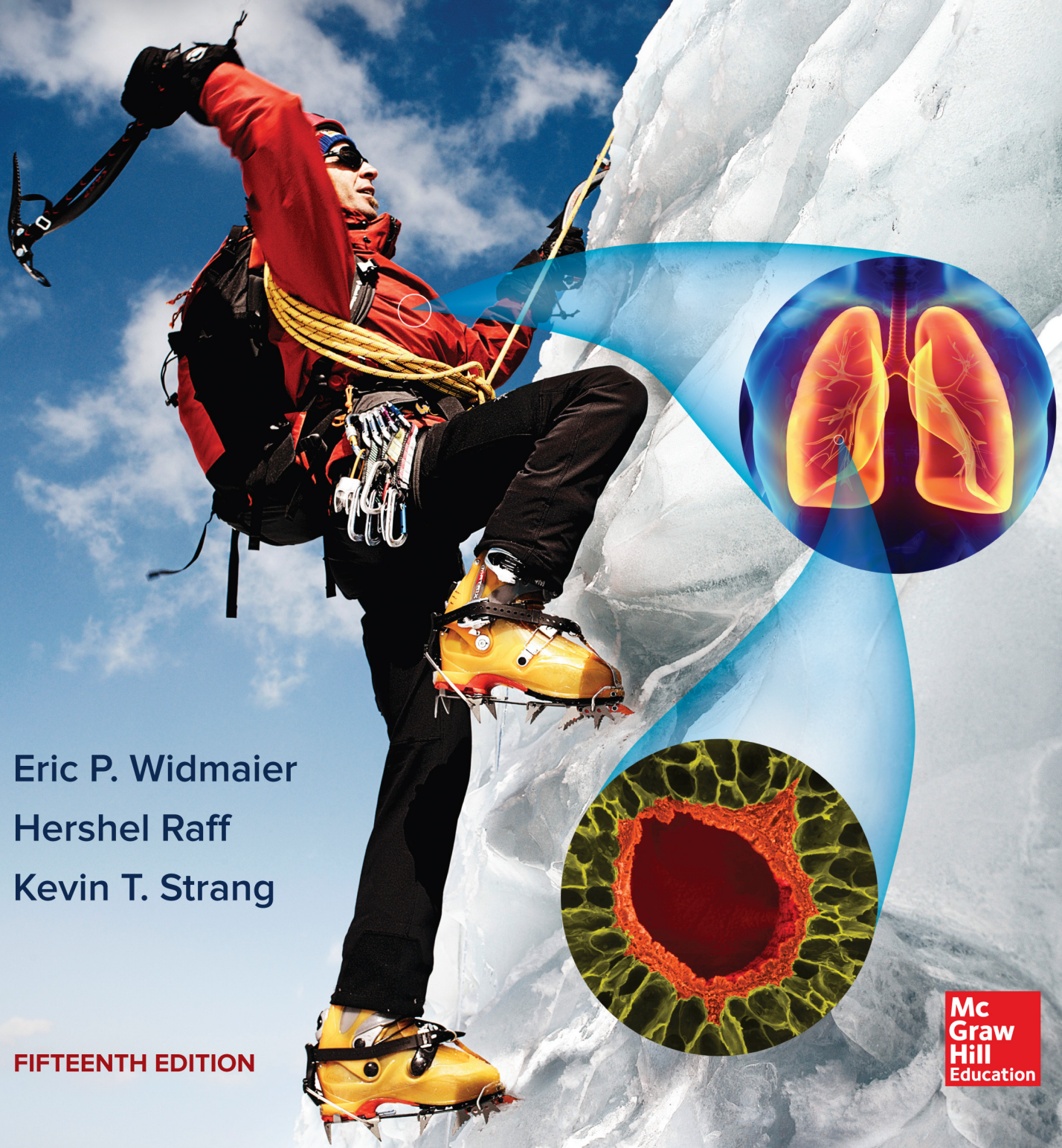
VANDER'S Human Physiology

THE MECHANISMS OF BODY FUNCTION



Eric P. Widmaier
Hershel Raff
Kevin T. Strang

FIFTEENTH EDITION

Mc Graw Hill Education

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VANDER'S Human Physiology

The Mechanisms of Body Function

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BOSTON UNIVERSITY

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

This book is printed on acid-free paper.

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

ISBN 978-1-259-90388-5
MHID 1-259-90388-5

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Library of Congress Cataloging-in-Publication Data

Names: Widmaier, Eric P., author. | Vander, Arthur J., 1933- Human physiology.
Title: Vander's human physiology : the mechanisms of body function.
Other titles: Human physiology
Description: Fifteenth edition / Eric P. Widmaier, Boston University [and three others]. | New York, NY : McGraw-Hill Education, [2019] | Includes index.
Identifiers: LCCN 2017048599 | ISBN 9781259903885 (alk. paper)
Subjects: LCSH: Human physiology. | Human physiology—Problems, exercises, etc.
Classification: LCC QP34.5 .W47 2019 | DDC 612—dc23 LC record available at https://lccn.loc.gov/2017048599

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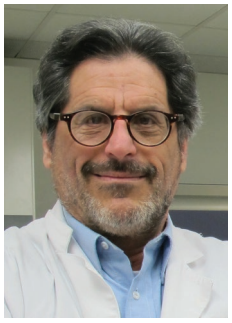
Brief Contents

Meet the Authors

©Maria Widmaier

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



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

©Kevin Strang

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

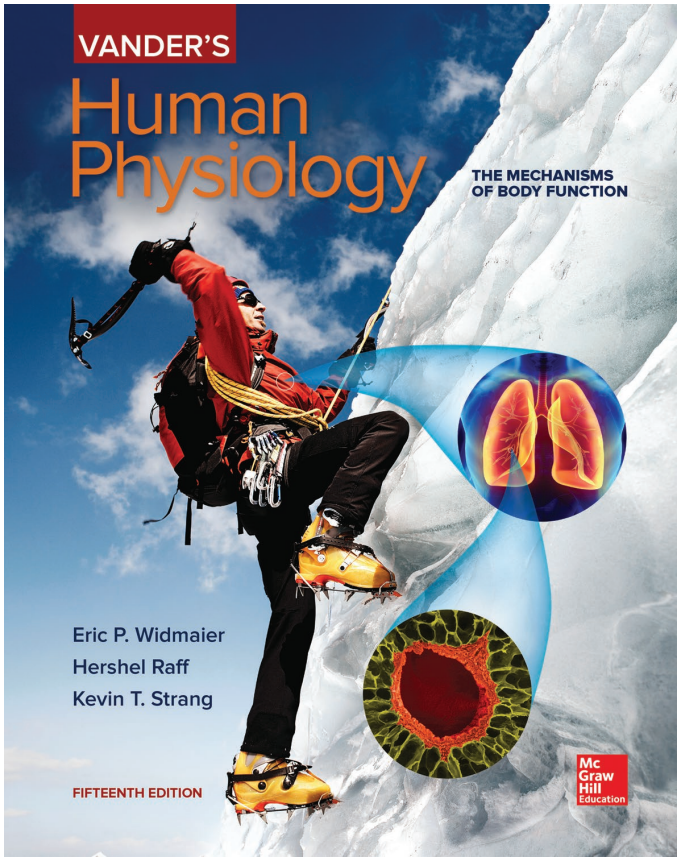
©Jon Rou

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

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

From the Authors

Lifeline to success in physiology



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

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

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

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

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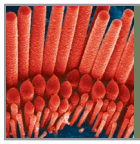

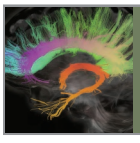

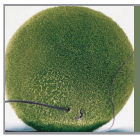

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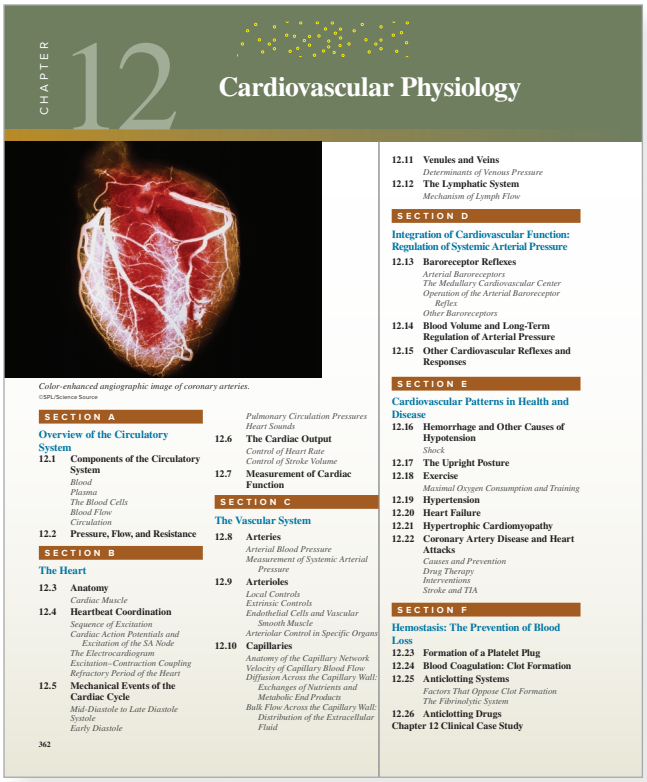
Index of Exercise Physiology

Guided Tour Through a Chapter



CHAPTER 12

Cardiovascular Physiology

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

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Chapter Outline

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

General Principles of Physiology

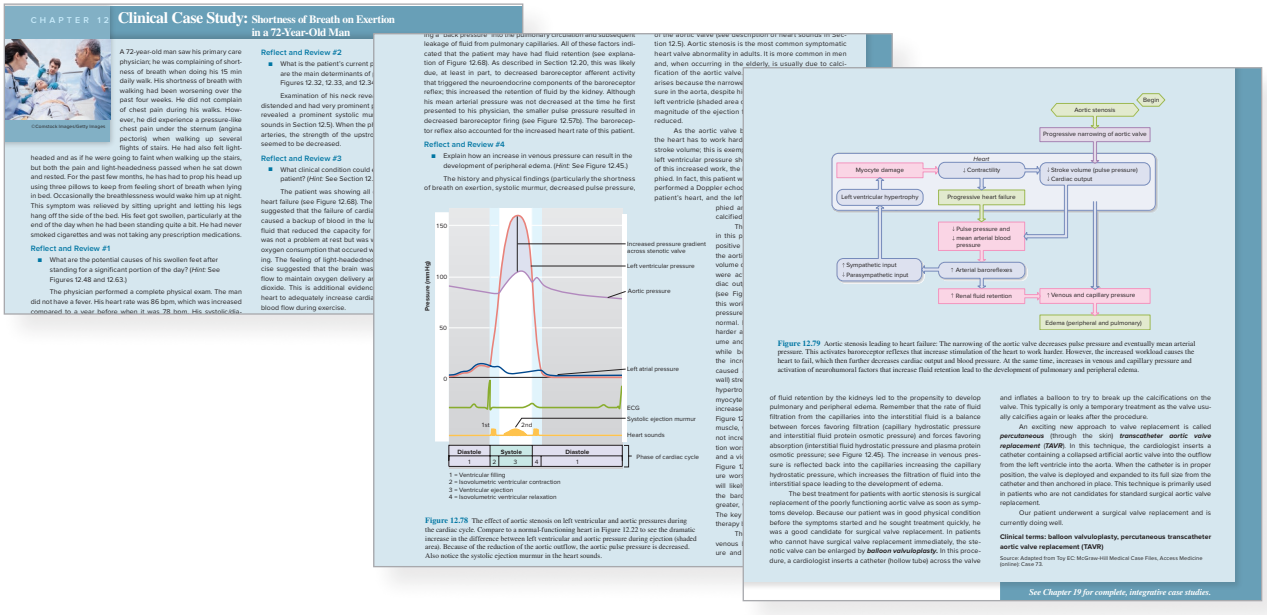
First introduced in the 13th edition to wide acclaim, General Principles of Physiology have been integrated throughout each chapter in order to continually reinforce their importance. Each chapter opens with a preview of those principles that are particularly relevant for the material covered in that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

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

The general principles of physiology described in Chapter 1 are abundantly represented in this chapter. In Section A, you will learn about the relationships between blood pressure, blood flow, and resistance to blood flow, a classic illustration of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The general principle of physiology that structure is a determinant of—and has coevolved with—function is apparent throughout the chapter; as one example, you will learn how the structures of different types of blood vessels determine whether they participate in fluid exchange, regulate blood pressure, or provide a reservoir of blood (Section C). The general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition, is exemplified by the hormonal and neural regulation of blood vessel diameter and blood volume (Sections C and D), as well as by the opposing mechanisms that create and dissolve blood clots (Section F). Sections D and E explain how the regulation of arterial blood pressure exemplifies that homeostasis is essential for health and survival, yet another general principle of physiology. Finally, multiple examples demonstrate the general principle of physiology that the functions of organ systems are coordinated with each other; for example, the circulatory and urinary systems work together to control blood pressure, blood volume, and sodium balance. ■

Clinical Case Studies

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



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

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

Reflect and Review #1

- What are the potential causes of his swollen feet after standing for a significant portion of the day? (Hint: See Figures 12.48 and 12.63.)

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

Reflect and Review #2

- What is the patient's current p... are the main determinants of ... Figures 12.32, 12.33, and 12.3...

Examination of his neck revea... distended and had very prominent ... revealed a prominent systolic mu... sounds in Section 12.5). When the pl... arteries, the strength of the upstro... seemed to be decreased.

Reflect and Review #3

- What clinical condition could ... patient? (Hint: See Section 12...

The patient was showing all ... heart failure (see Figure 12.6B). The... suggested that the failure of cardia... caused a backup of blood in the lu... fluid that reduced the capacity for ... was not a problem at rest but was ... oxygen consumption that occured w... ing. The feeling of light-headedne... cise suggested that the brain was... flow to maintain oxygen delivery a... dioxide. This is additional evidenc... heart to adequately increase cardia... blood flow during exercise.

Reflect and Review #4

- Explain how an increase in venous pressure can result in the development of peripheral edema. (Hint: See Figure 12.45.)

The history and physical findings (particularly the shortness of breath on exertion, systolic murmur, decreased pulse pressure, ... of the aortic valve (see description of heart sounds in Section 12.5). Aortic stenosis is the most common symptomatic heart valve abnormality in adults. It is more common in men and, when occurring in the elderly, is usually due to calcification of the aortic valve ... arises because the narrowing in the aorta, despite hi... left ventricle (shaded area ... magnitude of the ejection ... reduced.

As the aortic valve b... the heart has to work hard... stroke volume; this is exem... left ventricular pressure sh... of this increased work, the ... phied. In fact, this patient w... performed a Doppler echoc... patient's heart, and the lef... phied as ... calcified ...

Th... in this p... positive ... the aorti... volume ... were ac... diac out... (see Fig... this wor... pressure ... normal. ... harder a... ume and ... while be... the incr... caused ... wall) stre... hypertro... myocyte ... increase ... Figure 12... muscle, ... not incre... tion wor... and a vi... Figure 1... ure wor... will likel... the bac... greater, ... The key ... therapy ... Th... venous ... ure and ...

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

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

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

The best treatment for patients with aortic stenosis is surgical replacement of the poorly functioning aortic valve as soon as symptoms develop. Because our patient was in good physical condition before the symptoms started and he sought treatment quickly, he was a good candidate for surgical valve replacement. In patients who cannot have surgical valve replacement immediately, the stenotic valve can be enlarged by ***balloon valvuloplasty.*** In this procedure, a cardiologist inserts a catheter (hollow tube) across the valve and inflates a balloon to try to break up the calcifications on the valve. This typically is only a temporary treatment as the valve usually calcifies again or leaks after the procedure.

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

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

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

Source: Adapted from Toy EC: McGraw-Hill Medical Case Files, Access Medicine (online) Case 73.

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 12.3 The Circulatory System

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

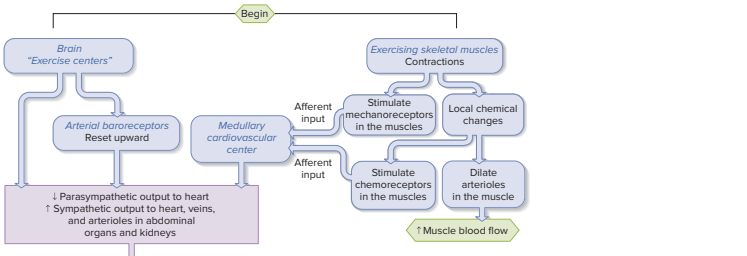


Figure 12.66 Control of the cardiovascular system during exercise. The primary outflow to the sympathetic and parasympathetic neurons is via pathways from "exercise centers" in the brain. Afferent input from mechanoreceptors and chemoreceptors in the exercising muscles and from reset arterial baroreceptors also influences the autonomic neurons by way of the medullary cardiovascular center.

PHYSIOLOGICAL INQUIRY

- How do the homeostatic responses during exercise highlight the general principle of physiology described in Chapter 1 that the functions of organ systems are coordinated with each other?

Answer can be found at end of chapter.

Physiological Inquiries

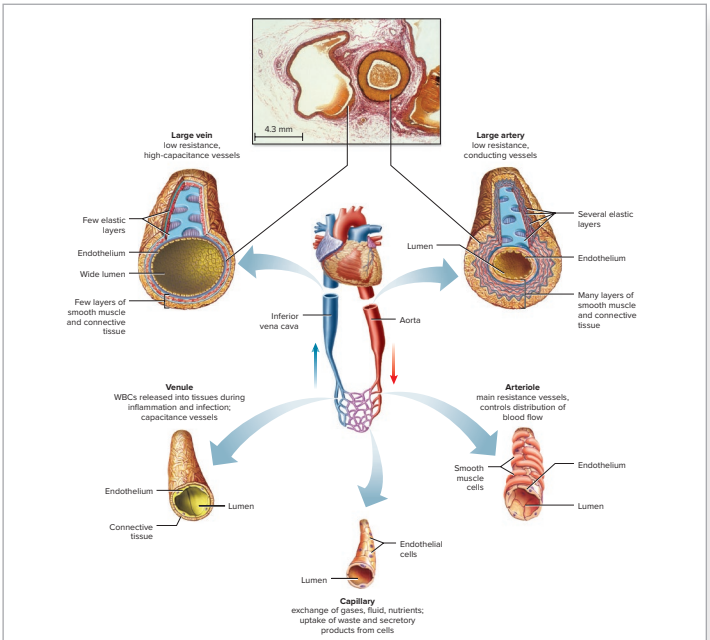
The authors have continued to refine and expand the number of higher Bloom's level critical-thinking questions based on many figures from all chapters. These concept checks were introduced in the eleventh edition and continue to prove extremely popular with users of the textbook. They are designed to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

Anatomy and Physiology REVEALED® (APR) Icon

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

Descriptive Art Style

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



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

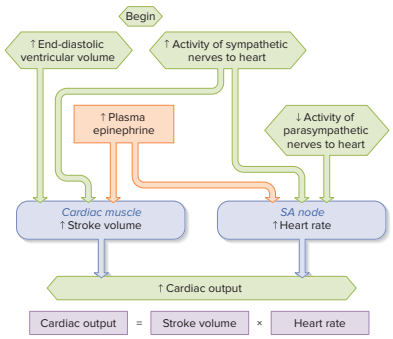


Figure 12.30 Major factors involved in increasing cardiac output. Reversal of all arrows in the boxes would illustrate how cardiac output can be decreased.

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

Flow Diagrams

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

Key to Flow Diagrams

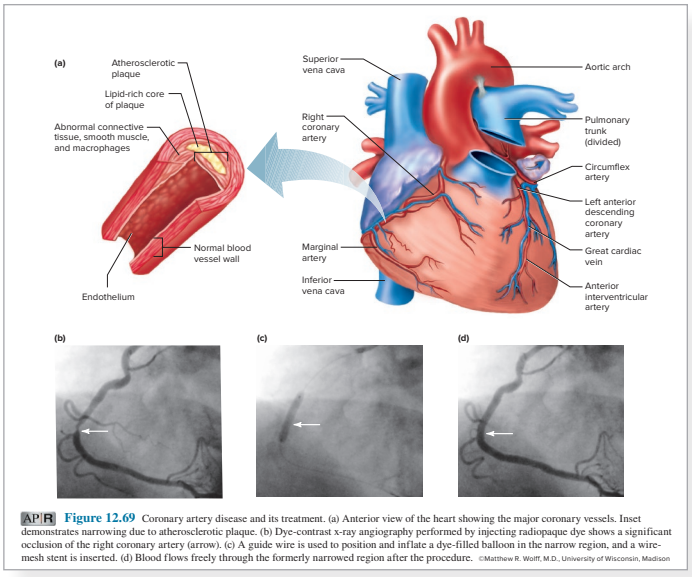
- The beginning boxes of the diagrams are color-coded green.
- Other boxes are consistently color-coded throughout the book.
- Structures are always shown in three-dimensional form.

Uniform Color-Coded Illustrations

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

Multilevel Perspective

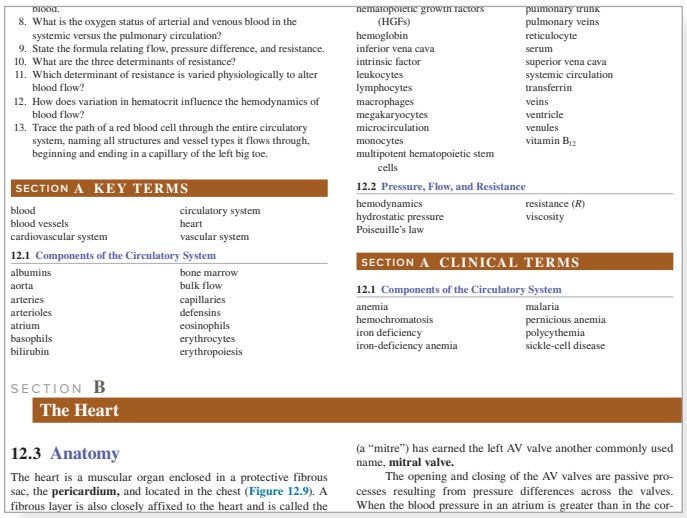
Illustrations depicting complex structures or processes combine macroscopic and microscopic views to help students see the relationships between increasingly detailed drawings.



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

End of Section

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



blood.

8. What is the oxygen status of arterial and venous blood in the systemic versus the pulmonary circulation?
9. State the formula relating flow, pressure difference, and resistance.
10. What are the three determinants of resistance?
11. Which determinant of resistance is varied physiologically to alter blood flow?
12. How does variation in hematocrit influence the hemodynamics of blood flow?
13. Trace the path of a red blood cell through the entire circulatory system, naming all structures and vessel types it flows through, beginning and ending in a capillary of the left big toe.

SECTION A KEY TERMS

blood
blood vessels
cardiovascular system
circulatory system
heart
vascular system

12.1 Components of the Circulatory System

albumins
aorta
arteries
arterioles
atrium
basophils
bilirubin
bone marrow
bulk flow
capillaries
defensins
eosinophils
erythrocytes
erythropoiesis
hematopoietic growth factors (HGFs)
hemoglobin
inferior vena cava
intrinsic factor
leukocytes
lymphocytes
macrophages
megakaryocytes
microcirculation
monocytes
multipotent hematopoietic stem cells
pulmonary trunk
pulmonary veins
reticulocyte
serum
superior vena cava
systemic circulation
transferrin
veins
ventricle
venules
vitamin B_{12}

12.2 Pressure, Flow, and Resistance

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

SECTION A CLINICAL TERMS

12.1 Components of the Circulatory System

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

SECTION B

The Heart

12.3 Anatomy

The heart is a muscular organ enclosed in a protective fibrous sac, the **pericardium,** and located in the chest (Figure 12.9). A fibrous layer is also closely affixed to the heart and is called the (a "mitre") has earned the left AV valve another commonly used name, **mitral valve.**

The opening and closing of the AV valves are passive processes resulting from pressure differences across the valves. When the blood pressure in an atrium is greater than in the cor-

End of Chapter

At the end of the chapters, you will find

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

CHAPTER 12 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

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

1. Hematocrit is increased
   a. when a person has a vitamin B_{12} deficiency.
   b. by an increase in secretion of erythropoietin.
   c. when the number of white blood cells is increased.
   d. by a hemorrhage.
   e. in response to excess oxygen delivery to the kidneys.
2. The principal site of erythrocyte production is
   a. the liver.
   b. the kidneys.
   c. the bone marrow.
   d. the spleen.
   e. the lymph nodes.
3. Which of the following contains blood with the lowest oxygen content?
   a. aorta
   b. left atrium
   c. right ventricle
   d. pulmonary veins
   e. systemic arterioles
4. If other factors are equal, which of the following vessels would have the lowest resistance?
   a. length = 1 cm, radius = 1 cm
   b. length = 4 cm, radius = 1 cm
   c. length = 8 cm, radius = 1 cm
   d. length = 1 cm, radius = 2 cm
   e. length = 0.5 cm, radius = 2 cm
5. Which of the following correctly ranks pressures during isovolumetric contraction of a normal cardiac cycle?
   a. left ventricular > aortic > left atrial
   b. aortic > left atrial > left ventricular
   c. left atrial > aortic > left ventricular
   d. aortic > left ventricular > left atrial
   e. left ventricular > left atrial > aortic
6. Considered as a whole, the body's capillaries have
   a. smaller cross-sectional area than the arteries.
   b. less total blood flow than in the veins.
   c. greater total resistance than the arterioles.
   d. slower blood velocity than in the arteries.
   e. greater total blood flow than in the arteries.
9. What is mainly responsible for the delay between the atrial and ventricular contractions?
   a. the shallow slope of AV node pacemaker potentials
   b. slow action potential conduction velocity of AV node cells
   c. slow action potential conduction velocity along atrial muscle cell membranes
   d. slow action potential conduction in the Purkinje network of the ventricles
   e. greater parasympathetic nerve firing to the ventricles than to the atria
10. Which of the following pressures is closest to the mean arterial blood pressure in a person whose systolic blood pressure is 135 mmHg and pulse pressure is 50 mmHg?
    a. 110 mmHg
    b. 78 mmHg
    c. 102 mmHg
    d. 152 mmHg
    e. 85 mmHg
11. Which of the following would help restore homeostasis in the first few moments after a person's mean arterial pressure became elevated?
    a. a decrease in baroreceptor action potential frequency
    b. a decrease in action potential frequency along parasympathetic neurons to the heart
    c. an increase in action potential frequency along sympathetic neurons to the heart
    d. a decrease in action potential frequency along sympathetic neurons to arterioles
    e. an increase in total peripheral resistance
12. Which is *false* about L-type Ca^{2+} channels in cardiac ventricular muscle cells?
    a. They are open during the plateau of the action potential.
    b. They allow Ca^{2+} entry that triggers sarcoplasmic reticulum Ca^{2+} release.
    c. They are found in the T-tubule membrane.
    d. They open in response to depolarization of the membrane.
    e. They contribute to the pacemaker potential.
13. Which correctly pairs an ECG phase with the cardiac event responsible?
    a. P wave: depolarization of the ventricles
    b. P wave: depolarization of the AV node
    c. QRS wave: depolarization of the ventricles
    d. QRS wave: repolarization of the ventricles
    e. T wave: repolarization of the atria

CHAPTER 12 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

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

1. A person is found to have a hematocrit of 35%. Can you conclude that there is a decreased volume of erythrocytes in the blood? Explain. *Hint:* See Figure 12.1 and remember the formula for hematocrit.
2. Which would cause a greater increase in resistance to flow, a doubling of blood viscosity or a halving of tube radius? *Hint:* See equation 12-2 in Section 12.2.

CHAPTER 12 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

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

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

CHAPTER 12 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

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

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

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

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

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Updates and Additions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chapter 16 The regulation of body temperature is now treated in its own new section, with a new subsection called General Principles of Thermoregulation. Lipoproteins are now described in detailed and distinguished from each other with additional text and a new figure showing their structures. A discussion of exercise-associated thermogenesis (EAT) and nonexercise activity thermogenesis (NEAT) has now been added to the section on energy balance. The terms *hunger*, *appetite*, and *satiety* are now defined and distinguished. Finally, the limitations of using BMI as an indicator of obesity and adiposity have been better elucidated.

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

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

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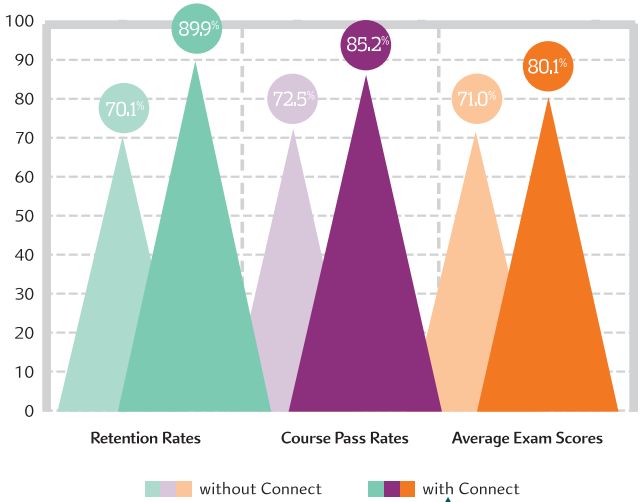

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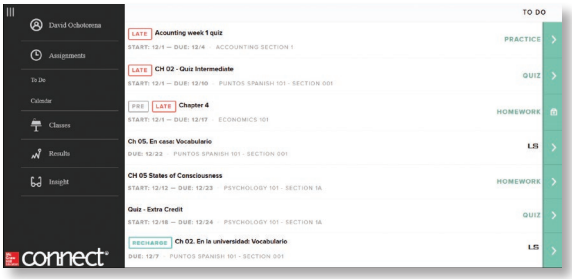

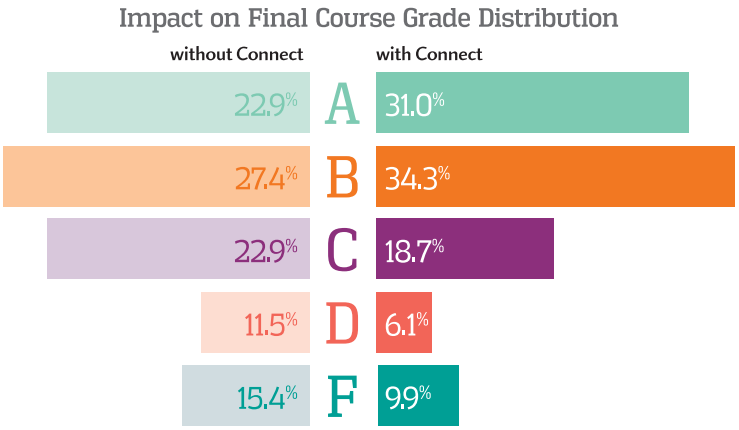

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Acknowledgments

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

Mark Alston,
University of Tennessee Knoxville
Brian Antonsen,
Marshall University
Jeffery Betts,
Central Michigan University
Patrick Cafferty,
Emory University
Jennifer Carr,
Harvard University Cambridge
Colin Carriker,
High Point University
Pat Clark,
IUPUI Indianapolis
Robert Fettiplace,
University of Wisconsin-Madison
Paul Goldspink,
Medical College of Wisconsin
Andrew Greene,
Medical College of Wisconsin
Suzanna Lesko Gribble,
University of Pittsburgh
Michael T. Griffin,
Angelo State University
Michael Guralnick,
Medical College of Wisconsin
Lisa Harrison-Bernard,
Louisiana State University School of Medicine
Lois Heller,
University of Minnesota - Duluth
Albert Herrera,
University of Southern California
Cecilia Hillard,
Medical College of Wisconsin
Grace Lee,
University of Wisconsin-Madison
Andrew Lokuta,
University of Wisconsin-Madison
Julian Lombard,
Medical College of Wisconsin
Steven Magill,
Medical College of Wisconsin
David Mattson,
Medical College of Wisconsin
Leanne May,
Rose State College
Monica McCullough,
Western Michigan University Kalamazoo
T. Richard Nichols,
Georgia Tech
Sandra Pfister,
Medical College of Wisconsin
John Pooler,
Emory University
Laurel Roberts,
University of Pittsburg
Jennifer Rogers,
University of Iowa- Iowa City
Virginia Shea,
University of North Carolina School of Medicine
Roy Silverstein,
Medical College of Wisconsin
Robert Stark,
California State University Bakersfield
Curt Walker,
Dixie State University

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

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

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

Homeostasis:

A Framework for Human Physiology

CHAPTER 1

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

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

1.1 The Scope of Human Physiology

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

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

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

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

1.2 How Is the Body Organized?

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

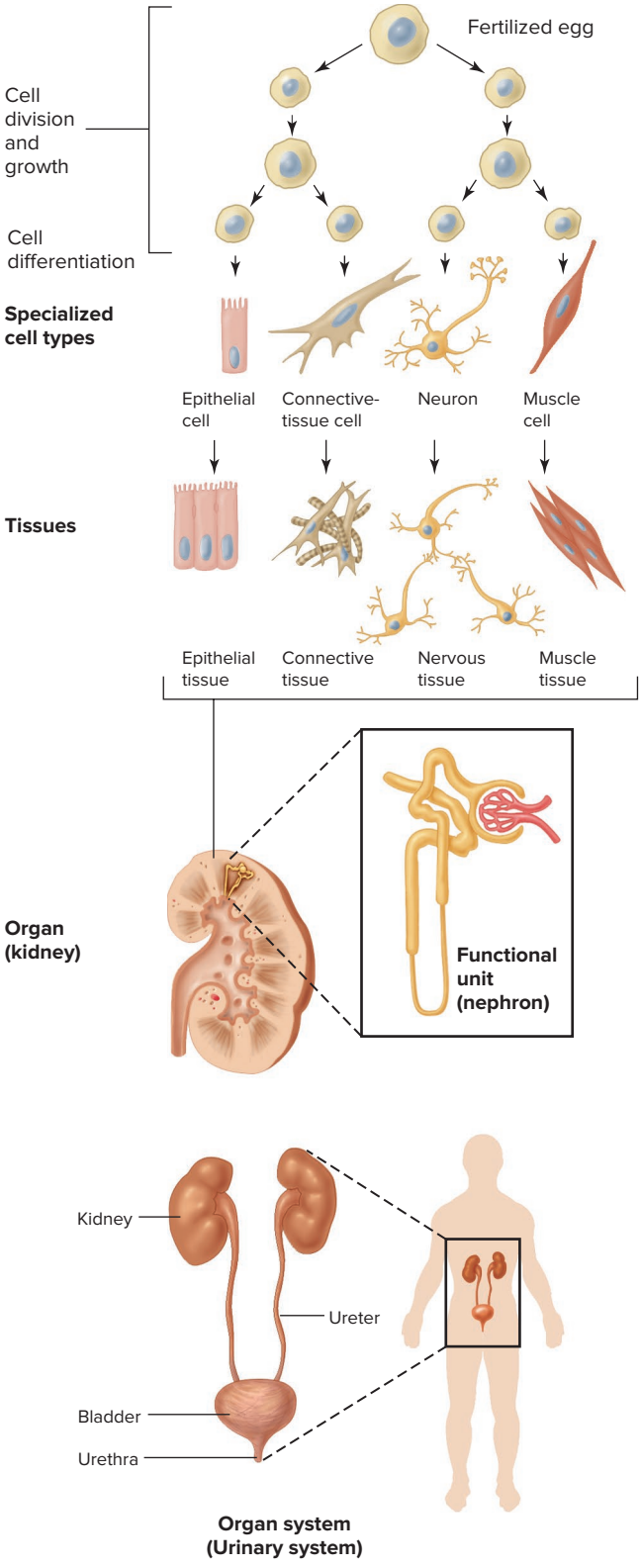

Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

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

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

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

Muscle Cells and Tissue

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

Neurons and Nervous Tissue

A **neuron** is a cell of the nervous system that is specialized to initiate, integrate, and conduct electrical signals to other cells, sometimes over long distances. A signal may initiate new electrical signals in other neurons, or it may stimulate a gland cell to secrete substances or a muscle cell to contract. Thus, neurons provide a major means of controlling the activities of other cells. The incredible complexity of connections between neurons underlies such phenomena as consciousness and perception. A collection of neurons forms nervous tissue, such as that of the brain or spinal cord. In some parts of the body, cellular extensions from many neurons are packaged together along with connective tissue (described shortly); these neuron extensions form a **nerve,** which carries the signals from many neurons between the nervous system and other parts of the body. Neurons, nervous tissue, and the nervous system will be covered in Chapter 6.

Epithelial Cells and Epithelial Tissue

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

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

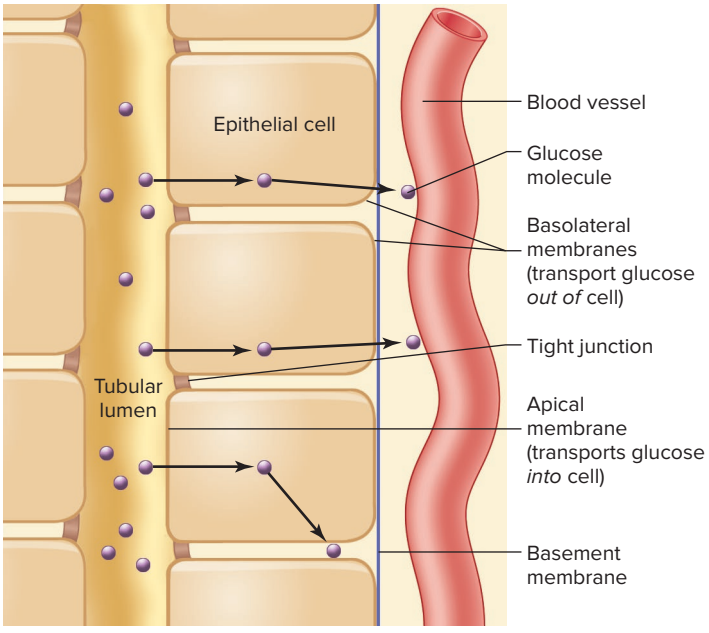

Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into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

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

Connective-Tissue Cells and Connective Tissue

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

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

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

Organs and Organ Systems

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

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

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

1.3 Body Fluid Compartments

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

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

TABLE 1.1 Organ Systems of the Body

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

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

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

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

1.4 Homeostasis: A Defining Feature of Physiology

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

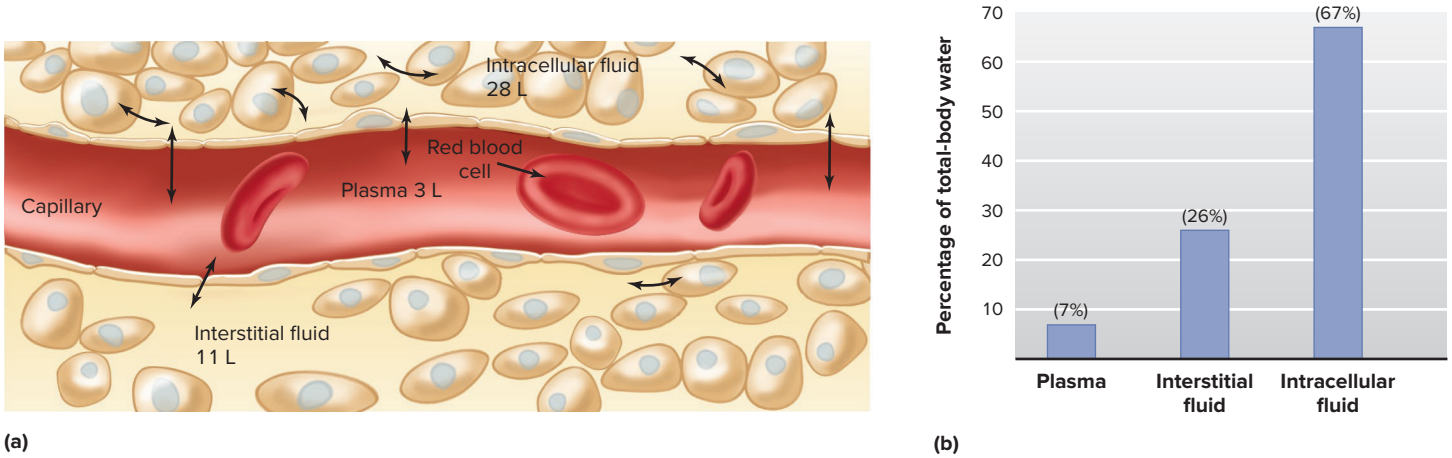

Figure 1.3 Fluid compartments of the body. Volumes are for a typical 70-kilogram (kg) (154-pound) person. (a) The bidirectional arrows indicate that fluid can move between any two adjacent compartments. Total-body water is about 42 liters (L), which makes up about 55%–60% of body weight. (b) The approximate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

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

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

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

Consider swings in the concentration of glucose in the blood over the course of a day (**Figure 1.4**). After a typical meal, carbohydrates in food are broken down in the intestines into glucose molecules, which are then absorbed across the intestinal epithelium and released into the blood. As a consequence, the blood glucose concentration increases considerably within a short time after eating. Clearly, such a large change in the blood concentration of glucose is not consistent with the idea of a stable or static internal environment. What is important is that once the concentration of glucose in the blood increases, compensatory mechanisms restore it toward the concentration it was before the meal. These homeostatic compensatory mechanisms do not, however, overshoot to any significant degree in the opposite direction. That is, the blood glucose usually does not decrease below the premeal concentration, or does so only slightly. In the case of glucose, the endocrine system is primarily responsible for this adjustment, but a wide variety of control systems may be initiated to regulate other homeostatic processes. In later chapters, we will see how every organ of the human body contributes to homeostasis, sometimes in multiple ways, and usually in concert with each other.

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

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

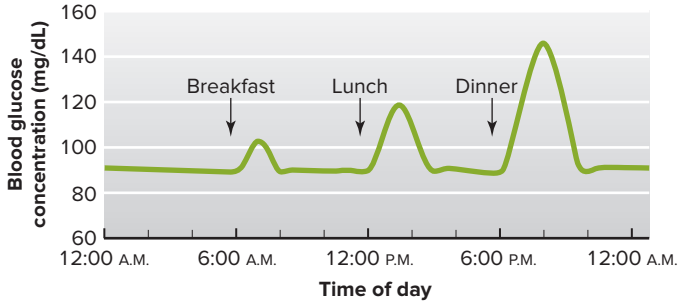

Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood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

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

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

1.5 General Characteristics of Homeostatic Control Systems

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

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

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

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

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

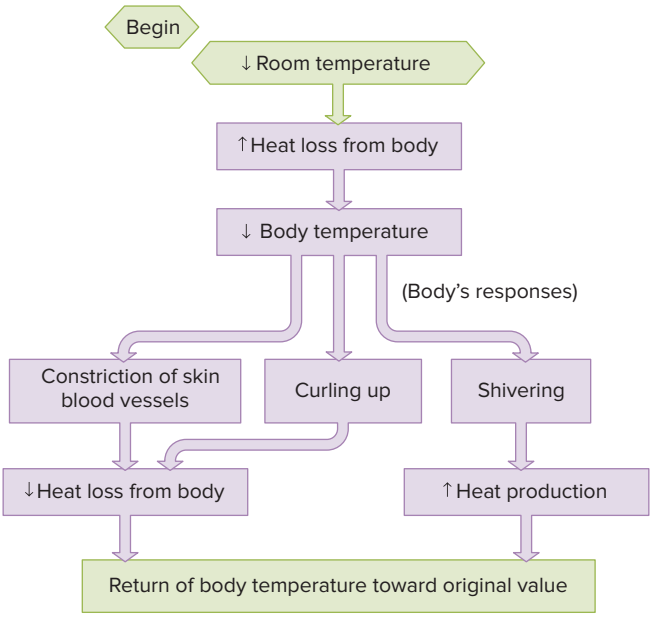

Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The "Begin" sign indicates where to start. The arrows next to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

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

Feedback Systems

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

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

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

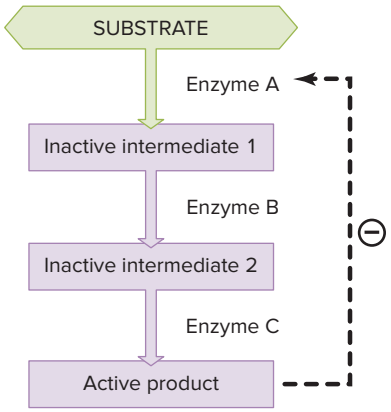

Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its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

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

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

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

Resetting of Set Points

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

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

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

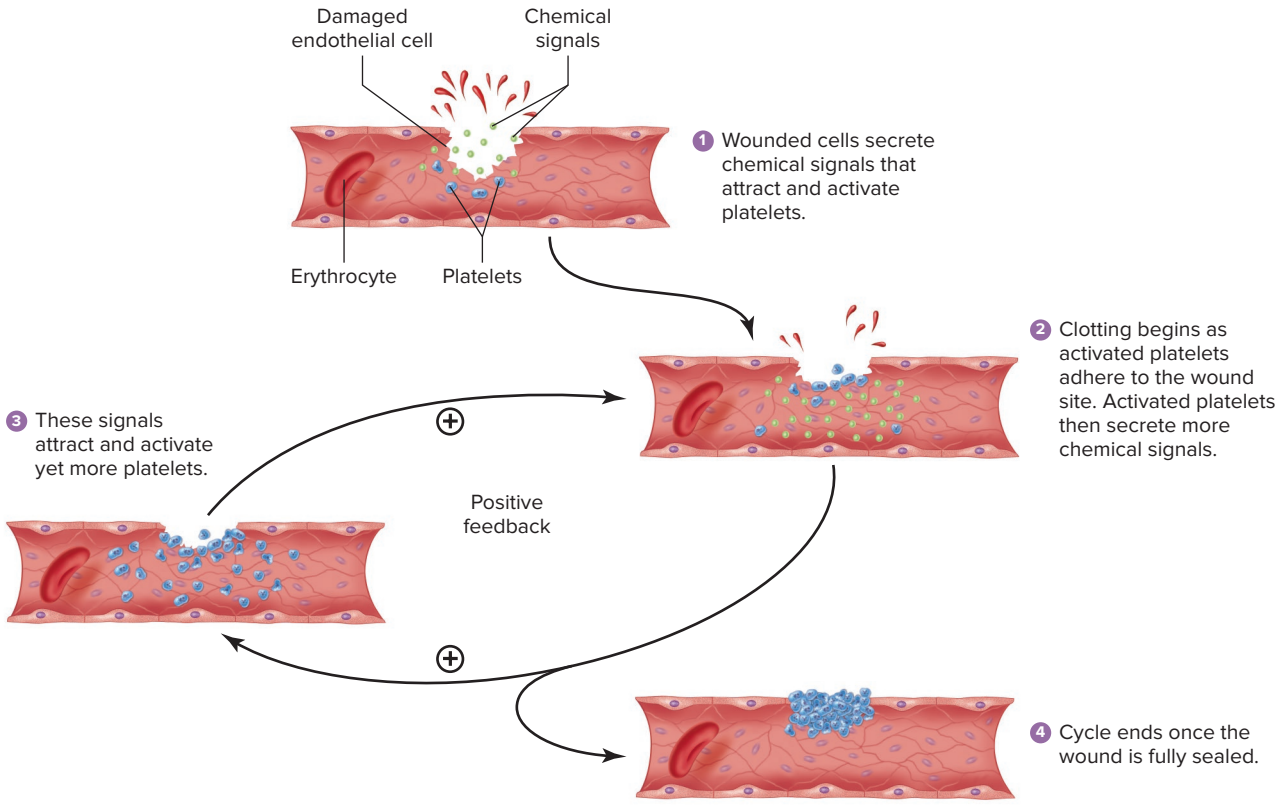

Figure 1.7 Positive feedback as illustrated by the clotting process in blood. Damaged endothelial cells (a type of epithelial cells) in the lining of a blood vessel secrete chemical signals that attract and activate platelets, tiny cell fragments that form clots. As clotting begins, the activated platelets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

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

The generalizations we have given about homeostatic control systems are summarized in **Table 1.2**. One additional point is that, as is illustrated by the regulation of body temperature, multiple systems usually control a single parameter. The adaptive value of such redundancy is that it provides much greater fine-tuning and also permits regulation to occur even when one of the systems is not functioning properly because of disease.

Feedforward Regulation

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

TABLE 1.2 Some Important Generalizations About Homeostatic Control Systems

Stability of an internal environmental variable is achieved by balancing inputs and outputs. It is not the absolute magnitudes of the inputs and outputs that matter but the balance between them.
In negative feedback, a change in the variable being regulated brings about responses that tend to move the variable in the direction opposite the original change—that is, back toward the initial value (set point).
Homeostatic control systems cannot maintain complete constancy of any given feature of the internal environment. Therefore, any regulated variable will have a more or less narrow range of normal values depending on the external environmental conditions.
The set point of some variables regulated by homeostatic control systems can be reset—that is, physiologically raised or lowered.
It is not always possible for homeostatic control systems to maintain every variable within a narrow normal range in response to an environmental challenge. There is a hierarchy of importance, so that certain variables may be altered markedly to maintain others within their normal range.