VANDER'S HUMAN PHYSIOLOGY

THE MECHANISMS OF BODY FUNCTION

THIRTEENTH EDITION

ERIC P. WIDMAIER HERSHEL RAFF KEVIN T. STRANG

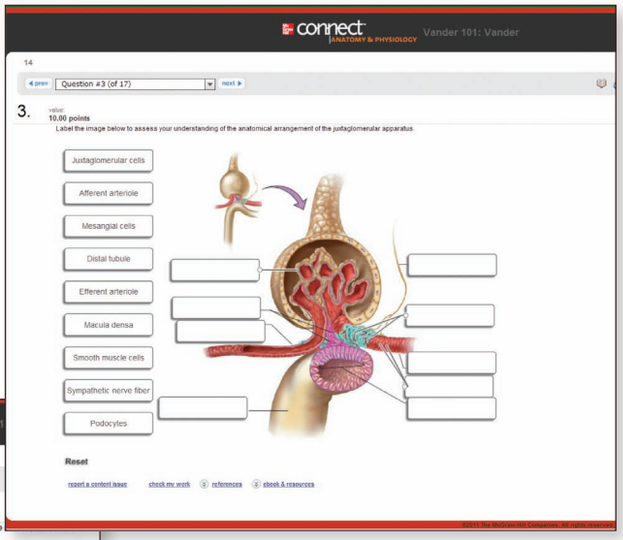
www.mhhe.com/widmaier13

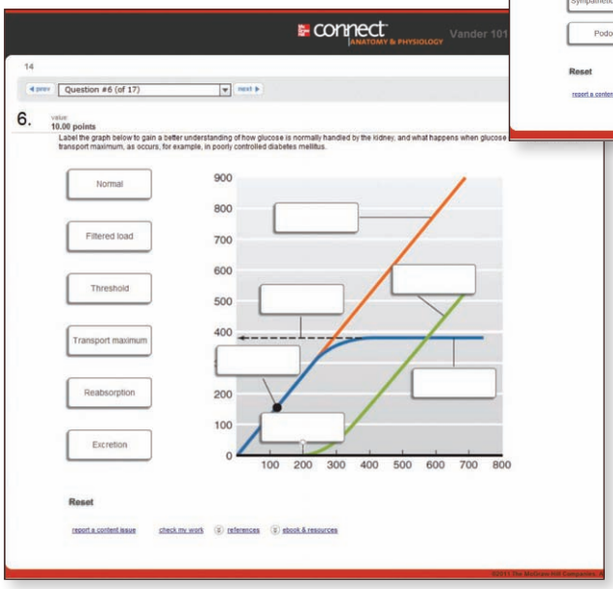
connect® plus+

anatomy & physiology

McGraw-Hill ConnectPlus™ Anatomy & Physiology interactive learning platform provides a customizable, assignable eBook, auto-graded assessments, an adaptive diagnostic tool, lecture capture, access to instructor resources, and powerful reporting—all in an easy-to-use interface.

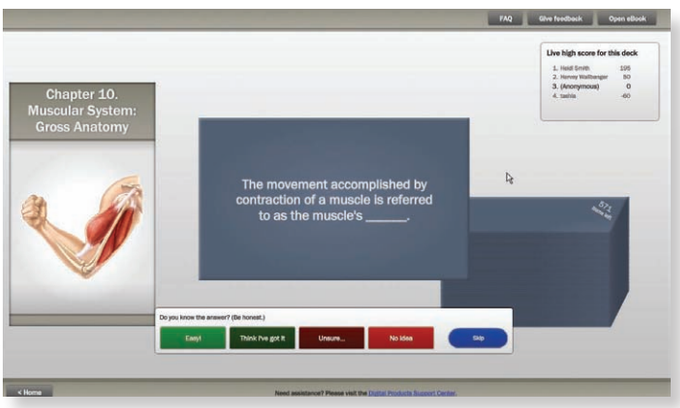
Learn more at www.mcgrawhillconnect.com





Learn Fast. Learn Easy. Learn Smart.

McGraw-Hill LearnSmart™ is an adaptive diagnostic tool that constantly assesses student knowledge of course material. Sophisticated diagnostics adapt to each student's individual knowledge base, and vary the questions to determine what the student knows, doesn't know, knows but has forgotten, and how to best improve their knowledge level. Students actively learn required course concepts, and instructors can access speci□c LearnSmart reports to monitor progress. For more information, go to **www.mhlearnsmart.com**

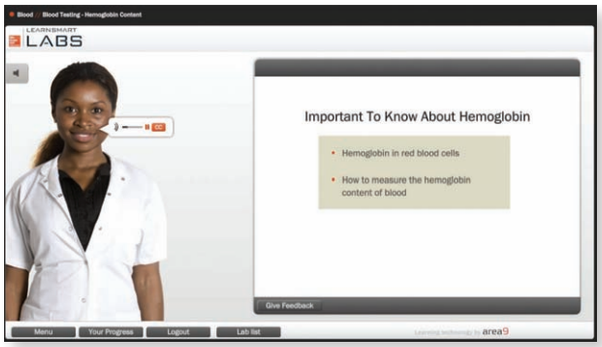


LEARNSMART LABS™

THE Virtual Lab Experience!

Based on the same world-class super-adaptive technology as McGraw-Hill LearnSmart™, LearnSmart Labs™ is a must-see, outcomes-based lab simulation. It assesses a student's knowledge and adaptively corrects deficiencies, allowing the student to learn faster and retain more knowledge with greater success.

First, a student's knowledge is adaptively leveled on core learning outcomes: Questioning reveals knowledge deficiencies that are corrected by the delivery of content that is conditional on a student's response.



Then, a simulated lab experience requires the student to think and act like a scientist: Recording, interpreting, and analyzing data using simulated equipment found in labs and clinics. The student is allowed to make mistakes—a powerful part of the learning experience!

A virtual coach provides subtle hints when needed; asks questions about the student's choices; and allows the student to reflect upon and correct those mistakes.

Whether your need is to overcome the logistical challenges of a traditional lab, provide better lab prep, improve student performance, or make your online experience one that rivals the real world, LearnSmart Labs accomplishes it all.

Learn more at www.learnsmartadvantagedemo.com

THIRTEENTH EDITION

VANDER'S Human Physiology

THE MECHANISMS OF BODY FUNCTION

ERIC P. WIDMAIER
BOSTON UNIVERSITY

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

KEVIN T. STRANG
UNIVERSITY OF WISCONSIN–MADISON

Mc Graw Hill
Connect
Learn
Succeed™

The McGraw-Hill Companies

Connect Learn Succeed™

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

This book is printed on acid-free paper.

1 2 3 4 5 6 7 8 9 0 DOW/DOW 1 0 9 8 7 6 5 4 3

ISBN 978–0–07–337830–5
MHID 0–07–337830–5

Senior Vice President, Products & Markets: *Kurt L. Strand*
Vice President, General Manager, Products & Markets: *Marty Lange*
Vice President, Content Production & Technology Services: *Kimberly Meriwether David*
Managing Director: *Michael S. Hackett*
Director: *James F. Connely*
Brand Manager: *Marija Magner*
Senior Developmental Editor: *Fran Simon*
Director, Content Production: *Terri Schiesl*
Project Manager: *Sherry L. Kane*
Senior Buyer: *Sandy Ludovissy*
Designer: *Tara McDermott*
Cover/Interior Designer: *Elise Lansdon*
Cover Images: *(girl drinking water) © JGI/Blend Images LLC/RF; (MRI midsagittal section) © ISM/Phototake; (freeze fractured bundle) © Steve Gschmeissner/Photo Researchers; (stress test) © Michael Krasowitz/Getty Images; (leather spine) © Siede Preis/Getty Images/RF*
Senior Content Licensing Specialist: *John C. Leland*
Photo Research: *David Tietz/Editorial Image, LLC*
Compositor: *Laserwords Private Limited*
Typeface: *10/12 Janson Text LT Std*
Printer: *R. R. Donnelley*

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

Library of Congress Cataloging-in-Publication Data

Widmaier, Eric P.
Vander's human physiology : the mechanisms of body function. – Thirteenth edition / Eric P. Widmaier, Department of Biology, Boston University, Hershel Raff, Medical College of Wisconsin, Aurora St. Luke's Medical Center, Kevin T. Strang, Department of Neuroscience, University of Wisconsin.
pages cm
Includes index.
ISBN 978–0–07–337830–5 — ISBN 0–07–337830–5 (hard copy : alk. paper) 1. Human physiology. I. Raff, Hershel, 1953- II. Strang, Kevin T. III. Vander, Arthur J., 1933– Human physiology. IV. Title. V. Title: Human physiology.
QP34.5.W47 2014
612–dc23

2012041775

www.mhhe.com

Meet the Authors

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

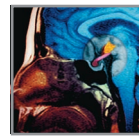
HERSHEL RAFF received his Ph.D. in Environmental Physiology from the *Johns Hopkins University* in 1981 and did postdoctoral training in Endocrinology at the *University of California at San Francisco.* He is now a Professor of Medicine (Endocrinology, Metabolism, and Clinical Nutrition), Surgery, and Physiology at the *Medical College of Wisconsin* and Director of the Endocrine Research Laboratory at *Aurora St. Luke's Medical Center.* At the *Medical College of Wisconsin*, he teaches physiology and pharmacology to medical and graduate students, and is the Endocrinology/Reproduction Unit Director for the new integrated curriculum. He was an inaugural inductee into the Society of Teaching Scholars, received the Beckman Basic Science Teaching Award three times, received the Outstanding Teacher Award from the Graduate School, and has been one of the MCW's Outstanding Medical Student Teachers for each year the award has been given. He is also an Adjunct Professor of Biomedical Sciences at *Marquette University.* He is the former Associate Editor of *Advances in Physiology Education*. Dr. Raff's basic research focuses on the adaptation to low oxygen (hypoxia). His clinical interest focuses on pituitary and adrenal diseases, with a special focus on laboratory tests for the diagnosis of Cushing's syndrome. He resides outside Milwaukee with his wife Judy and son Jonathan.

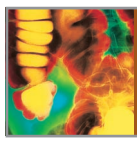
KEVIN T. STRANG received his Master's Degree in Zoology (1988) and his Ph.D. in Physiology (1994) from the *University of Wisconsin at Madison.* His research area is cellular mechanisms of contractility modulation in cardiac muscle. He teaches a large undergraduate systems physiology course as well as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

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

Brief Contents

Table of Contents





Index of Exercise Physiology

From the Authors

It is with great pleasure that we present the thirteenth edition of *Vander's Human Physiology*. The cover of this edition reflects some of the major themes of the textbook: homeostasis, exercise, pathophysiology, and cellular and molecular mechanisms of body function. These themes and others have now been introduced in Chapter 1, called "General Principles of Physiology." These principles have been integrated throughout the remaining chapters 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. Finally, assessments are provided at the end of each chapter to provide immediate feedback for students to gauge their understanding of the chapter material and its relationship to physiological principles. These assessments tend to require analytical and critical thinking; answers are provided in an appendix.

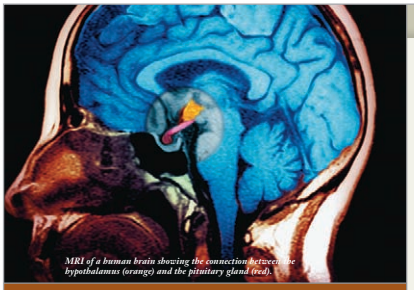
Users of the book will also benefit from expanded assessments of the traditional type, such as multiple choice and thought questions, as well as additional Physiological Inquiries associated with various key figures. In total, approximately 70 new assessment questions have been added to the textbook; this is in addition to the several hundred test questions available on the McGraw-Hill Connect site associated with the book.

As in earlier editions, there is extensive coverage of exercise physiology (see the special exercise index that follows the detailed Table of Contents), and special attention to the clinical relevance of much of the basic science (see the Index of Clinical Terms in Appendix B). This index is organized according to disease; infectious or causative agents; and the treatments, diagnostics, and therapeutic drugs used to treat disease. This is a very useful resource for instructors and students interested in the extensive medical applications of human physiology that are covered in this book.

As textbooks become more integrated with digital content, we are pleased that McGraw-Hill has provided ***Vander's Human Physiology*** with cutting-edge digital content that continues to expand and develop. Students will again find a Connect Plus site associated with the text. The assessments have been updated and are now authored by one of the author team, Kevin Strang. For the first time we also have LearnSmart! McGraw-Hill LearnSmart™ is an adaptive diagnostic tool that constantly assesses student knowledge of course material.

We are always grateful to receive e-mail messages from instructors and students worldwide who are using the book and wish to offer suggestions regarding content. Finally, no textbook such as this could be written without the expert and critical eyes of our many reviewers; we are thankful to those colleagues who took time from their busy schedules to read all or a portion of a chapter (or more) and provide us with their insights and suggestions for improvements.

Guided Tour Through a Chapter



MRI of a human brain showing the connection between the hypothalamus (orange) and the pituitary gland (red).

11 The Endocrine System

SECTION A
General Characteristics of Hormones and Hormonal Control Systems

11.1 Hormones and Endocrine Glands
11.2 Hormone Structures and Synthesis
Amine Hormones
Peptide and Protein Hormones
Steroid Hormones
11.3 Hormone Transport in the Blood
11.4 Hormone Metabolism and Excretion
11.5 Mechanisms of Hormone Action
Hormone Receptors
Events Elicited by Hormone–Receptor Binding
Pharmacological Effects of Hormones
11.6 Inputs That Control Hormone Secretion
Control by Plasma Concentrations of Mineral Ions or Organic Nutrients
Control by Neurons
Control by Other Hormones
11.7 Types of Endocrine Disorders
Hyposecretion
Hypersecretion
Hyporesponsiveness and Hyperresponsiveness

SECTION B
The Hypothalamus and Pituitary Gland

11.8 Control Systems Involving the Hypothalamus and Pituitary Gland
Posterior Pituitary Hormones
Anterior Pituitary Gland Hormones and the Hypothalamus

SECTION C
The Thyroid Gland

11.9 Synthesis of Thyroid Hormone
11.10 Control of Thyroid Function
11.11 Actions of Thyroid Hormone
Metabolic Actions
Permissive Actions
Growth and Development
11.12 Hypothyroidism and Hyperthyroidism

SECTION D
The Endocrine Response to Stress

11.13 Physiological Functions of Cortisol
11.14 Functions of Cortisol in Stress
11.15 Adrenal Insufficiency and Cushing's Syndrome
11.16 Other Hormones Released During Stress

SECTION E
Endocrine Control of Growth

11.17 Bone Growth
11.18 Environmental Factors Influencing Growth
11.19 Hormonal Influences on Growth
Growth Hormone and Insulin-Like Growth Factors
Thyroid Hormone
Insulin
Sex Steroids
Cortisol

SECTION F
Endocrine Control of Ca^{21} Homeostasis

11.20 Effector Sites for Ca^{21} Homeostasis
Bone
Kidneys
Gastrointestinal Tract
11.21 Hormonal Controls
Parathyroid Hormone
1,25-Dihydroxyvitamin D
Calcitonin
11.22 Metabolic Bone Diseases
Hypercalcemia
Hypocalcemia
Chapter 11 Clinical Case Study

319

Chapter Outline

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

General Principles of Physiology—NEW!

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.

In Chapters 6–8 and 10, you learned that the nervous system is one of the two major control systems of the body, and now we turn our attention to the other—the endocrine system. The endocrine system consists of all those glands, called endocrine glands, that secrete hormones, as well as hormone-secreting cells located in various organs such as the heart, kidneys, liver, and stomach. Hormones are chemical messengers that enter the blood, which carries them from their site of secretion to the cells upon which they act. The cells a particular hormone influences are known as the target cells for that hormone. The aim of this chapter is to first present a detailed overview of endocrinology—that is, a structural and functional analysis of general features of hormones—followed by a more detailed analysis of several important hormonal systems. Before continuing, you should review the principles of ligand-receptor interactions and cell signaling that were described in Chapter 3 (Section C) and Chapter 5, because they pertain to the mechanisms by which hormones exert their actions.

Hormones functionally link various organ systems together. As such, several of the general principles of physiology first introduced in Chapter 1 apply to the study of the endocrine system, including the principle that the functions of organ systems are coordinated with each other. This coordination is key to the maintenance of homeostasis, another important general principle of physiology that will be covered in Sections C, D, and F. In many cases, the actions of one hormone can be potentiated, inhibited, or counterbalanced by the actions of another. This illustrates the general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition. It will be especially relevant in the sections on the endocrine control of metabolism and the control of pituitary gland function. Finally, this chapter exemplifies the general principle of physiology that information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes.

Clinical Case Studies

The authors have drawn from their teaching and research experiences and the clinical experiences of colleagues to provide students with real-life applications through clinical case studies in each chapter.

CHAPTER 11

Clinical Case Study: Mouth Pain, Sleep Apnea, and Enlargement of the Hands in a 35-Year-Old Man

A 35-year-old man visited his dentist with a complaint of chronic mouth pain and headaches. After examining the patient, the dentist concluded that there was no dental disease but that the patient's jaw appeared enlarged and his tongue was thickened and large. The dentist referred the patient to a physician. The physician noted enlargement of the jaw and tongue, enlargement of the fingers and toes, and a very deep voice. The patient acknowledged that his voice seemed to have deepened over the past few years and that he no longer wore his wedding ring because it was too tight. The patient's height and weight were within normal ranges. His blood pressure was significantly elevated, as was his fasting plasma glucose concentration. The patient also mentioned that his wife could no longer sleep in the same room as he because of his loud snoring and sleep apnea. Based on these signs and symptoms, the physician referred the patient to an endocrinologist, who ordered a series of tests to better elucidate the cause of the diverse symptoms.

The enlarged bones and facial features suggested the possibility of ***acromegaly*** (from the Greek *akros,* "extreme" or "extremities," and *megalos,* "large"), a disease characterized by excess growth hormone and IGF-1 concentrations in the blood. This was confirmed with a blood test that revealed greatly elevated concentrations of both hormones. Based on these results, an MRI scan was ordered to look for a possible tumor of the anterior pituitary gland. A 1.5 cm mass was discovered in the sella turcica, consistent with the possibility of a growth hormone–secreting tumor. Because the patient was of normal height, it was concluded that the tumor arose at some point after puberty, when linear growth ceased because of closure of the epiphyseal plates. Had the tumor developed prior to puberty, the man would have been well above normal height because of the growth-promoting actions of growth hormone and IGF-1. Such individuals are known as pituitary giants and have a condition called ***gigantism.*** In many cases, the affected person develops both gigantism and later acromegaly, as occurred in the individual shown in **Figure 11.33**.

Acromegaly and gigantism arise when chronic, excess amounts of growth hormone are secreted into the blood. In almost all cases, acromegaly and gigantism are caused by benign (noncancerous) tumors of the anterior pituitary gland that secrete growth hormone at very high rates, which in turn results in elevated IGF-1 concentrations in the blood. Because these tumors are abnormal tissue, they are not suppressed adequately by normal negative feedback inhibitors like IGF-1, so the growth hormone concentrations remain elevated. These tumors are typically very slow growing, and, if they arise after puberty, it may be many years before a person realizes that there is something wrong. In our patient, the changes in his appearance were gradual enough that he attributed them simply to "aging," despite his relative youth.

Even when linear growth is no longer possible (after the growth plates have fused), very high plasma concentrations of

(continued)

358 Chapter 11

(continued)

Figure 11.33 Appearance of an individual with gigantism and acromegaly.

growth hormone and IGF-1 result in the thickening of many bones in the body, most noticeably in the hands, feet, and head. The jaw, particularly, enlarges to give the characteristic facial appearance called ***prognathism*** (from the Greek *pro,* "forward," and *gnathos,* "jaw") that is associated with acromegaly. This was likely the cause of our patient's chronic mouth pain. The enlarged sinuses that resulted from the thickening of his skull bones may have been responsible in part for his headaches. In addition, many internal organs—such as the heart—also become enlarged due to growth hormone and IGF-1-induced hypertrophy, and this can interfere with their ability to function normally. In some acromegalics, the tissues comprising the larynx enlarge, resulting in a deepening of the voice as in our subject. The enlarged and deformed tongue was likely a contributor to the sleep apnea and snoring reported by the patient; this is called obstructive sleep apnea because the tongue base weakens and, consequently, the tongue obstructs the upper airway (see Chapter 13 for a discussion of sleep apnea). Finally, roughly half of all people with acromegaly have elevated blood pressure (hypertension). The cause of the hypertension is uncertain, but it is a serious medical condition that requires treatment with antihypertensive drugs.

As described earlier, adults continue to make and secrete growth hormone even after growth ceases. That is because growth hormone has metabolic actions in addition to its effects on growth. The major actions of growth hormone in metabolism are to increase the concentrations of glucose and fatty acids in the blood and decrease the sensitivity of skeletal muscle and adipose tissue to insulin. Not surprisingly, therefore, one of the stimuli that increases growth hormone concentrations in the healthy adult is a decrease in blood glucose or fatty acids. The secretion of growth hormone during these metabolic crises, however, is transient; once glucose or fatty acid concentrations are restored to normal, growth hormone concentrations decrease to baseline. In acromegaly, however, growth hormone concentrations are almost always increased. Consequently, acromegaly is often associated with increased plasma concentrations of glucose and fatty acids, in some cases even reaching the concentrations observed in diabetes mellitus. As in Cushing's syndrome (Section D), therefore, the presence of chronically increased concentrations of growth hormone may result in diabetes-like symptoms. This explains why our patient had a high fasting plasma glucose concentration.

Our subject was fortunate to have had a quick diagnosis. This case study illustrates one of the confounding features of endocrine disorders. The rarity of some endocrine diseases (e.g., acromegaly occurs in roughly 4 per million individuals), together with the fact that the symptoms of a given endocrine disease can be varied and insidious in their onset, often results in a delayed diagnosis. This means that in many cases, a patient is subjected to numerous tests for more common disorders before a diagnosis of endocrine disease is made.

Treatment of gigantism and acromegaly usually requires surgical removal of the pituitary tumor. The residual normal pituitary tissue is then sufficient to maintain baseline growth hormone concentrations. If this treatment is impossible or not successful, treatment with long-acting analogs of somatostatin is sometimes necessary. (Recall that somatostatin is the hypothalamic hormone that inhibits GH secretion.) Our patient elected to have surgery. This resulted in a reduction in his plasma growth hormone and IGF-1 concentrations. With time, several of his symptoms were reduced, including the increased plasma glucose concentrations. However, within 2 years, his growth hormone and IGF-1 concentrations were three times higher than the normal range for his age and a follow-up MRI revealed that the tumor had regrown. Not wanting a second surgery, the patient was treated with radiation therapy focused on the pituitary tumor, followed by regular administration of somatostatin analogs. This treatment decreased but did not completely normalize his hormone concentrations. His blood pressure remained elevated and was treated with two different antihypertensive drugs (see Chapter 12).

Clinical terms: acromegaly, gigantism, prognathism

See Chapter 19 for complete, integrative case studies.

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 11.6 Major Hormones Influencing Growth

Hormone	Principal Actions
Growth hormone	Major stimulus of postnatal growth: Induces precursor cells to differentiate and secrete insulin-like growth factor 1 (IGF-1), which stimulates cell division Stimulates liver to secrete IGF-1 Stimulates protein synthesis
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-1 Stimulates protein synthesis
Thyroid hormone	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone Causes eventual epiphyseal closure Stimulates protein synthesis in male
Estrogen	Stimulates the secretion of growth hormone at puberty Causes eventual epiphyseal closure
Cortisol	Inhibits growth Stimulates protein catabolism

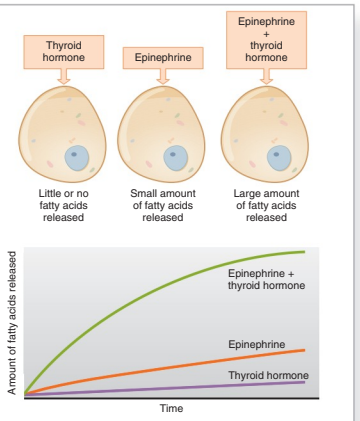


Figure 11.9 The ability of thyroid hormone to "permit" epinephrine-induced release of fatty acids from adipose tissue cells. Thyroid hormone exerts this effect by causing an increased number of beta-adrenergic receptors on the cell. Thyroid hormone by itself stimulates only a small amount of fatty acid release.

PHYSIOLOGICAL INQUIRY

- A patient is observed to have symptoms that are consistent with elevated concentrations of epinephrine in the blood, including a rapid heart rate, anxiety, and elevated fatty acid concentrations. However, the circulating epinephrine concentrations are tested and found to be in the normal range. What might explain this?

Answer can be found at end of chapter.

Physiological Inquiries

The authors have continued to refine and expand the number of 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.

Anatomy and Physiology Revealed (APR) Icon—NEW!

APR icons are found in figure legends. These icons indicate that there is a direct link to APR available in the eBook provided with Connect Plus for this title!

Descriptive Art Style

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

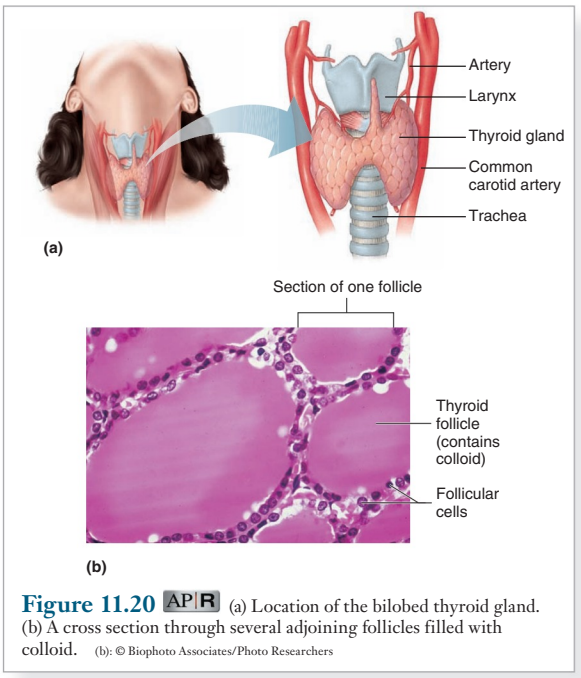


Figure 11.20 APR (a) Location of the bilobed thyroid gland. (b) A cross section through several adjoining follicles filled with colloid. (b): © Biophoto Associates/Photo Researchers

Guided Tour Through a Chapter

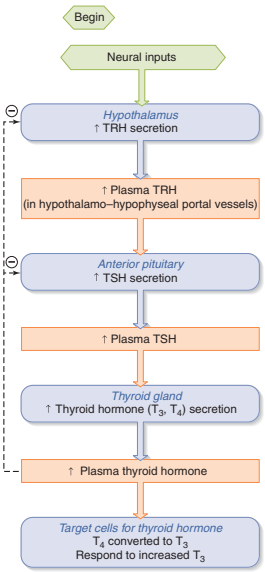


Figure 11.22 TRH-TSH-thyroid hormone sequence. T_3 and T_4 inhibit secretion of TSH and TRH by negative feedback, indicated by the ⊖ symbol.

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.

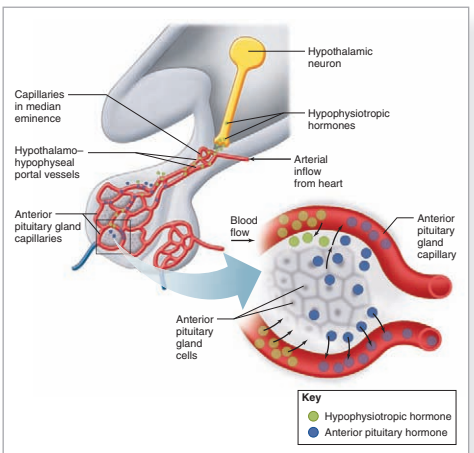


Figure 11.16 AP|R Hormone secretion by the anterior pituitary gland is controlled by hypophysiotropic hormones released by hypothalamic neurons and reaching the anterior pituitary gland by way of the hypothalamo–hypophyseal portal vessels.

End of Section

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

SECTION F SUMMARY

Effector Sites for Ca^{2+} Homeostasis

I. The effector sites for the regulation of plasma Ca^{2+} concentration are bone, the gastrointestinal tract, and the kidneys.
II. Approximately 99% of total-body Ca^{2+} is contained in bone as minerals on a collagen matrix. Bone is constantly remodeled as a result of the interaction of osteoblasts and osteoclasts, a process that determines bone mass and provides a means for raising or lowering plasma Ca^{2+} concentration.
III. Ca^{2+} is actively absorbed by the gastrointestinal tract, and this process is under hormonal control.

SECTION F REVIEW QUESTIONS

1. Describe bone remodeling.
2. Describe the handling of Ca^{2+} by the kidneys and gastrointestinal tract.
3. What controls the secretion of parathyroid hormone, and what are the major effects of this hormone?
4. Describe the formation and action of 1,25-$(OH)_2$D. How does parathyroid hormone influence the production of this hormone?

SECTION F KEY TERMS

calcitonin 356
1,25-$(OH)_2$D 355
hydroxyapatite 354
hypercalcemia 356
hypocalcemia 357
mineralization 354
osteoclast 354
osteocyte 354
osteoid 353
parathyroid gland 355
parathyroid hormone (PTH) 354
vitamin D 355
vitamin D_2 (ergocalciferol) 355
vitamin D_3 (cholecalciferol) 355

SECTION F CLINICAL TERMS

bisphosphonate 356
humoral hypercalcemia of malignancy 357
hypocalcemic tetany 357
osteomalacia 356
osteoporosis 356
primary hyperparathyroidism 356
primary hypoparathyroidism 357
pseudohypoparathyroidism 357
PTH-related peptide (PTHrp) 357
rickets 356
secondary hyperparathyroidism 357
selective estrogen receptor modulator (SERM) 356

End of Chapter

At the end of the chapters, you will find

- Test Questions that are designed to test student comprehension of key concepts.
- ***NEW!***—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.
- Quantitative and Thought 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.
- Answers to the Physiological Inquiries in that chapter.

CHAPTER 11 TEST QUESTIONS

Answers found in Appendix A.

1–5: Match the hormone with the function or feature (choices a–e).

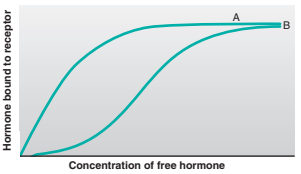
Hormone:

1. vasopressin
2. ACTH
3. oxytocin
4. prolactin
5. luteinizing hormone

Function:

a. tropic for the adrenal cortex
b. is controlled by an amine-derived hormone of the hypothalamus
c. antidiuresis
d. stimulation of testosterone production
e. stimulation of uterine contractions during labor

6. In the following figure, which hormone (A or B) binds to receptor X with higher affinity?



7. Which is *not* a symptom of Cushing's disease?
   a. high blood pressure
   b. bone loss
   c. suppressed immune function
   d. goiter
   e. hyperglycemia (increased blood glucose)
8. Tremors, nervousness, and increased heart rate can all be symptoms of
   a. increased activation of the sympathetic nervous system.
   b. excessive secretion of epinephrine from the adrenal medulla.
   c. hyperthyroidism.
   d. hypothyroidism.
   e. answers a, b, and c (all are correct).
9. Which of the following could theoretically result in short stature?
   a. pituitary tumor making excess thyroid-stimulating hormone
   b. mutations that result in inactive IGF-1 receptors
   c. delayed onset of puberty
   d. decreased hypothalamic concentrations of somatostatin
   e. normal plasma GH but decreased feedback of GH on GHRH
10. Choose the correct statement.
    a. During times of stress, cortisol acts as an anabolic hormone in muscle and adipose tissue.
    b. A deficiency of thyroid hormone would result in increased cellular concentrations of Na^+/K^+-ATPase pumps in target tissues.
    c. The posterior pituitary is connected to the hypothalamus by long portal vessels.
    d. Adrenal insufficiency often results in increased blood pressure and increased plasma glucose concentrations.
    e. A lack of iodide in the diet will have no significant effect on the concentration of circulating thyroid hormone for at least several weeks.
11. A lower-than-normal concentration of plasma Ca^{2+} causes
    a. a PTH-mediated increase in 25-OH D.
    b. a decrease in renal 1-hydroxylase activity.
    c. a decrease in the urinary excretion of Ca^{2+}.
    d. a decrease in bone resorption.
    e. an increase in vitamin D release from the skin.
12. Which of the following is *not* consistent with primary hyperparathyroidism?
    a. hypercalcemia
    b. elevated plasma 1,25-$(OH)_2$D
    c. increased urinary excretion of phosphate ions
    d. a decrease in Ca^{2+} resorption from bone
    e. an increase in Ca^{2+} reabsorption in the kidney

True or False

13. T_4 is the chief circulating form of thyroid hormone but is less active than T_3.
14. Acromegaly is usually associated with hypoglycemia and hypotension.
15. Thyroid hormone and cortisol are both permissive for the actions of epinephrine.

CHAPTER 11 GENERAL PRINCIPLES ASSESSMENT

Answers found in Appendix A.

1. Referring back to Tables 11.3, 11.4, and 11.5, explain how certain of the actions of epinephrine, cortisol, and growth hormone illustrate in part the general principle of physiology that *most physiological functions are controlled by multiple regulatory systems, often working in opposition.*
2. Another general principle of physiology is that *structure is a determinant of—and has coevolved with—function.* The structure of the thyroid gland is very unlike other endocrine glands. How is the structure of this gland related to its function?
3. *Homeostasis is essential for health and survival.* How do parathyroid hormone, ADH, and thyroid hormone contribute to homeostasis? What might be the consequence of having too little of each of those hormones?

CHAPTER 11 QUANTITATIVE AND THOUGHT QUESTIONS

Answers found at www.mhhe.com/widmaier13.

1. In an experimental animal, the sympathetic preganglionic fibers to the adrenal medulla are cut. What happens to the plasma concentration of epinephrine at rest and during stress?
2. During pregnancy, there is an increase in the liver's production and, consequently, the plasma concentration of the major plasma binding protein for thyroid hormone. This causes a sequence of events involving feedback that results in an increase in the plasma concentrations of T_3 but no evidence of hyperthyroidism. Describe the sequence of events.
3. A child shows the following symptoms: deficient growth, failure to show sexual development, decreased ability to respond to stress. What is the most likely cause of all these symptoms?
4. If all the neural connections between the hypothalamus and pituitary gland below the median eminence were severed, the secretion of which pituitary gland hormones would be affected? Which pituitary gland hormones would not be affected?
5. Typically, an antibody to a peptide combines with the peptide and renders it nonfunctional. If an animal were given an antibody to somatostatin, the secretion of which anterior pituitary gland hormone would change and in what direction?
6. A drug that blocks the action of norepinephrine is injected directly into the hypothalamus of an experimental animal, and the secretion rates of several anterior pituitary gland hormones are observed to change. How is this possible, given the fact that norepinephrine is not a hypophysiotropic hormone?

CHAPTER 11 ANSWERS TO PHYSIOLOGICAL INQUIRIES

Figure 11.3 By storing large amounts of hormone in an endocrine cell, the plasma concentration of the hormone can be increased within seconds when the cell is stimulated. Such rapid responses may be critical for an appropriate response to a challenge to homeostasis. Packaging peptides in this way also prevents intracellular degradation.

Figure 11.5 Because steroid hormones are derived from cholesterol, they are lipophilic. Consequently, they can freely diffuse through lipid bilayers, including those that constitute secretory vesicles. Therefore, once a steroid hormone is synthesized, it diffuses out of the cell.

Figure 11.9 One explanation for this patient's symptoms may be that his or her circulating concentration of thyroid hormone was elevated. This might occur if the person's thyroid was overstimulated due, for example, to thyroid disease. The control of the anterior pituitary gland by a very small number of discrete neurons within the hypothalamus.

Figure 11.21 Iodine is not widely found in foods; in the absence of iodized salt, an acute or chronic deficiency in dietary iodine is possible. The colloid permits a long-term store of iodinated thyroglobulin that can be used during times when dietary iodine intake is reduced or absent.

Figure 11.24 Plasma cortisol concentrations would increase. This would result in decreased ACTH concentrations in the systemic blood, and CRH concentrations in the portal vein blood, due to increased negative feedback at the pituitary gland and hypothalamus, respectively. The right adrenal gland would shrink in size (atrophy) as a consequence of the decreased ACTH concentrations (decreased "trophic" stimulation of the adrenal cortex).

Figure 11.28 Note from the figure that a decrease in plasma glucose concentrations results in an increase in growth hormone concentrations. This makes sense, because one of the metabolic actions of growth hormone is to increase the concentrations will decrease. This is a form of secondary hypoparathyroidism.

Visit this book's website at **www.mhhe.com/widmaier13** for chapter quizzes, interactive learning exercises, and other study tools.

Updates and Additions

In addition to updating material throughout the text to reflect cutting-edge changes in physiology and medicine, the authors have introduced the following:

- A new unifying theme has been integrated into all chapters based on fundamental, key principles of physiology. These are outlined in Chapter 1 in a new section called General Principles of Physiology, and include such things as homeostasis, structure/function relationships, information flow, and several others. Beginning with Chapter 2, the introduction to each chapter provides a preview for the student of the general principles that will be covered in that chapter. Within the chapter, the principles are reinforced where appropriate. At the end of each chapter, one or more assessments are provided that enable the student to relate the material in that chapter to an understanding of unifying physiological themes.
- The number of Test Questions and Quantitative and Thought Questions has been expanded. These assessments complement the many test questions available free of charge to students on the McGraw-Hill website that accompanies the textbook.
- The Physiological Inquiries feature has been retained and expanded. Continued positive feedback from users of the text indicated that this learning tool is extremely valuable, and thus we have added additional inquiries associated with key figures.

In addition to new assessments, and the usual editing to make sure the text remains even more reader-friendly, up-to-date, and accurate, approximately 25 new pieces of art have been added, and another 25 existing pieces of art have been considerably modified to provide updated information. A sampling of substantive changes to each chapter follows.

Chapter 1 Homeostasis: A Framework for Human Physiology

New section introducing and describing the important General Principles of Physiology, providing an instructional framework that unifies all the chapters.

Chapter 2 Chemical Composition of the Body

Increased emphasis on the physiological relevance of chemical principles; expanded discussion of the use of isotopes in physiology with a new PET scan figure; ionic bonds treated in a new section.

Chapter 3 Cellular Structure, Proteins, and Metabolism

Importance of cholesterol in determining membrane fluidity is now discussed and illustrated.

Chapter 4 Movement of Molecules Across Cell Membranes

Compensatory endocytosis now discussed.

Chapter 5 Control of Cells by Chemical Messengers

Illustrations of receptor conformations with and without bound ligand are now depicted to emphasize binding-induced shape changes linked to receptor activation; IP_3 receptor/ion channel now depicted in illustration of cell signaling.

Chapter 6 Neuronal Signaling and the Structure of the Nervous System

New discussion about the use of adult stem cells to treat neurological diseases; new figure illustrating the way in which synapses that increase chloride conductance stabilize the membrane potential.

Chapter 7 Sensory Physiology

A new table has been added summarizing the general principles of sensory stimulus processing; discussion of Müller cells added to section on retinal function; expanded discussion and illustration of the mechanism by which retinal dissociates from its opsin and is enzymatically reassociated.

Chapter 8 Consciousness, the Brain, and Behavior

A comparison between PET, MRI, and EEG as effective tools for assessing tumors, clots, or hemorrhages in the brain has been added; new discussion of high-frequency gamma-wave patterns; updated the NREM designations to the new Phase N1–N3 nomenclature; discussion of hypnic jerk movements added; new section added describing the neural basis of the conscious state, including the role of RAS monoamine, orexins/hypocretins, and the "sleep center" of the brain; discussion of narcolepsy; new discussion regarding the role of the right cerebral hemisphere in the emotional context of language; new figure illustrating brain regions

involved in consciousness; a new figure showing a model of the regulation of sleep/wake transitions; new figure of a CT scan of the brain of a person with an epidural hemorrhage.

Chapter 9 Muscle

A new figure illustrating cardiac muscle excitation–contraction coupling; reorganization of the first two sections of the chapter such that events are described in the order in which they occur: excitation, E–C coupling, sliding filament mechanism; updated discussion about muscle fatigue; new discussion about myostatin and its role in muscle mass; new discussion about caldesmon's role in smooth muscle function.

Chapter 10 Control of Body Movement

Interconnections of structures participating in the motor control hierarchy have been updated; new example demonstrating the importance of association areas in motor control.

Chapter 11 The Endocrine System

Role of pendrin in thyroid hormone synthesis now introduced and illustrated; steroid synthetic pathway simplified to illustrate major events; improved illustration of anatomical relationship between hypothalamus and anterior pituitary gland; addition of numerous specific examples to highlight general principles, such as hyporesponsiveness; new figure showing production of insulin from proinsulin.

Chapter 12 Cardiovascular Physiology

Numerous figures have been updated or improved for clarity, or modified to include additional important information; discussion added about internodal pathways between the SA and AV nodes; new description about transient outward K^1 channels in myocytes; new table added comparing hemodynamics of systemic and pulmonary circuits; new discussion about VEGF antibodies and angiogenesis; section on hypertension has been updated to include the latest information about the effects of a high-salt diet, the findings of the DASH diet study, and other environmental causes or links to hypertension.

Chapter 13 Respiratory Physiology

New information about the cystic fibrosis channel mutation and treatment of cystic fibrosis; new figure showing the muscles of respiration; new improved illustration of respiratory cycle; enhanced illustration of the factors that change the shape of the O_2 dissociation curve including a panel on fetal hemoglobin; new figure on brainstem respiratory control centers and simplification of the description of respiratory control.

Chapter 14 The Kidneys and Regulation of Water and Inorganic Ions

New figure showing major anatomical structures of the kidney; new figure and text describing the effects of vasopressin on the volume and osmolarity of the filtrate along the length of the nephron; revised and expanded discussion of the local and central control of micturition.

Chapter 15 The Digestion and Absorption of Food

New figure and text updating the control of bicarbonate secretion in the pancreatic duct cells and the role of the cystic fibrosis transmembrane conductance regulator (CFTR) in this process; reorganization of portions of the text to improve the flow of the chapter.

Chapter 16 Regulation of Organic Metabolism and Energy Balance

New figure on energy expenditure during common activities; streamlined text with greater emphasis on general principles of physiology.

Chapter 17 Reproduction

Reorganization of first two sections into a single new section entitled Gametogenesis, Sex Determination, and Sex Differentiation; General Principles of Reproductive Endocrinology; several new figures illustrating the events of gametogenesis, embryonic development of the male and female reproductive tracts, development of external genitalia in males and females, and synthesis of gonadal steroids; new section on anabolic steroid use.

Chapter 18 The Immune System

Additional artwork and photographs including a new micrograph of a human blood smear, a new micrograph of a leukocyte undergoing diapedesis, and a computer model of an immunoglobulin.

Chapter 19 Medical Physiology: Integration Using Clinical Cases

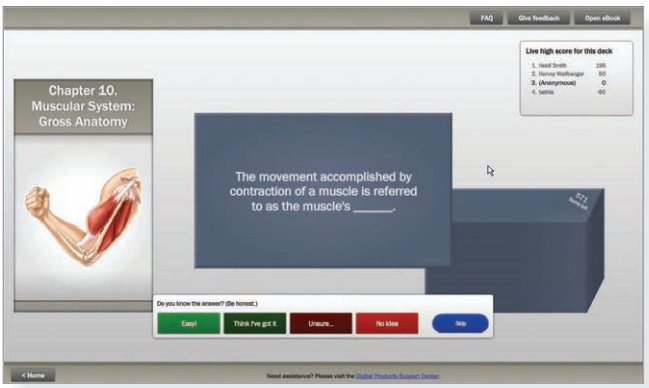
This chapter reinforces the General Physiological Principles introduced in Chapter 1 by demonstrating how these principles relate to human disease.

Teaching and Learning Supplements

NEW! McGraw-Hill LearnSmart™

McGraw-Hill LearnSmart™ is an online diagnostic learning system that determines the level of student knowledge, and feeds the students suitable content for their physiology course. Students learn faster and study more effectively. As a student works within the system, LearnSmart develops a personal learning path adapted to what the student has learned and retained. LearnSmart is able to recommend additional study resources to help the student master topics. This innovative and outstanding study tool also has features for instructors where they can see exactly what students have accomplished, and a built-in assessment tool for graded assignments.

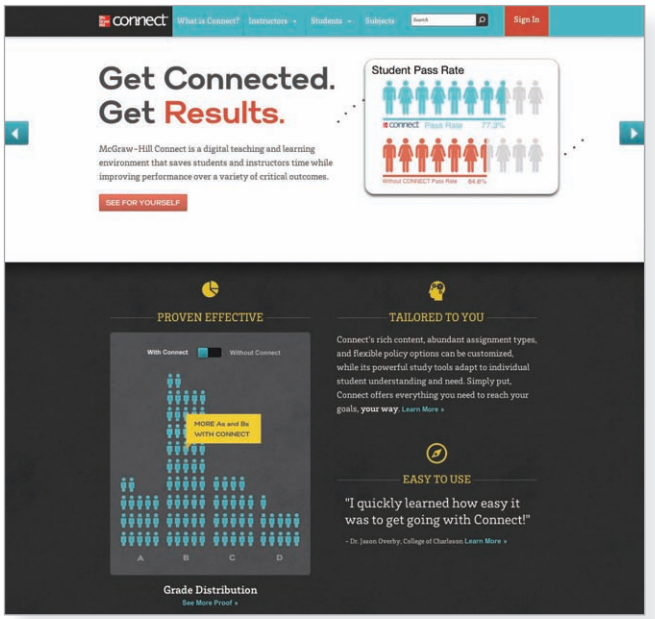
For more information, go to www.mhlearnsmart.com.



McGraw-Hill Connect™ Anatomy & Physiology

This Web-based assignment and assessment platform that gives students the means to better connect with their coursework, with their instructors, and with the important concepts that they will need to know for success now and in the future.

With Connect, instructors can deliver assignments, quizzes, and tests online. Questions are presented in an auto-gradable format and tied to the organization of the textbook. Instructors can edit existing questions and author entirely new problems; track individual student performance—by question, assignment, or in relation to the class overall—with detailed grade reports; integrate grade reports easily with learning management systems (LMS) such as WebCT and Blackboard; and much more. By choosing Connect, instructors are providing their students with a powerful tool for improving academic performance and truly mastering course material. Connect allows students to practice important skills at their own pace and on their own schedule.

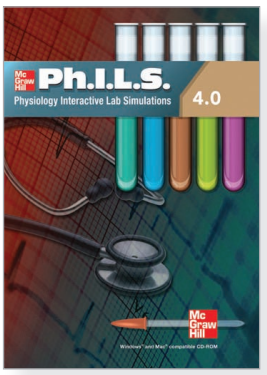


Importantly, students' assessment results and instructors' feedback are all saved online—so students can continually review their progress and plot their course to success.

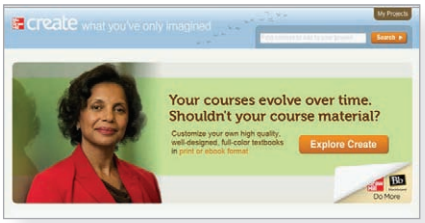
Some instructors may also choose ConnectPlus™ for their students. Like Connect, ConnectPlus provides students with online assignments and assessments, plus 24/7 online access to an eBook—an online edition of the text—to aid them in successfully completing their work, wherever and whenever they choose.

Physiology Interactive Lab Simulations (Ph.I.L.S.)

NEW! 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 lab 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!



Craft your teaching resources to match the way you teach! With McGraw-Hill Create™, www.mcgrawhillcreate.com, you can easily rearrange chapters, combine material from other content sources, and quickly upload content you have written, like your course syllabus or teaching notes. Find the content you need in Create by searching through thousands of leading McGraw-Hill textbooks. Arrange your book to fit your teaching style. Create even allows you to personalize your book's appearance by selecting the cover and adding your name, school, and course information. Order a Create book and you'll receive a complimentary print review copy in 3–5 business days or a complimentary electronic review copy (eComp) via e-mail in minutes. Go to www.mcgrawhillcreate.com today and register to experience how McGraw-Hill Create™ empowers you to teach *your* students *your* way.

Text Website—www.mhhe.com/widmaier13

The text website that accompanies this text offers an extensive array of learning and teaching tools.

- Interactive Activities—Fun and exciting learning experiences await the student at *Vander's Human Physiology* text website. Chapters offer a series of interactive activities like art labeling, animations, vocabulary flashcards, and more!
- Practice Quizzes at the *Vander's Human Physiology* text website contain hundreds of test questions that gauge student mastery of chapter content. Each chapter quiz is specifically constructed to test student comprehension of key concepts. Immediate feedback to student responses explains why an answer is correct or incorrect.
- Presentation Center is an online digital library containing assets such as photos, artwork, animations, and PowerPoints that can be used to create customized lectures, visually enhanced tests and quizzes, compelling course website, or attractive printed support materials.

Test Bank

Written by the textbook authors, a computerized test bank that uses testing software to quickly create customized exams is available for this text. The user-friendly program allows instructors to search for questions by topic or format, edit existing questions or add new ones, and scramble questions for multiple versions of the same test. Word files of the test bank questions are provided for those instructors who prefer to work outside the test-generator software.

Instructor's Manual

The Instructor's Manual is available on the text website (www.mhhe.com/widmaier13). It contains teaching/learning objectives, sample lecture outlines, and the answers to Review Questions for each chapter.

The Best of Both Worlds

McGraw-Hill and Blackboard®
McGraw-Hill Higher Education and Blackboard have teamed up. What does this partnership mean for you? Blackboard users will find the single sign-on and deep Integration of ConnectPlus within their Blackboard course an invaluable benefit. Even if your school is not using Blackboard, we have a solution for you. Learn more at www.domorenow.com.

Acknowledgments

The authors are deeply indebted to the following individuals for their contributions to the thirteenth edition of *Vander's Human Physiology*. Their feedback on the twelfth edition or their critique of the revised text provided invaluable assistance and greatly improved the final product. Any errors that may remain are solely the responsibility of the authors.

Allan Albig, *Indiana State University*
Lisa Carney Anderson, *University of Minnesota*
Heather Wilson-Ashworth, *Utah Valley University*
Kim Barrett, *University of California, San Diego*
Daniel Bergman, *Grand Valley State University*
Nicole Berthelemy, *Weber State University*
Robert W. Blair, *University of Oklahoma Health Sciences Center*
Eric Blough, *Marshall University*
Carol A. Britson, *University of Mississippi*
George A. Brooks, *University of California–Berkeley*
Martin G. Burg, *Grand Valley State University*
Patricia Cai, *Brooklyn College of CUNY*
Edwin R. Chapman, *University of Wisconsin–Madison*
Pat Clark, *IUPUI*
Maria Elena de Bellard, *CSUN*
Lee D. Faucher, *University of Wisconsin–Madison SMPH*
James S. Ferraro, *Southern Illinois University–School of Medicine*
Margaret Flanigan Skinner, *University of Wyoming*
Kennon M. Garrett, *University of Oklahoma Health Sciences Center*
Nicholas Geist, *Sonoma State University*
Brian Geraghty, *CUNY @ Brooklyn College & Kingsborough Community College*
Chaya Gopalan, *St. Louis College of Pharmacy*
Marion Greaser, *University of Wisconsin–Madison*
Eric Green, *Salt Lake Community College*
Chi-Ming Hai, *Brown University*
Janet L. Haynes, *Long Island University*
Steve Henderson, *California State University*
David W. Johnson, *University of New England*
Kelly Johnson, *Kansas University*
Tim Juergens, *University of Wisconsin–Madison SMPH*
Kenneth Kaloustian, *Quinnipiac University*
David King, *Nova Southeastern University*
Brian H. Kipp, *Grand Valley State University*
Sumana Koduri, *Medical College of Wisconsin*
Dean V. Lauritzen, *City College of San Francisco*
Mingyu Liang, *Medical College of Wisconsin*
Christian Lytle, *University of California, Riverside*
Steven Magill, *Medical College of Wisconsin*
David L. Mattson, *Medical College of Wisconsin*
Donald W. Michielli, *Brooklyn College of the City University of New York*
Kevin Middleton, *California State University*
Paul Nealen, *Indiana University of PA*
Lisa Parks, *North Carolina State University*
Mark Paternostro, *West Virginia University*
Timothy Plagge, *San Diego Mesa College*
Jocelyn Parks Ramos, *Ivy Tech Community College*
Laurel B. Roberts, *University of Pittsburgh*
Angela M. Seliga, *Boston University*
Virginia K. Shea, *University of North Carolina*
Mark Smith, *Santiago Canyon College*
Andrea Sobieraj, *Brown University*
Nadja Spitzer, *Marshall University*
Ruy Tchao, *University of the Sciences*
Dana K. Vaughan, *University of Wisconsin–Oshkosh*
Gordon M. Wahler, *Midwestern University*
R. Douglas Watson, *University of Alabama at Birmingham*
Eliot Williams, *University of Wisconsin–Madison SMPH*
Loren E. Wold, *The Research Institute at Nationwide Children's Hospital/The Ohio State University*
Yuri Zagvazdin, *Nova Southeastern University*

The authors are indebted to the many individuals who assisted with the numerous digital and ancillary products associated with these text. Thank you to Beth Altschafl, Patti Atkins, Janet Casagrand, Patricia Clark, Mike Griffin, David Johnson, Tami Mau, Carla Reinstadtl, Laurel Bridges Roberts, Rebecca Sheller, Andrea Jeanne Sobieraj, Nadja Spitzer, and Melanie Waite-Wright.

The authors are also indebted to the editors and staff at McGraw-Hill Higher Education who contributed to the development and publication of this text, particularly Developmental Editor Fran Simon, Brand Manager Marija Magner, Project Manager Sherry Kane, Production Supervisor Sandy Ludovissy, Designer Tara McDermott, and Photo Researcher John Leland. We also thank freelance copy editor C. Jeanne Patterson and freelance proofreader Beatrice Sussman. As always, we are grateful to the many students and faculty who have provided us with critiques and suggestions for improvement.

Eric P. Widmaier
Hershel Raff
Kevin T. Strang

Maintenance of body temperature is an example of homeostasis.

1 Homeostasis:

A FRAMEWORK FOR HUMAN PHYSIOLOGY

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. An understanding of the functions 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, and organ systems. Lastly, several "General Principles of Physiology" are introduced. These serve as unifying themes throughout the textbook, and the student 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. As applied to human beings, its scope is extremely broad. At one end of the spectrum, it includes the study of individual molecules—for example, how a particular protein's shape and electrical properties 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 work 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. . . ."

In this regard, a very important point must be made about the present and future status of physiology. It is easy for a student to gain the impression from a textbook that almost everything is known about the subject, but nothing could be farther from the truth for physiology. Many areas of function are still only poorly understood, such as how the workings of the brain produce conscious thought and memory.

Finally, in many areas of this text, we will relate physiology to medicine. 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 pathophysiology to illustrate the basic physiology that underlies the disease. A handy index of all the diseases and medical conditions discussed in this text appears in Appendix B. We begin our study of physiology by describing the organization of the structures of the human body.

1.2 How Is the Body Organized?

Before exploring how the human body works, it is necessary to understand the components of the body and their anatomical relationships to each other. 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**

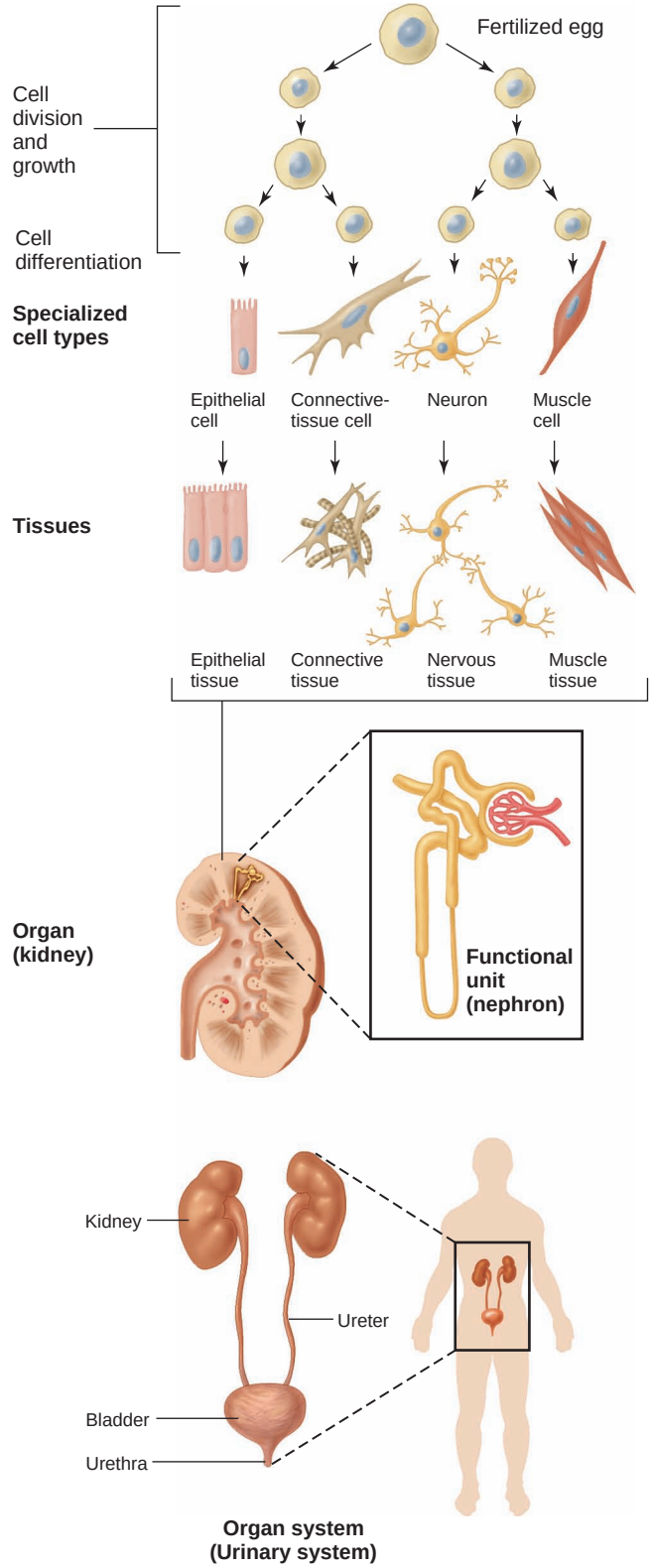


Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

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, 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 surround 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 kidney (see Figure 1.1), is called the apical 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 by extracellular barriers called tight junctions (look ahead to Figure 3.9, b and c, for a depiction of tight junctions). Tight junctions enable epithelia to form boundaries between body compartments and to function as selective barriers regulating the exchange of molecules. For

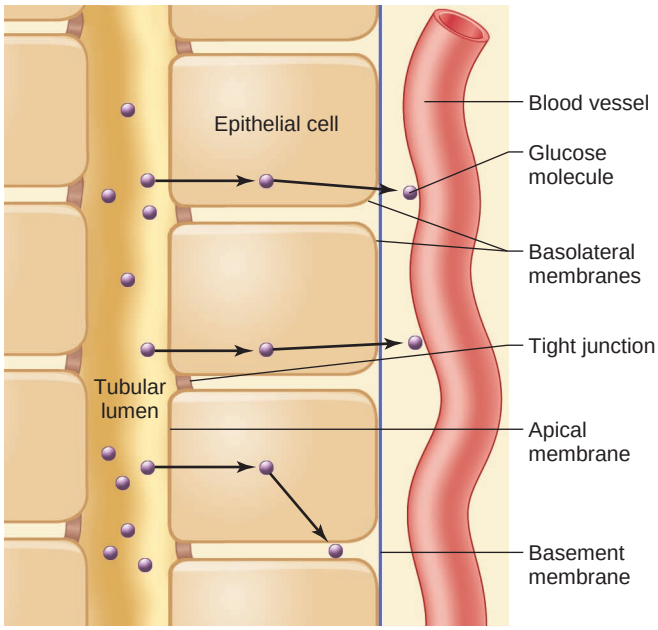


Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is moved across the epithelium, first directed into the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

example, the epithelial cells at the surface of the skin form a barrier that prevents most substances in the external environment from entering the body through the skin. In 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 immediate environment that surrounds each individual cell in the body is the **extracellular fluid.** Actually, this fluid is interspersed within a complex ECM consisting of a mixture of proteins; polysaccharides (chains of sugar molecules); and, in some cases, minerals, specific for any given tissue. The matrix 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.

The proteins of the extracellular matrix consist of proteins called **fibers**—ropelike **collagen fibers** and rubberband-like **elastin fibers**—and a mixture of nonfibrous proteins that contain carbohydrate. In some ways, the extracellular matrix 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; (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. For example, 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, constitute the urinary system. **Table 1.1** lists the components and functions of the organ systems in the body.

To sum up, the human body can be viewed as a complex society of differentiated cells that combine structurally and functionally to carry out the functions essential to the survival of the entire organism. The individual cells constitute the basic units of this society, and almost all of these cells individually exhibit the fundamental activities common to all forms of life, such as metabolism and replication. Key to the survival of all body cells is the **internal environment** of the body; this refers to the fluids that surround cells and exist in the blood. These fluid compartments and one other—that which exists inside cells—are described next.

TABLE 1.1 Organ Systems of the Body

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

1.3 Body Fluid Compartments

Water is present within and around the cells of the body, and within all the blood vessels. When we refer to "body fluids," we are referring to a watery solution of dissolved substances such as oxygen, nutrients, and wastes. 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 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

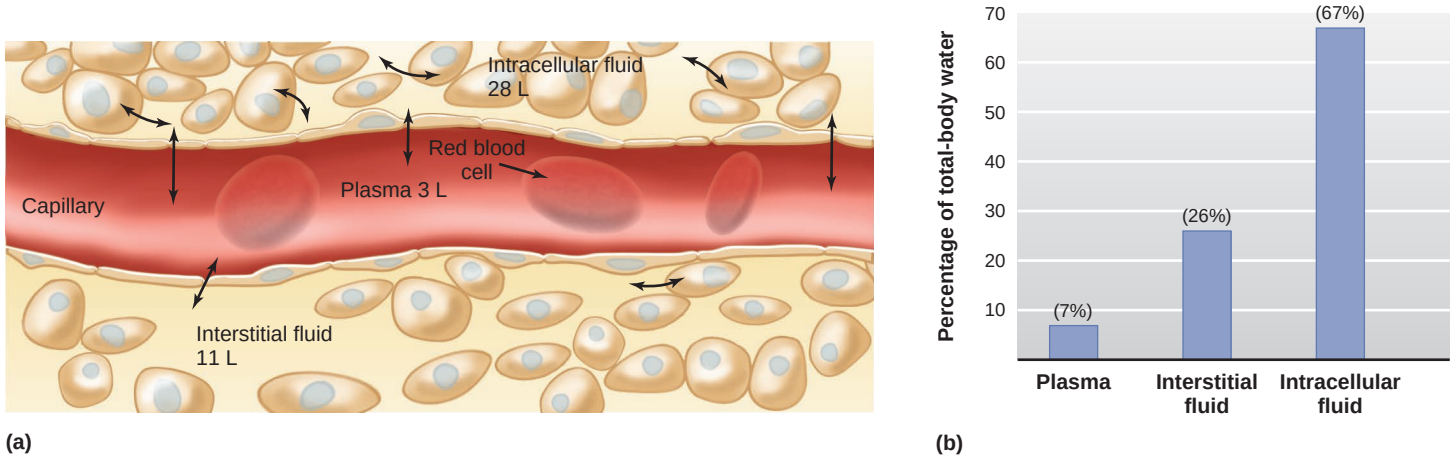


Figure 1.3 Fluid compartments of the body. Volumes are for an average 70-kilogram (kg) (154-pound [lb]) person. (a) The bidirectional arrows indicate that fluid can move between any two adjacent compartments. Total-body water is about 42 liters (L), which makes up about 55%–60% of body weight. (b) The 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 this person's body weight is due to extracellular body water?

Answer can be found at end of chapter.

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 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 by the wall of the blood vessels. Chapter 12 discusses how this barrier normally keeps 75%–80% 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 achieved 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 1.3).

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.

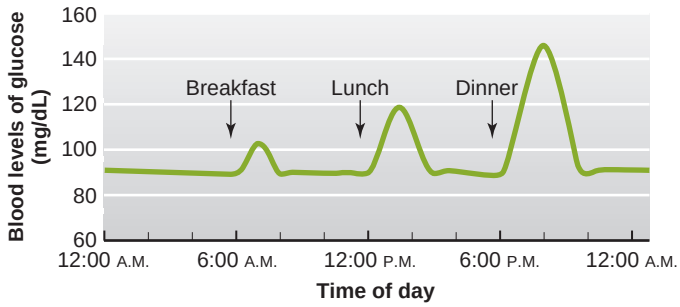


Figure 1.4 Changes in blood glucose concentrations during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood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

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, blood glucose concentrations increase 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 processes. In later chapters, we will see how every organ and tissue 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 level in the blood of a healthy person breathing air at sea level is measured, it barely changes over the course of time, even if the person exercises. Such a system is said to be 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 a few percentage points of its normal range, sodium homeostasis exists. However, a person whose sodium ion concentrations are homeostatic may suffer from other disturbances, such as abnormally high carbon dioxide levels in the blood resulting from lung 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 dramatically 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 to help 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 208C and moderate humidity. His internal body temperature is 378C, 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 constant 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 reduce the temperature of the room, say to 58C, 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 reduces heat loss from the blood to the environment and helps maintain body temperature. At a room temperature of 58C, however, blood vessel constriction cannot completely eliminate the extra heat loss from the skin. Like the person shown in the chapter opening photo, 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 excessive 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.

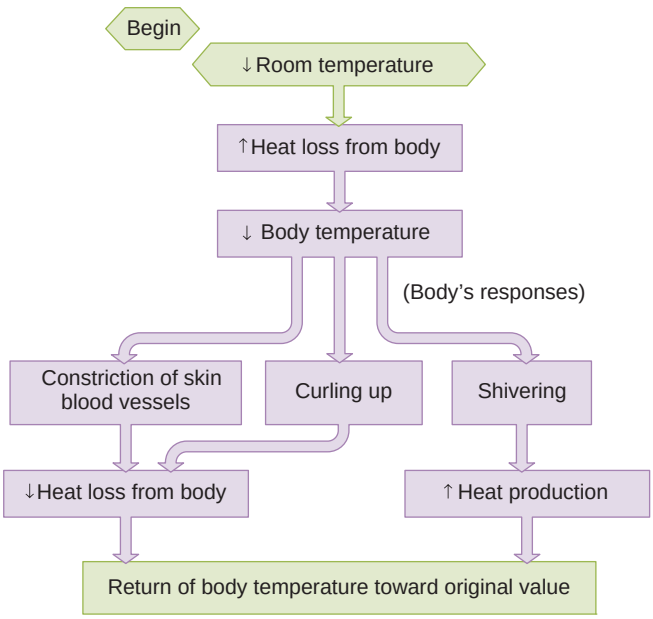


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The "Begin" sign indicates where to start. The arrows next to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

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 plays 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.) 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 principle of homeostasis, because positive feedback has no obvious means of stopping. Not surprisingly, therefore, positive feedback is much less

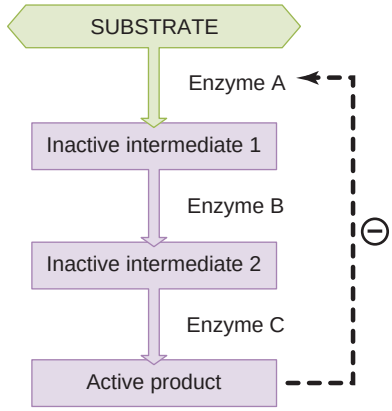


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its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

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 Chapter 17, is the process of parturition (birth). As the uterine muscles contract and a baby's head is pressed against the mother's cervix during labor, signals are relayed via nerves from the cervix to the mother's brain. The brain initiates the secretion into the blood of a molecule called oxytocin from the mother's pituitary gland. Oxytocin is a potent stimulator of further uterine contractions. As the uterus contracts even harder in response to oxytocin, the baby's head is pushed harder against the cervix, causing it to stretch more; this stimulates yet more nerve signals to the mother's brain, resulting in yet more oxytocin secretion. This self-perpetuating cycle continues until finally the baby pushes through the stretched cervix and is born.

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 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*. Let us give an example of feedforward and then define it. The temperature-sensitive neurons that trigger negative feedback regulation of body temperature when

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.