused by insulin's action inhibits further insulin secretion. This closed-loop control system is called **negative feedback inhibition** (fig. 1.7*a*).

Homeostasis of blood glucose is too important—the brain uses blood glucose as its primary source of energy—to entrust to the regulation of only one hormone, insulin. So, when blood glucose falls during fasting, several mechanisms prevent it from falling too far (fig. 1.7*b*). First, insulin secretion decreases, preventing muscle, liver, and adipose cells from taking too much glucose from the blood. Second, the secretion of a hormone antagonistic to insulin, called *glucagon,* increases. Glucagon stimulates processes in the liver (breakdown of a stored, starchlike molecule called glycogen; chapter 2, section 2.2) that cause it to secrete glucose into the blood. Through these and other antagonistic negative feedback mechanisms, the blood glucose is maintained within a homeostatic range.