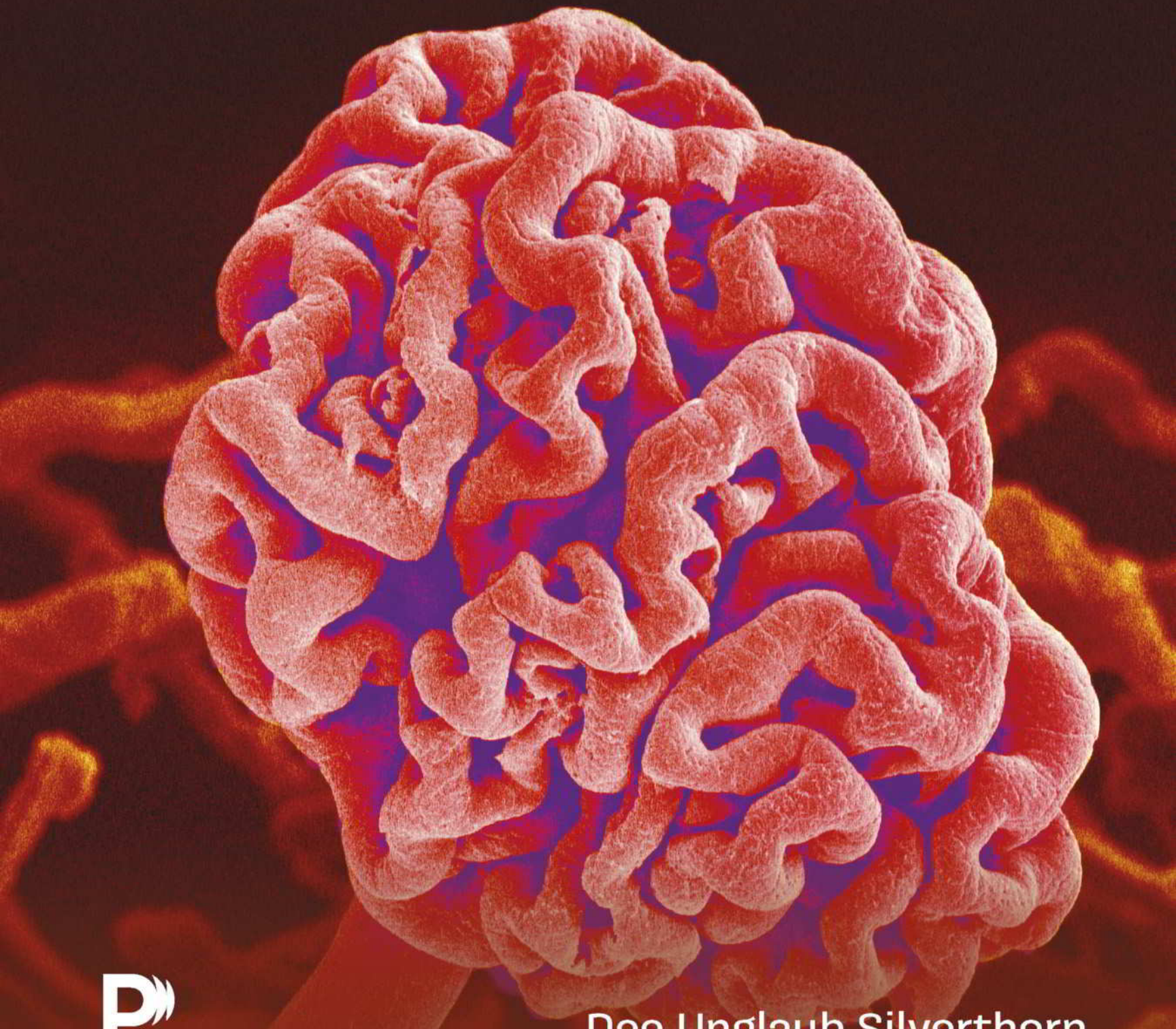
HUMAN PHYSIOLOGY

AN INTEGRATED APPROACH NINTH EDITION



Dee Unglaub Silverthorn

This page intentionally left blank

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- **Bioflix:** Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- **Bioflix:** Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- **Bioflix:** Electron Transport System
- **Bioflix:** Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- **Physiology in Action:** Osmolarity and Tonicity

Module 5.2

- **A&P Flix:** Membrane Transport

Module 5.7

- **Physiology in Action:** Membrane Potential
- **A&P Flix:** Resting Membrane Potential

Chapter 5 Links to Resources

- **Interactive Physiology Animation:** Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- **Microbiology Animation:** Host Defenses

Module 7.3

- **Microbiology Animation:** Antigen Processing and Presentation: Overview

Module 7.7

- **Microbiology Animation:** Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- **Bioflix:** Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- **BioFlix:** How Synapses Work

Module 9.3

- **Interactive Physiology Animation:** Generation of an Action Potential
- **BioFlix:** Action Potential Conduction

Chapter 9 Links to Resources

- **Interactive Physiology 2.0 Animation:** Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- **Biointeractives:** Circadian Rhythms and the SCN

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

Module 12.2

- **A&P Flix:** The Cross Bridge Cycle

Chapter 13 Muscles

Module 13.1

- **A&P Flix:** The Cross Bridge Cycle
- **Interactive Physiology Animation:** Neuromuscular Junction
- **Interactive Physiology 2.0 Animation:** Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- **Interactive Physiology Animation:** Pathway of Blood through the Heart
- **Interactive Physiology Animation:** Action Potentials in Autorhythmic Cells

Module 15.4

- **Physiology in Action:** Electrocardiogram
- **Interactive Physiology Animation:** Intrinsic Conduction System of the Heart
- **Interactive Physiology Animation:** Cardiac Output

Chapter 15 Links to Resources

- **Interactive Physiology 2.0 Animation:** Electrical Activity of the Heart
- **Interactive Physiology 2.0 Animation:** Cardiac Cycle
- **Interactive Physiology 2.0 Animation:** Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- **Physiology in Action:** Orthostatic Hypotension
- **Interactive Physiology Animation:** Arterial Baroreceptor Reflex

Chapter 16 Links to Resources

- **Interactive Physiology Animation:** Factors Affecting Blood Pressure
- **Interactive Physiology 2.0 Animations:** Factors Affecting Blood Pressure

Chapter 18 Mechanics of Breathing

Module 18.3

- **Physiology in Action:** The Spirometer
- **Physiology in Action:** Subatmospheric Pleural Cavity
- **Physiology in Action:** Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- **BioFlix:** Gas Exchange
- **Physiology in Action:** Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- **Interactive Physiology 2.0 Animation:** Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- **Interactive Physiology Animation:** Glomerular Filtration

Module 20.6

- **Interactive Physiology 2.0 Animation:** Prox tubule Reabsorption & Secretion

Module 20.7

- **Physiology in Action:** Renal Clearance

Chapter 20 Links to Resources

- **Interactive Physiology 2.0 Animation:** Glomerular Filtration
- **Interactive Physiology Animation:** Anatomy Review: Urinary System
- **Interactive Physiology 2.0 Animation:** Tubular Reabsorption & Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- **Interactive Physiology Animation:** Aldosterone and ADH in Salt & Water Processing
- **Interactive Physiology Animation:** Mechanisms for Acid-Base Homeostasis
- **Interactive Physiology Animation:** Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- **Interactive Physiology Animation:** Anatomy Review
- **Interactive Physiology Animation:** Control of Digestion
- **Interactive Physiology Animation:** Digestive System Secretion
- **Interactive Physiology Animation:** Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- **Physiology in Action:** Blood Pressure and Exercise

Strategies for Success

Top Ten Ways to Succeed in Classes that Use Active Learning

By Marilla Svinicki, Ph.D., former Director of the University of Texas Center for Teaching Effectiveness

1. Make the switch from an authority-based conception of learning to a self-regulated conception of learning. Recognize and accept your own responsibility for learning.
2. Be willing to take risks and go beyond what is presented in class or the text.
3. Be able to tolerate ambiguity and frustration in the interest of understanding.
4. See errors as opportunities to learn rather than failures. Be willing to make mistakes in class or in study groups so that you can learn from them.
5. Engage in active listening to what's happening in class.
6. Trust the instructor's experience in designing class activities and participate willingly if not enthusiastically.
7. Be willing to express an opinion or hazard a guess.
8. Accept feedback in the spirit of learning rather than as a reflection of you as a person.
9. Prepare for class physically, mentally, and materially (do the reading, work the problems, etc.).
10. Provide support for your classmate's attempts to learn. The best way to learn something well is to teach it to someone who doesn't understand.

Dr. Dee's Eleventh Rule:
DON'T PANIC! Pushing yourself beyond the comfort zone is scary, but you have to do it in order to improve.

Word Roots for Physiology

Simplify physiology and medicine by learning Latin and Greek word roots. The list below has some of the most common ones.

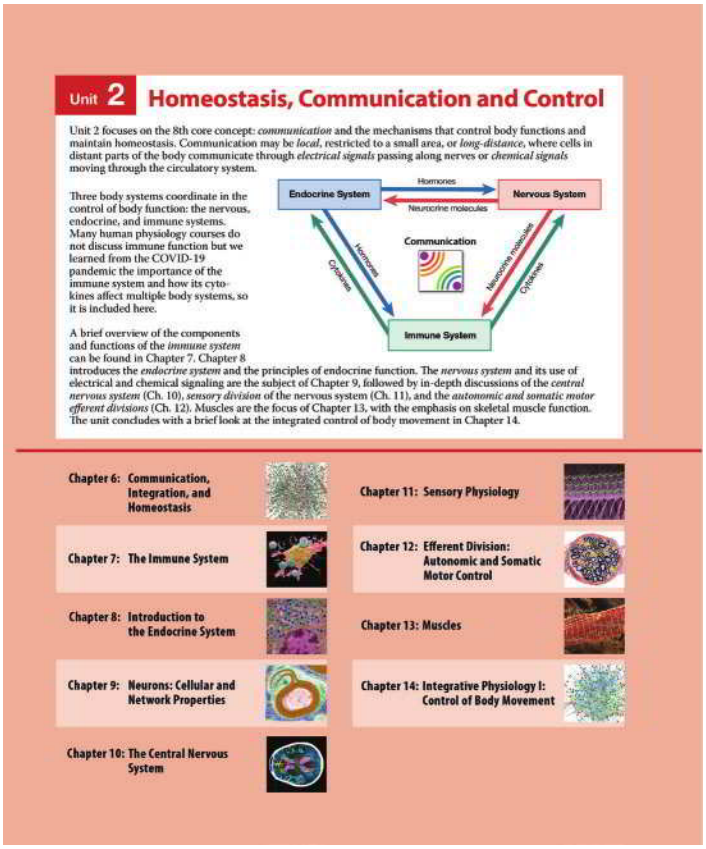
Using the list, can you figure out what *hyperkalemia* means?*

a- or **an-** without, absence
anti- against
-ase signifies an enzyme
auto self
bi- two
brady- slow
cardio- heart
cephalo- head
cerebro- brain
contra- against
-crine a secretion
crypt- hidden
cutan- skin
-cyte or **cyto-** cell
de- without, lacking
di- two
dys- difficult, faulty
-elle small
-emia in the blood
endo- inside or within
epi- over
erythro- red
exo- outside
extra- outside
gastro- stomach
-gen, -genie produce
gluco-, glyco- sugar or sweet
hemi- half
hemo- blood
hepato- liver
homo- same
hydro- water
hyper- above or excess
hypo- beneath or deficient
inter- between
intra- within
-itis inflammation of
kali- potassium
leuko- white
lipo- fat
lumen inside of a hollow tube
-lysis split apart or rupture
macro- large
micro- small
mono- one
multi- many
myo- muscle
oligo- little, few
para- near, close
patho-, -pathy related to disease
peri- around
poly- many
post- after
pre- before
pro- before
pseudo- false
re- again
retro- backward or behind
semi- half
sub- below
super- above, beyond
supra- above, on top of
tachy- rapid
trans- across, through

*Hyper = excess, kali = potassium, -emia = in the blood, or elevated blood potassium

Owner's Manual

Welcome to Human Physiology! As you begin your study of the human body, one of your main tasks will be to construct for yourself a global view of the body, its systems, and the many processes that keep the systems working. This "big picture" is what physiologists call the integration of systems, and it is a key theme in this book. To integrate information, however, you must do more than simply memorize it. You need to truly understand it and be able to use it to solve problems that you have never encountered before. If you are headed for a career in the health professions, you will do this in the clinics. If you plan a career in biology, you will solve problems in the laboratory, field, or classroom. Analyzing, synthesizing, and evaluating information are skills you need to develop while you are in school, and I hope that the features of this book will help you with this goal.



Pattern recognition is important for all healthcare professionals, so you can begin to develop this skill by learning the **core concepts of physiology** that repeat over and over as you study different organ systems. The core concepts are introduced in Unit 1, and each chapter begins with a brief summary of the core concepts in that chapter.

We have also retained the four approaches to learning physiology that proved so popular since this book was first published.

1. **Cellular and Molecular Physiology**
   Most physiological research today is being done at the cellular and molecular level, and there are constantly exciting developments in molecular medicine and physiology. For example, scientists have discovered a new method of cell-to-cell communication: exosomes and ectosomes. We are still learning how these extracellular vesicles play a role in health and disease. Look for similar links between molecular and cellular biology, physiology, and medicine throughout the book.

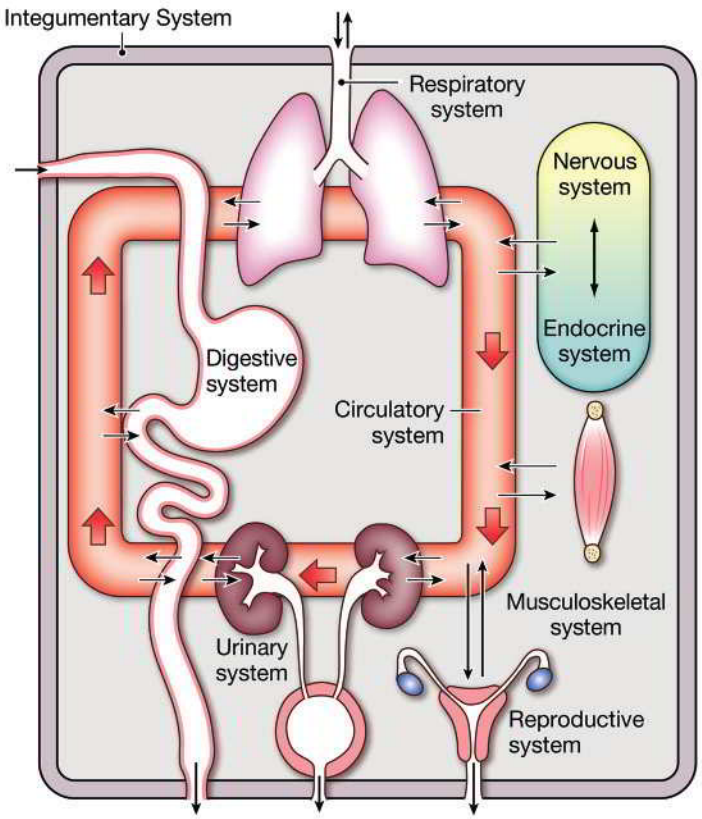
2. **Physiology is a Dynamic Field**
   Physiology is a dynamic discipline, with numerous unanswered questions that merit further investigation and research. Many of the "facts" presented in this text are really only our current theories, so you should be prepared to update your mental models as new information emerges from scientific research.

3. **Physiology is Integrative**
   The organ systems of the body do not work in isolation, although we study them one at a time. To emphasize the integrative nature of physiology, three chapters (Chapters 14, 21, and 25) focus on how the physiological processes of multiple organ systems coordinate with each other, especially when homeostasis is challenged.

4. **A Focus on Problem Solving**
   One of the most valuable life skills all students should acquire is the ability to think critically and use information to solve problems. As you study physiology, you should be prepared to practice these skills. You will find a number of "test yourself" questions designed to challenge your critical thinking and analysis skills.

One of my aims is to provide you not only with information about how the human body functions but also with tips for studying and problem solving. Many of these study aids have been developed with the input of my students, so I think you may find them particularly helpful. The list below is a brief tour of the special features of the book, especially those that you may not have encountered previously in textbooks. Please take a few minutes to read about them so that you can make optimum use of the book as you study.

- **Learning Outcomes** on the chapter opening page list the key questions you should be able to answer by the end of the chapter.
- **Background Basics**, also on the chapter opening page, lists topics you will need to master for understanding the material that follows. The terms include links for review.
- **Anatomy Summaries** provide succinct visual overviews of a physiological system from a macro to micro perspective. Whether you are learning the anatomy for the first time or refreshing your memory, these summaries show you the essential features of each system in a single figure
- **Essentials and Review figures** occur throughout the book. These figures distill the basics about a topic onto one or two pages, much as the Anatomy Summaries do. My students tell me they find them particularly useful for review when there isn't time to go back and read all the text.
- **Reflex Pathways & Concept Maps** organize physiological processes and details into a logical, visual format. These figures use consistent colors and shapes to represent different steps, making it easier to understand complex physiological processes. Chapter 1 includes a special Focus On feature showing you how to do your own concept mapping.
- **Running Problems** in each chapter are clinical scenarios related to the chapter topic. Read the segments as you work through the text and see if you can answer the questions that ask you to apply what you're learning to the problem. Answers are in the summary table at the conclusion of the problem.



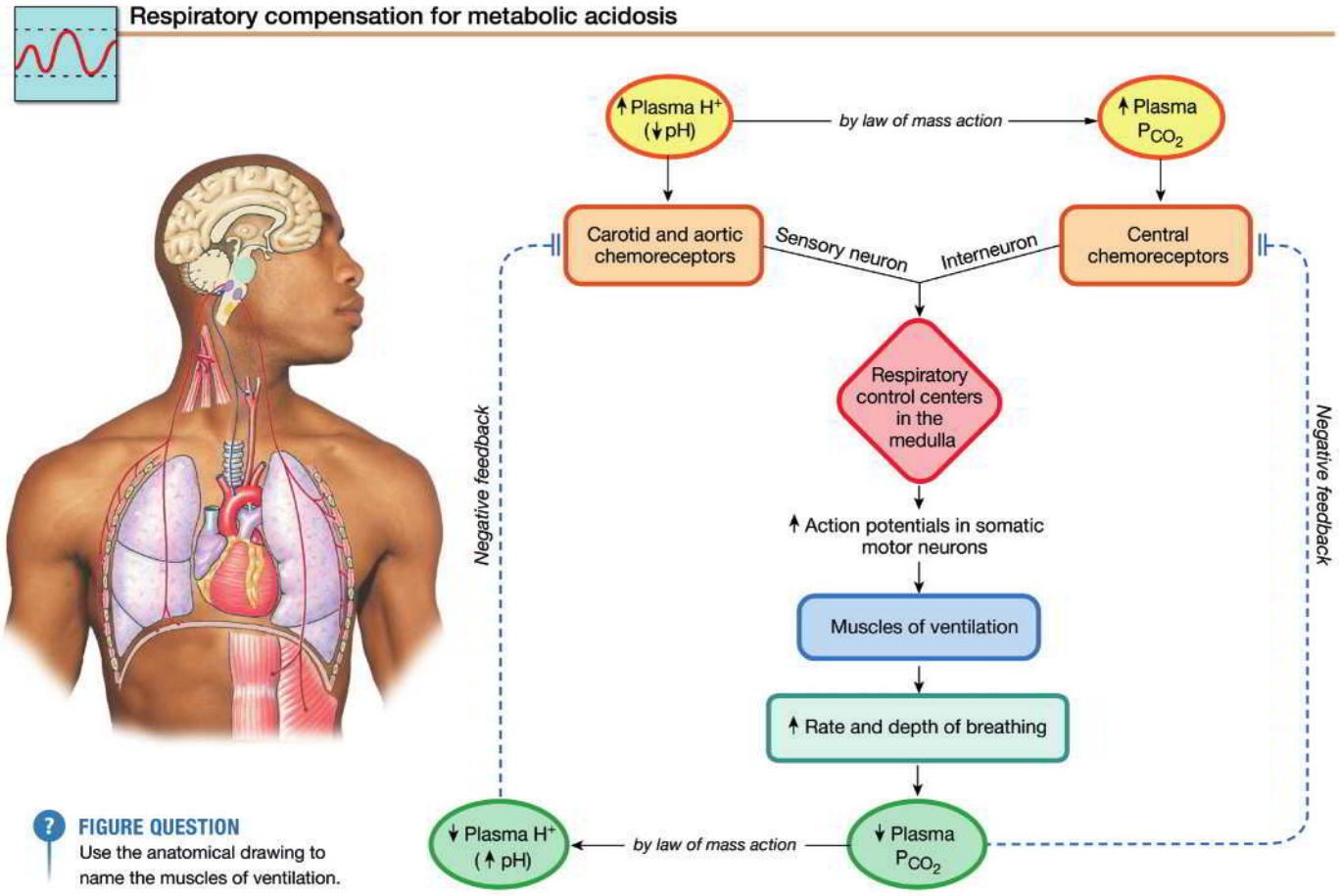
- **Figure Questions and Graph Questions** challenge you to apply visual literacy or data interpretation skills as you read an illustration, photo, or graph.
- **Concept Checks** are placed at intervals throughout the chapters, helping to test your understanding before continuing to the next topic. Click the interactive buttons to show the answer or get a hint.
- **Quick Reference to Integrated Media by Chapter** provides an easy reference to key animations and videos.
- The **Appendices** have answers to the end-of-chapter questions, as well as reviews of physics, logarithms, and basic genetics.
- The **Useful Resources** section of the eTextbook includes a periodic table of the elements, diagrams of anatomical positions of the body, tables with unit conversions. and normal values of blood components.

Take a few minutes to look at all these features so that you can make optimum use of them.

It is my hope that by using this book, you will develop an integrated view of physiology that allows you to enter your chosen profession with respect for the complexity of the human body and a clear vision of the potential of physiological and biomedical research. May you find physiology as fun and exciting I do. Good luck with your studies!

Warmest regards,

Dr. Dee (as my students call me)
silverthorn@utexas.edu



Human Physiology

An Integrated Approach

Ninth Edition

Dee Unglaub Silverthorn, Ph.D.
UNIVERSITY OF TEXAS, AUSTIN

with contributions by

Bruce R. Johnson, Ph.D.
CORNELL UNIVERSITY

Michael Chirillo, M.D., Ph.D.
UNIVERSITY OF RHODE ISLAND

and

William C. Ober, M.D.
ILLUSTRATION COORDINATOR

Claire E. Ober, R.N.
ILLUSTRATOR

Anita Impagliazzo
ILLUSTRATOR

Andrew C. Silverthorn, M.D.
CLINICAL CONSULTANT

Pearson

Content and Product Management: Michael Gillespie; Serina Beauparlant; Alexa Frank; Caroline Ayres; Ayushi Khandelwal
Content Production: Katie Foley; Titas Basu; Win Clark; Sharon Cahill; Francesca Monaco; Annamarie Boley, *Straive*; Kerri Tomasso, *Straive*; Rajesh Kumar Rajan, *Straive*; Carrie Keller, *Straive*; Krishnamurthy Muralidharan, *Straive*; Rebecca Marshall, *Lachina*; Molly Montanaro, *Lachina*; Cathryn Gear, *Lachina*; Lalitha Srinivasan, *Continual Engine*; Kani Kapoor, *Integra*
Product Marketing: Courtney Davis, Tim Galligan, Yez Alayan
Rights and Permissions: Ben Ferrini; Matthew Perry, *Straive*; Chenley Calites, *Straive*

Please contact www.AskPearsonSupport.com with any queries on this content.

Pearson puts care into the creation of our products. Our learning materials undergo content reviews to minimize bias and ensure the content is inclusive, accurate, and relevant. Please use this link to report instances of bias and inaccuracies: https://www.pearson.com/report-bias.html

You can learn more about Pearson's commitment to accessibility at https://www.pearson.com/us/accessibility.html

Cover Image by Susumu Nishinaga/Science Source.

Library of Congress Cataloging-in-Publication Data
Library of Congress Control Number: 2025938090

$PrintCode

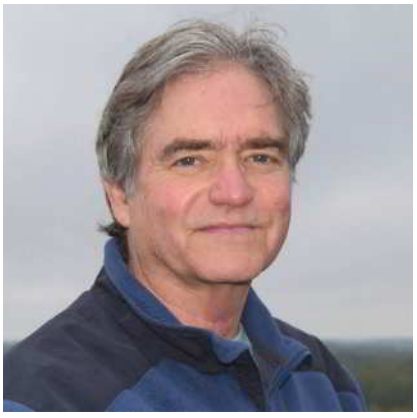
Pearson

ISBN 10: 0-135-31445-3
ISBN 13: 978-0-135-31445-6

About the Author

DEE UNGLAUB SILVERTHORN studied biology as an undergraduate at Newcomb College of Tulane University, where she did research on cockroaches. For graduate school, she switched to studying crabs and received a PhD in marine science from the Belle W. Baruch Institute for Marine and Coastal Sciences at the University of South Carolina. Her research interest is epithelial transport in systems ranging from the crab gill to the chick allantoic membrane. Dr. Dee has taught in a variety of settings, from medical schools (Medical University of South Carolina, Dell Medical School, UT-Austin) to high school. For most of her career, at the University of Texas–Austin, she has taught undergraduate and graduate physiology lectures and labs, and she trains graduate students to develop teaching skills in the life sciences. Dr. Dee has received numerous teaching awards and honors, including a UT System Regents' Outstanding Teaching Award, the American Physiological Society (APS) Arthur C. Guyton Physiology Educator of the Year, and multiple UT–Austin awards, including the Burnt Orange Apple Award. Dr. Dee is past-president of the APS (2022–23) and the Human Anatomy and Physiology Society (2012–2013). She has served as editor-in-chief of *Advances in Physiology Education*, and she is currently an associate editor. Dr. Dee works with members of the International Union of Physiological Sciences to improve physiology education globally, and this book has been translated into seven languages. Her free time is spent creating multimedia fiber art, gardening, and enjoying the Texas hill country with her husband, Andrew, and their dogs.

About the Contributors



Bruce Johnson, PhD is a Senior Lecturer in the Department of Neurobiology and Behavior at Cornell University. He earned biology degrees at Florida State University (BA), Florida Atlantic University (MS), and at the Marine Biological Laboratory in Woods Hole (PhD) through the Boston University Marine Program. He directs Cornell's Principles of Neurophysiology course that he joined in 1988, in which undergraduate and graduate students receive hands-on instruction in principles and methods of neurophysiology. He is a coauthor of *Crawdad: a CD-ROM Lab Manual for Neurophysiology* and the *Laboratory Manual for Physiology*. Bruce has directed and taught in faculty workshops for neuroscience laboratory teaching sponsored by NSF (Crawdad), ADInstruments (CrawFly), the Grass Foundation and the Faculty for Undergraduate Neuroscience (FUN). He has taught in international workshops and neuroscience courses at the Universities of Copenhagen (Denmark), Cologne (Germany), Ibadan (Nigeria), and the Marine Biological Laboratory. Bruce was named a Most Influential Faculty Member by the graduating senior class at Cornell and awarded the John M. and Emily B. Clark Award for Distinguished Teaching at Cornell. His other teaching awards include the FUN Educator of the Year Award, FUN Career Service Award, and he is a co-recipient of the 2016 Award for Education in Neuroscience, sponsored by the Society for Neuroscience. He is currently Senior Editor of the *Journal of Undergraduate Neuroscience Education*. Bruce's research addressed the cellular and synaptic mechanisms of motor network plasticity. His work now focuses on development of open-source neurophysiology and imaging equipment for laboratory teaching and research.

Michael Chirillo, MD, PhD is an assistant teaching professor at the University of Rhode Island in the College of the Environment and Life Sciences. He earned degrees in music performance (BM) at the College-Conservatory of Music at the University of Cincinnati and at the Butler School of Music at UT Austin (MM). He completed concurrent degrees in medicine (MD) at the McGovern Medical School in the Texas Medical Center in Houston and in neuroscience (PhD) at UT Austin. During his time as a doctoral student in Austin, Michael met and worked with Dr. Silverthorn on best teaching practices in the undergraduate physiology classroom. Following his internship in internal medicine-pediatrics at the University of Utah, he was awarded a Fulbright U.S. Scholar Grant to work with colleagues at the University of Belgrade in Serbia, investigating how to best incorporate core concepts of physiology into introductory courses. He frequently travels to southeastern Europe to continue this work.

About the Illustrators

William C. Ober, MD (*art coordinator and illustrator*) received his undergraduate degree from Washington and Lee University and his M.D. from the University of Virginia. He also studied in the Department of Art as Applied to Medicine at Johns Hopkins University. After graduation, Dr. Ober completed a residency in Family Practice and later was on the faculty at the University of Virginia in the Department of Family Medicine and in the Department of Sports Medicine. He also served as Chief of Medicine of Martha Jefferson Hospital in Charlottesville, VA. He most recently taught at Washington & Lee University, where he also led student trips to the Galapagos Islands. He was part of the Core Faculty at Shoals Marine Laboratory, where he taught Biological Illustration for 22 years. The textbooks illustrated by Medical & Scientific Illustration have won numerous design and illustration awards.

Claire E. Ober, RN (*illustrator*) practiced pediatric and obstetric nursing before turning to medical illustration as a full-time career. She returned to school at Mary Baldwin College where she received her degree with distinction in studio art. Following a five-year apprenticeship, she has worked as Dr. Ober's partner in Medical and Scientific Illustration since 1986. She was also on the Core Faculty at Shoals Marine Laboratory and co-taught Biological Illustration at both Shoals Marine Lab and at Washington and Lee University.

Anita Impagliazzo, MA is a medical and scientific illustrator in Howardsville, VA. She studied art and biology at the University of Virginia and obtained her graduate degree in biomedical illustration from University of Texas Southwestern Medical Center at Dallas in 1987. She has contributed to many textbooks, creates exhibits for medical malpractice cases, and illustrates current discoveries for research labs across the US.

About the Clinical Consultant

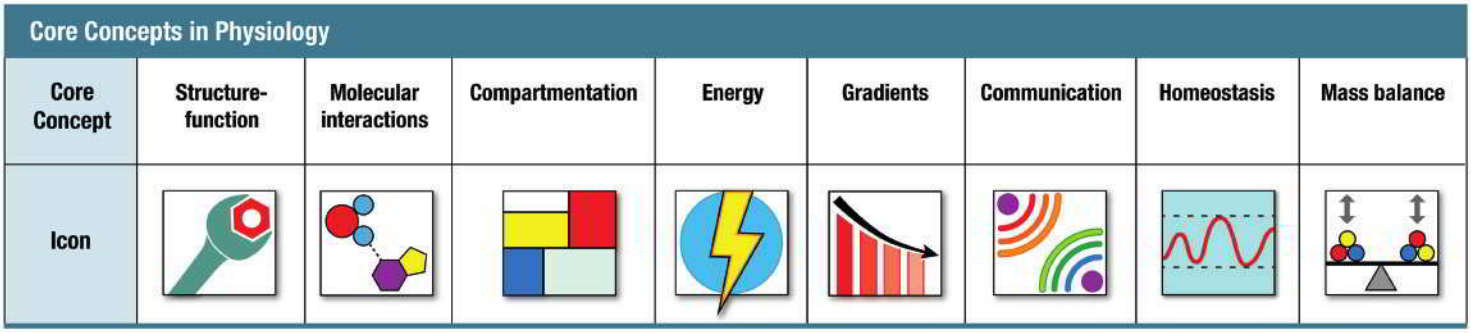
Andrew C. Silverthorn, MD is a graduate of the United States Military Academy (West Point). He served in the infantry in Vietnam, and upon his return entered medical school at the Medical University of South Carolina in Charleston. He was chief resident in family medicine at the University of Texas Medical Branch, Galveston, and is a family physician in solo practice in Austin, Texas. When Andrew is not busy with patients, he may be found on the golf course or playing with his two rescue dogs, Molly and Callie.

Dedication

I would like to dedicate this 9th edition to all the people who have worked out of the spotlight on different aspects of this book as it evolved through the years: physiologists, educators, and publishing professionals alike. A special thanks goes to two of my editors—DKB and AAR—for their vision and support.

New to this Edition

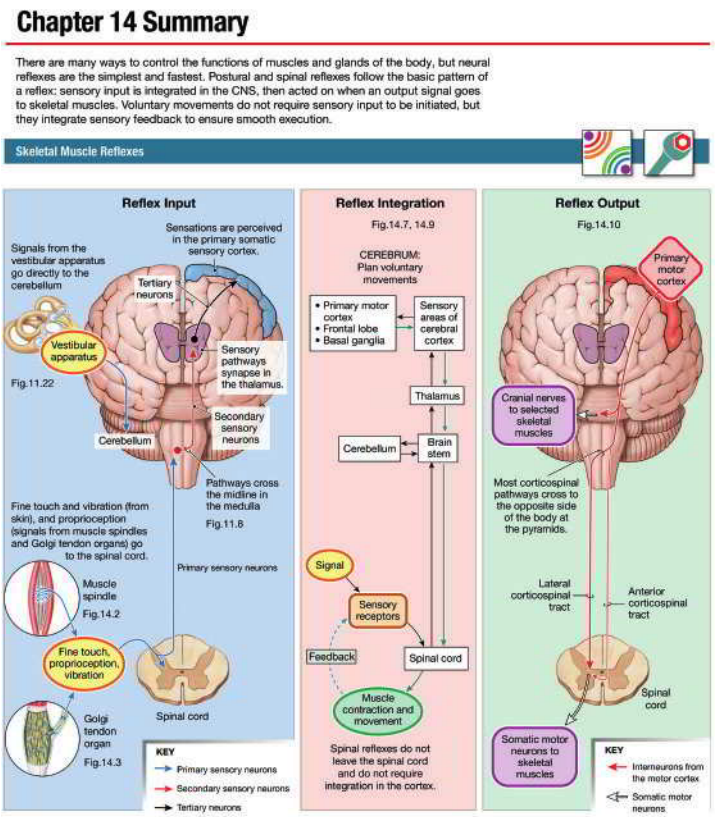
The Ninth Edition of *Human Physiology: An Integrated Approach* builds upon the thorough coverage of integrative and molecular physiology topics that have always been the foundation of this book. It has been nearly eight years since the last revision, and a lot has changed in the world of physiology and medicine, including the global SARS-CoV-2 pandemic. Studying the pathophysiology of COVID-19 made biomedical scientists aware of how the immune system influences body functions in ways we had not previously realized. In recognition of that fact, we have **promoted the immune system from Chapter 24 in the last edition to Chapter 7**, giving it new status as the third control system, coordinating with the nervous and endocrine systems through chemical signals.



The other major change in this edition is a focus throughout the book on the **core concepts of physiology**. The eight selected core concepts are introduced and discussed, along with their icons, in Unit 1, then become a unifying theme throughout the text. The four units in the book—Core Concepts in Physiology; Homeostasis, Communication, and Control; Integration of Function; and Metabolism, Growth, and Reproduction—are now introduced with a visual overview page that previews the unit's chapters. Each chapter begins with a brief introduction to the core concepts featured in that chapter. Core concept icons can be found on many pieces of art, challenging students to see if they can find the core concept represented in the art. Finally, the **text chapter summaries have been replaced with visual summaries**, many featuring new art, that review the key ideas covered in the chapter.

This edition was written to take advantage of the interactive features available only in the eTextbook. Answers to the Concept Checks and Figure and Graph questions are now visible with a click on the SHOW ANSWER button, as are HINTS. Key words have popup definitions, and the links for quick review of topics covered earlier in the book take you to that content. Short animations and the Physiology in Action videos featuring two of my early-career colleagues are embedded right in the eTextbook. Learn more about the other features of Pearson eTextbooks after the Owner's Manual.

Finally, when revising this book, we kept in mind the new **HAPS Physiology Learning Outcomes (PLOs) for Human Physiology**. *https://www.hapsweb.org/haps-learning-outcomes/haps-physiology-learning-outcomes/*. There can be tremendous variability in how introductory physiology is taught, so a **correlation guide** between this ninth edition's learning outcomes and the HAPS PLOs has been provided within the Instructor Resources. In addition, we reviewed the entire text and updated language



to be more inclusive, following suggested guidelines from the U.S. National Institutes of Health and various biomedical and clinical societies. All art has been updated to reflect the latest WCAG guidelines to ensure our figures are fully accessible to all learners.

As always, the major focus of the book is to incorporate the latest findings from biomedical research and relate them to the physiology that is the basis for human health and disease. The list that follows highlights the new content in this ninth edition.

Chapter-by-Chapter Changes in the Ninth Edition

Chapter 1 Introduction to Physiology

- Revised themes into eight core concepts. Added gradients as a core concept
- New core concepts figure with icons
- Updated discussion of reflex loops
  - Adds open-loop and closed-loop control systems to address misconception that all reflexes are for homeostasis
  - Difference between regulated and controlled variables
- New table of 10 key regulated physiological variables
- New figure of homeostatic control system model with a regulated variable
- New Running Problem on searching for information about health benefits of probiotics; added artificial intelligence as a search method
- Updated
  - "Omics" box and added *multiomics*
  - Use of the word *normal*

Chapter 2 Molecular Interaction

- Updated research on chromium picolinate (Running Problem)
- Revised Section 2.3 on protein binding interactions
- Added *motor proteins* to protein function list

Chapter 3 Compartmentation: Cells and Tissues

- Added *transcellular compartments* to body compartmentation
- Section 3.3 on Cells updated and revised. New art and table in Fig. 3.4
  - Updated discussion on mitochondrial dynamics
  - Primary cilia moved from Emerging Topics box into the text
  - New topics: biomolecular condensates, proteasomes and ubiquitin
  - Clearly distinguished inclusions from nonmembranous organelles
- Section 3.4 Tissues
  - Clarification of difference between basal lamina and basement membrane
  - Added specialized epithelia as a sixth category
  - Added the ependyma to ciliated epithelia
- Section 3.5: Updated discussion on stem cells includes organoids and regenerative medicine

Chapter 4 Energy and Cellular Metabolism

- New figure on the electron transport system

Chapter 5 Membrane Dynamics

- Updated Section 5.5 on vesicular transport
  - Revised mechanisms: micropinocytosis, clathrin-dependent and -independent endocytosis
  - Extracellular vesicles: exosomes and ectosomes
  - New map of vesicular transport
- Added discussion of ectoenzymes
- Updated information on cystic fibrosis

Chapter 6 Communication, Integration, and Homeostasis

- Added immune system as the third control system
- Updated information on cytokines
- New figure showing neuro-endo-immune interactions
- Added extracellular vesicles to discussion and art

Chapter 7 The Immune System

This chapter was rewritten to focus on the immune system's role as a control system.

- Multiple figures were significantly revised. Added two new figures
- Updated ethnic distributions of blood types table
- Added information on:
  - Lifestyle-associated molecular patterns or LAMPs
  - Toll-like receptors (TLRs)
  - Pro-inflammatory cytokines
  - SARS-CoV-2, COVID-19, coronavirus

Chapter 8 Introduction to the Endocrine System

- Updated information on calcitonin gene-related peptide (CGRP) and migraine
- Updated information on oxytocin and autism

Chapter 9 Neurons: Cellular and Network Properties

- New introduction on undergraduate researchers and cone snail toxins
- Updated discussions and revised figures:
  - Neuron structure and function

- Channel activation and inactivation
- Axonal transport
- mRNA transport and neuronal protein synthesis
- Glial cell functions
- Types of neurotransmitter receptors (Tbl. 9.4)
- Signaling by gaseous signal molecules
- Mechanisms for LTP and LTD, including local protein synthesis in dendrites
- Plasticity

- Updated Try It! box on Venus flytrap action potential mechanism

Chapter 10 The Central Nervous System

- Moved glymphatics from Emerging Concepts box into the text
  - New art for blood-brain barrier
  - Paravascular CSF flow
- Note on changing terminology for CNS directions
- New section on mind-body interactions and psychoneuroimmunology
- Updated information on:
  - Alzheimer's
  - BRAIN initiative progress
  - Emergent properties
  - Evolution of electrical signaling
- Added:
  - Nonmotor functions of the cerebellum
  - Role of pericytes in control of cerebral blood flow
  - Associative learning doesn't require a brain

Chapter 11 Sensory Physiology

- New introduction to Meniere's Running Problem (astronaut Alan Shepard)
- New box on COVID-19 and loss of taste and smell
- Updated model of pain and nociception
  - Gate control theory of pain is no longer the current model
- Updated:
  - Sound transduction
  - Melanopsin and mRCG cells
  - Models for taste cell transduction
- Added:
  - Piezo cation channels and TRPV1 ion channels for somatic senses
  - 2021 Nobel Prize in Physiology or Medicine for sensory receptors
  - Intrinsically photosensitive retinal ganglion cell (ipRGC)
  - Blood-retinal barrier

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

- Expanded somatic motor disorders
  - Myasthenia gravis
  - Poliomyelitis
  - Lambert-Eaton myasthenic syndrome
- Transcutaneous vagal nerve stimulation in medicine
- Updated information on nicotine addiction to include vaping and recent statistics

Chapter 13 Muscles

- Changed sliding filament theory to sliding filament mechanism
- Updated information about myosin family of proteins
- Updated figure of muscle fiber mitochondrial anatomy
- Introduced new theories:
  - Role of titin in muscle contraction
  - Branching of sarcomeres
  - Myosin activation in sliding filament mechanism

Chapter 14 Integrative Physiology I: Control of Body Movement

- Revised discussion of proprioception
  - Updated functions of spindles, joint receptors, Golgi tendon organs
  - Add Piezo2 ion channels
- Updated information on deep brain stimulation for Parkinson's
- New examples of innate reflexes
- Clinical applications of reflex testing

Chapter 15 Cardiovascular Physiology

- New title for Section 15.2 Core Concept: Gradients and Flow
  - Review gradients from earlier chapters and relate to pressure gradients
- Expanded discussion of cyanosis to reflect signs in people with dark skin
- Introduced sinoatrial and atrioventricular nodes and Purkinje fiber cells as the three autorhythmic tissues of the heart
- New terminology: His-Purkinje system
  - Clarify that all ventricular conducting cells are Purkinje fiber cells

Chapter 16 Blood Flow and the Control of Blood Pressure

- Added focus on core concepts of mass balance and homeostasis

- Corrected model for anatomy of the microcirculation, with new text and new art
- Reorganized discussion on blood pressure, resistance, and flow to tissues
- Added intraosseous infusion into bone marrow sinusoids
- Updated:
  - Vasovagal (neurocardiogenic) syncope
  - Lymphatics, with new art
  - Myogenic autoregulation
  - Cardiovascular disease

Chapter 17 Blood

- Consolidated discussion of iron homeostasis with 2 new figures
  - Ferroportin (FPN)
  - Hepcidin
- Updated:
  - Thrombopoietin and thrombopoietin receptor agonists (TPO-RAs)
  - Gene therapy for sickle cell disease
  - Platelet-rich plasma
  - Schematic of hematopoietic stem cells and hematopoietic cytokines
  - Gene therapy for hemophilia

Chapter 18 Mechanics of Breathing

- New introduction about COVID-19 and the respiratory system
- New discussion, figure, and table of airway epithelial cells
  - Club cells, ionocytes, tuft cells, pulmonary neuroendocrine cells, and basal cells
  - Periciliary mucus layer
- New section on respiratory system defense mechanisms
- Revised:
  - Discussion of gas laws
  - Effect of altitude on gas partial pressures
- Updated type II alveolar cell functions

Chapter 19 Gas Exchange and Transport

- Revised model and new figure on central control of breathing
  - Respiratory central pattern generator (rCPG)
  - Pontine-medullary network
- Updated:
  - Factors that affect pulse oximeter accuracy
  - Blood substitutes
  - Protective reflexes

Chapter 20 The Kidneys

- Added alternate terminology for anatomical structures
- Updated:
  - Mesangial cell functions
  - Gout and uric acid excretion
  - SGLT2 inhibitors and urate excretion
- Moved Glucosuria and Diabetes Try It! activity to Chapter 23

Chapter 21 Integrative Physiology II: Fluid and Electrolyte Balance

- New Clinical Focus box and figure on SARS-CoV-2 and ACE2
- New Try It! box on Osmotic Diuresis with calculations
- Updated:
  - Cell volume regulation
  - Vasopressin pathologies

Chapter 22 The Digestive System

- Reorganized to put function before anatomy
  - Moved hepatic portal system to anatomy section
  - New discussion and figure of gut mucosal cells, including immune cells of the mucosa
    - Lymphoid follicles
    - Paneth cells
    - Enteroendocrine cells (EEC)
- New Section 22.3 on overview of digestive processes
- New Section 22.9 on microbiome and gut-brain communication
- Expanded discussion and new figure on bile salt recycling and enterohepatic circulation
- Updated:
  - Table 22.1 on signal peptides
  - Guanylin and uroguanylin in natriuretic peptide family
  - Role of immune system in digestive diseases
  - Section 22.8 on defense mechanisms
  - Information on colorectal cancer

Chapter 23 Metabolism and Energy Balance

- Reorganized introduction to put energy balance before food intake
- Revised model for control of food intake
  - Set point theory
  - Role of POMC and agouti-related peptide (AgRP)
- Updated discussion of body mass index (BMI)
- Updated:
  - Statistics on obesity and diabetes

- Table 23.4 on drugs for diabetes
  - Semaglutide
- New information on diagnosis and treatment of diabetes
  - Hemoglobin A1C (HbA1c)
  - New section on how physiology is related to drug development for diabetes
  - Try It! box on glucosuria and insulin

Chapter 24 Endocrine Control of Growth and Metabolism

- Updated information on growth hormone therapy
- Updated information on control of bone remodeling
  - Coupling of bone remodeling
  - Clastokines
- Updated information on calcitonin
  - Calcitonin gene-related peptide (CGRP)

Chapter 25 Integrative Physiology III: Exercise

- Updated model of autonomic control of heart rate increase during exercise
- Discussion of difficulty of doing research on exercise
- Updated chemical signals affecting exercise metabolism
  - Myokines and exerkines

Chapter 26 Reproduction and Development

- Updated discussions on:
  - Biological sex and gender
  - Sex as a biological variable and the importance of sex in health and disease
- Revised discussion of sex determination and differentiation
  - X chromosome inactivation
  - Testis-determining genes: SRY and SOX9 genes
- Revised figure and explanation of gametogenesis
- Introduction of differences of sex development (DSD) and ambiguous genitalia
  - Non-invasive prenatal testing (NIPT)
- Role of exosomes in sperm maturation
- Updated table on contractive methods
- Revised model for endocrine control of initiation of labor

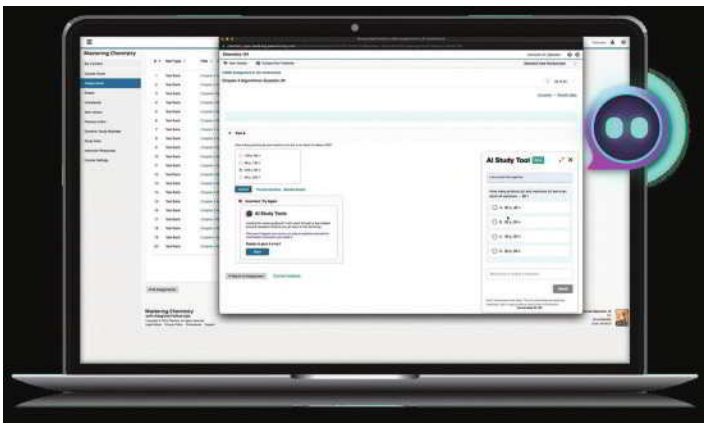
Pearson eTextbook

The Pearson eTextbook is a simple-to-use, mobile-optimized, personalized reading experience. It allows students to easily highlight, take notes, listen to the textbook, and review vocabulary all in one—even when offline. Students using the Pearson eTextbook will reap all the benefits of the new text features, while also benefitting from the following new and existing interactive features, which are integrated directly into the online text:

EXPANDED! Over 50 animations and videos embedded in the Pearson eTextbook bring A&P concepts to life featuring A&P Flix, Interactive Physiology, BioFlix, and more.

NEW! Hot Topics in Physiology bring regularly updated author-written articles to the eTextbook to inform readers of new research and developments in human physiology today. Located in each unit opener, these articles help students relate core content to the world around them.

NEW! AI Study Tool pulls from vetted Pearson content to help students achieve proficiency and master key course concepts. Our generative AI chat tool goes beyond a one-size-fits-all approach to provide individualized support, practice and feedback that meet the unique needs of every learner.

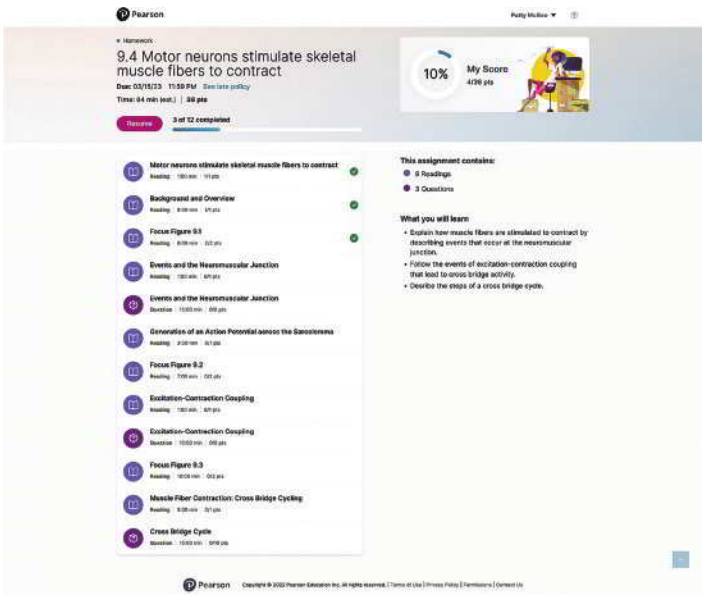


NEW! Quick Reference—Pearson eTextbook Integrated Media by Chapter provides easy reference to key animations and videos available for each chapter in the eTextbook and in Mastering. Media call-outs are also highlighted in the relevant chapter pages.

What's New in Mastering A&P

Mastering A&P is the most widely used online assessment and tutorial program for A&P, providing an extensive library of hundreds of animations, tutorials, and questions that are graded automatically.

NEW: Interactive Reading Assignments let students read, watch and practice in one seamless experience. Instructors can now assign specific sections of the eTextbook plus coaching and drag and drop assignments, and more for auto-grading.



NEW! Interactive Labs for Anatomy and Physiology are a fully customizable and auto-graded wet lab experience for your specific course objectives. Students engage with thought-provoking readings, videos, and realistic simulations aimed at critical thinking and data interpretation. These virtual labs can be assigned as a wet lab replacement, pre-lab preparation, post-lab review, or as a make-up lab. We recommend previewing the pre-built learning path by navigating to the Assignment Manager>Create>Import Pre-Built Assignment. See section below on Assignment Settings, Scoring, and LMS Integration.

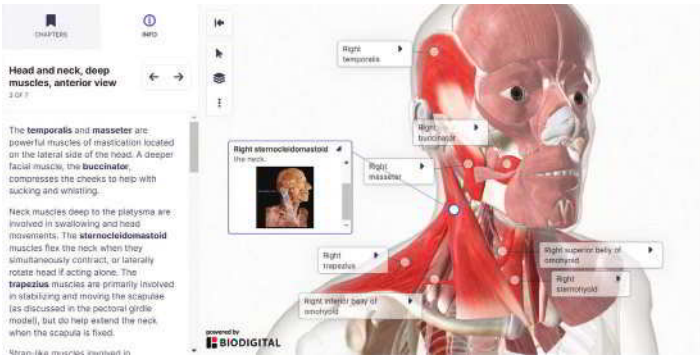
EXPANDED! Interactive Physiology 2.0 helps students advance beyond memorization to a genuine understanding of the toughest topics in A&P. Fully accessible on all mobile devices. I.P. 2.0 tutorials are assignable as coaching activities in Mastering A&P. New topics include Carbon Dioxide Transport and Exchange and Propagation of an Action Potential.

PhysioEx™10.0 Laboratory Simulations in Physiology provide newly formatted exercises in HTML for increased stability, web browser flexibility, and improved accessibility. The 12 Exercises contain 63 easy-to-use laboratory simulation activities that complement or replace wet labs, including those that are expensive or time-consuming to perform in class. PhysioEx allows students to repeat labs as often as they like, perform experiments without harming live animals, and conduct experiments that are difficult to perform in a wet lab environment because of time, cost, or safety concerns.

NEW! Gap Finder: A&P Diagnostic Assessment identifies any student knowledge gaps for material they should know for success in the course. This Diagnostic module contains approximately 130 questions based on these topics: Study Skills, Math Essentials, Chemistry Basics, Cell Biology Basics, and Biology Basics. Instructors can deselect as many questions as they want. There's no minimum number they have to adhere to in order for the program to work.

NEW and UPDATED! Dynamic Study Modules have been updated to reflect new content in the ninth edition. In addition, shadow questions, that change the root of the question, have been created for select questions to help keep students from memorizing questions.

NEW! Practice Anatomy Lab (PAL 4.0) featuring fully interactive 3-D models and custom assignability of your structure list is available in Mastering Assignment Manager and student Study Area.



NEW! Histology Videos include 10 new videos of histology tissues that provide short, focused walk-throughs of commonly covered tissue types in A&P.

NEW! TEAS and HESI exam practice questions help students prep for nursing school entrance exams with 150 TEAS and 300 HESI multiple-choice questions with wrong answer feedback for all questions.

UPDATED! Instructor Resources. This area of Mastering provides one-stop shopping for PowerPoint Lecture Presentations; all figures in JPEG and PPT format; Instructor Guide with Running Problems; Test Bank; animations; videos; Interactive Physiology (including the worksheets); Clinical Case Studies with Teaching Strategies and case study worksheets; PAL 4.0 Resources; PhysioEx

Resources; Interactive Lab Resources; and the new HAPS Learning Outcomes Correlation Guide.

NEW! Teaching Strategies for Active Learning is an invaluable resource for instructors looking for strategies for actively engaging students in the classroom. Edited by Cathy Whiting, this manual includes over 40 hands-on activities on key topics in A&P submitted by thought leaders across the country. Each activity is tied to HAPS Learning Outcomes and includes estimated time for the activity.

Learning Catalytics allows students to use their smartphone, tablet, or laptop to respond to questions in class. For more information, visit learningcatalytics.com.

Study Area features Resources by chapter; Practice Quizzes; TEAS & HESI Exam Practice, Animations and Videos including "Physiology in Action"; Interactive Physiology 2.0; Practice Anatomy Lab 4.0; Physio Ex; Clinical Case Studies, and more.

Acknowledgements

Writing, editing, and publishing a textbook is a group project that requires the talent and expertise of many people. No one scientist has the detailed background needed in all areas to write a book of this scope, and I am indebted to all my colleagues who so generously share their expertise in each edition. I particularly want to acknowledge Bruce Johnson, Cornell University, Department of Neurobiology and Behavior, a superb neurobiologist and educator, who once again ensured that the chapters on neurobiology are accurate and reflect the latest developments in that rapidly changing field. Bruce was joined in this edition by Michael Chirillo, UT-Austin Center for Learning and Memory, a former graduate teaching assistant of mine who has worked with me for over ten years. You can meet Michael if you watch the Physiology in Action videos.

The art team of Bill Ober, MD, and Claire Ober, RN, has worked with me since the first edition, and I am always grateful for their scientifically astute suggestions and revisions. They have been joined by Anita Impagliazzo, who brings a fresh eye and new figure ideas to our illustration program.

As we were developing the new core concepts chapter introductions and visual summaries for this edition, I relied on feedback from several colleagues to tell me if what I was creating would be helpful for their teaching. Thanks go to Jennifer Stokes, Jan M. Machart, Jennifer L. Thompson, and Meg Flemming for their prompt and honest input.

Special thanks go to some of my former students who over the years suggested topics and created storyboards for running problems: Matt Pahnke, Susan E. Johnson, Claire Conroy, and Douglas Shannon.

Instructors and students often contact me directly about the book, and for this edition I would particularly like to thank Collin Ellis, Heidi Engelhardt, and David Poole for comments and suggestions. Thanks also to my students who keep me informed of the typos that creep in no matter how many people look at the manuscript in production.

Many other people devoted their time and energy to making this book a reality, and I would like to thank them all, collectively and individually. I apologize in advance to anyone whose name I have omitted.

Ninth Edition Reviewers

I am particularly grateful to the instructors who reviewed one or more chapters of the last edition. There were many suggestions in their thoughtful reviews that I was unable to include in the text, but and others that I did. I appreciate the time and thought that went into their comments. The reviewers for this edition include:

- Sulekha Anand, *San Jose State University*
- Erwin Bautista, *University of California, Davis*
- Shawn Bearden, *Idaho State University*
- Simone Brito, *Fresno City College*
- George Brusch, *Oklahoma State University*
- Edward Eivers, *California State University, Los Angeles*
- Collin Ellis, *Santa Monica College*
- Heidi Engelhardt, *University of Waterloo*
- Luke Hoekstra, *Oklahoma State University*
- Erin Jacobs, *Mount Saint Mary's University*
- Mary Kinkel, *Appalachian State University*
- Catalina Reyes Gonzalez, *University of California, San Diego*
- Otto Sanchez, *University of Minnesota*

Many other instructors and students took time to write or e-mail queries or suggestions for clarification, for which I thank them. I am always delighted to have input, and I apologize that I do not have room to acknowledge them all individually.

Specialty Reviews

No one can be an expert in every area of physiology, and I am deeply grateful for my friends and colleagues who have reviewed entire chapters or answered specific questions over many editions. Even with their help, there may be errors, for which I take full responsibility.

In this edition, I am indebted to David Poole (Kansas State University) for his input on exercise physiology and for guidance to correct the erroneous figure of pre-capillary sphincters in the microcirculation (Chapter 16) that can be found in most physiology textbooks. Every instructor should read the article by Tatsuo Sakai and Yasue Hosoyamada (*https://link.springer.com/article/10.1007/s12576-013-0274-7*) to learn how we perpetuate errors in our teaching.

Photographs

I would like to thank Kristen Harris, University of Texas, who generously provided micrographs of dendritic spines from her research.

Supplements

Thank you to Meg Flemming, *Austin Community College* and Pat Clark, *Indiana University, Bloomington*, for updating the Test Bank, and to Eric Walsh, *University of Wisconsin-Madison,* for revising the PowerPoints for the ninth edition. Mastering assets for this edition were possible thanks to Catalina Reyes Gonzalez, *University of California, San Diego*, and to Max Adolphs, *University of Florida*, for their contributions to Mastering reading quizzes and chapter tests; as well as to Janet Casagrand, *University of Colorado Boulder*, and Simone Brito, *Fresno City College*, for their collective work on the improved Dynamic Study Modules. Additional thanks to *Pat Clark, Indiana University, Bloomington*, for

creating the prebuilt Interactive Reading Assignments for the ninth edition. Finally, thank you to Dr. Ryan Downey, *American University of the Caribbean School of Medicine; Georgetown University* and Genevieve Wager, *Cornell University* for their contributions to the Instructor Guide.

The Development and Production Team

Writing a manuscript is only a first step in the long and complicated process that results in a published book with all its ancillaries. The team that works with me on book development deserves a lot of credit for the finished product. Carie Keller at Straive designed the ninth edition's striking cover that continues our tradition of images that show science as art.

The team at Pearson Education worked tirelessly to see this edition move from manuscript to eText and bound book. My Editor and Commercial Product Manager, Alexa Frank, has been supportive, encouraging, and fun to work with as we scrambled to catch up on eight years of scientific advances and add the new emphasis on core concepts while staying on schedule. I also want to recognize Serina Beauparlant, Senior Manager of Product Management, who has been the one constant in the ebb and flow of publishing over many years. Serina's approach to the care and feeding of authors, especially during assorted crises, has kept writing and publishing fun.

Behind the scenes, thanks go to Ayushi Khandelwal, Editorial Assistant, who kept track of reviewers and feedback for this revision. Thank you also to our Product Marketer, Courtney Davis, who used her talents to shine a spotlight on this important revision and to Caroline Ayres, Senior Digital Program Director, for her support in the new revision workflow.

Special recognition goes to my team of Content Producers. The revision workflow for this edition completely changed to put creation of the eText before the print text, and it was a major adjustment for the authors and illustrators. The team of Francesca Monaco, Sharon Cahill, and Win Clark guided us through the new process with cheerfulness and infinite patience. Thanks also go to Katie Foley, Managing Producer, and Titas Basu, Assistant Managing Producer. The old production sequence of reviewing page proofs is gone, and I am grateful for the help of Kerri Tomasso, Project Management, in figuring out where we were in the review process. Thanks to Molly Montanaro, Rebecca Marshall, and Cathryn Gear from Lachina Creative who prepared the art for production. I would also like to thank Ben Ferrini, Matthew Perry and Chenley Calites for their many roles contributing to the Rights and Permissions as well as Kani Kapoor, Krishnamurthy Muralidharan, and Rajesh Kumar for sharing their skills and talents to make this edition possible.

Special Thanks

As always, I would like to thank my students and colleagues who looked for errors and areas that needed improvement. I've learned that awarding one point of extra credit for being the first student to report a typo works really well. My graduate teaching assistants over the years have all played a huge role in my teaching, and their input has helped shape how I teach. Many of them are now faculty members themselves. They include:

Ari Berman, PhD; Lawrence Brewer, PhD; Kevin Christmas, PhD; Michael Chirillo, MD, PhD; Lynn Cialdella Kam, MS, MBA, PhD; Sarah Davies Kanke, PhD; Peter English, PhD; Carol C. Linder, PhD; Karina Loyo-Garcia, PhD; Jan M. Machart, PhD; Tonya Thompson, MD; Patti Thorn, PhD; Justin Trombold, PhD; Kurt Venator, PhD; and Kira Wenstrom, PhD.

Finally, special thanks to my colleagues in the American Physiological Society, the Human Anatomy and Physiology Society, and the International Union of Physiological Sciences whose experiences in the classroom have enriched my own understanding of how to teach physiology. I would also like to recognize a special group of friends for their continuing support: Penelope Hansen (Memorial University, St. John's), Mary Anne Rokitka (SUNY Buffalo), Rob Carroll (East Carolina University School of Medicine), Joel Michael (Rush Medical College), Jennifer Stokes (Southwestern University), and Ryan Downey (American University of the Caribbean), as well as Peter English, Jan M. Machart, Ruth Buskirk, and Marilla Svinicki (University of Texas).

As always, I thank my family and friends for their patience, understanding, and support during the chaos that seems inevitable with book revisions. The biggest thank you goes to my husband Andrew, whose love, support, and willingness to forgo home-cooked meals on occasion have helped me meet my deadlines for nine editions.

A Work in Progress

One of the most rewarding aspects of writing a textbook is the opportunity it has given me to meet or communicate with other instructors and students. In the many years since the first edition was published, I have heard from people around the world and have had the pleasure of hearing how the book has been incorporated into their teaching and learning.

Because science textbooks are revised periodically, they are always works in progress. I invite you to contact me or my publisher with any suggestions, corrections, or comments about this edition. I am most reachable through e-mail at silverthorn@utexas.edu.

Dee U. Silverthorn *silverthorn@utexas.edu* University of Texas Austin, Texas.

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- Bioflix: Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- Bioflix: Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- Bioflix: Electron Transport System
- Bioflix: Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- Physiology in Action: Osmolarity and Tonicity

Module 5.7

- Physiology in Action: Membrane Potential
- A&P Flix: Resting Membrane Potential

Chapter 5 Links to Resources

- Interactive Physiology Animation: Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- Microbiology Animation: Host Defenses

Module 7.3

- Microbiology Animation: Antigen Processing and Presentation: Overview

Module 7.7

- Microbiology Animation: Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- Bioflix: Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- BioFlix: How Synapses Work

Module 9.3

- Interactive Physiology Animation: Generation of an Action Potential
- BioFlix: Action Potential Conduction

Chapter 9 Links to Resources

- Interactive Physiology 2.0 Animation: Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- Biointeractives: Circadian Rhythms and the SCN

Chapter 13 Muscles

Module 13.1

- A&P Flix: The Cross Bridge Cycle
- Interactive Physiology Animation: Neuromuscular Junction
- Interactive Physiology 2.0 Animation: Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- Interactive Physiology Animation: Pathway of Blood through the Heart
- Interactive Physiology Animation: Action Potentials in Autorhythmic Cells

Module 15.4

- Physiology in Action: Electrocardiogram
- Interactive Physiology Animation: Intrinsic Conduction System of the Heart
- Interactive Physiology Animation: Cardiac Output

Chapter 15 Links to Resources

- Interactive Physiology 2.0 Animation: Electrical Activity of the Heart
- Interactive Physiology 2.0 Animation: Cardiac Cycle
- Interactive Physiology 2.0 Animation: Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- Physiology in Action: Orthostatic Hypotension
- Interactive Physiology Animation: Arterial Baroreceptor Reflex

Chapter 18 Mechanics of Breathing

Module 18.3

- Physiology in Action: The Spirometer
- Physiology in Action: Subatmospheric Pleural Cavity
- Physiology in Action: Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- BioFlix: Gas Exchange
- Physiology in Action: Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- Interactive Physiology 2.0 Animation: Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- Interactive Physiology Animation: Glomerular Filtration

Module 20.6

- Interactive Physiology 2.0 Animation: Proximal Tubule Reabsorption and Secretion

Module 20.7

- Physiology in Action: Renal Clearance

Chapter 20 Links to Resources

- Interactive Physiology 2.0 Animation: Glomerular Filtration
- Interactive Physiology Animation: Anatomy Review: Urinary System
- Interactive Physiology 2.0 Animation: Tubular Reabsorption and Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- Interactive Physiology Animation: Aldosterone and ADH in Salt and Water Processing
- Interactive Physiology Animation: Mechanisms for Acid-Base Homeostasis
- Interactive Physiology Animation: Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- Interactive Physiology Animation: Anatomy Review
- Interactive Physiology Animation: Control of Digestion
- Interactive Physiology Animation: Digestive System Secretion
- Interactive Physiology Animation: Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- Physiology in Action: Blood Pressure and Exercise

Brief Contents

Contents

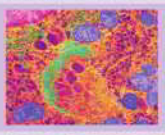
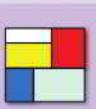
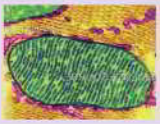
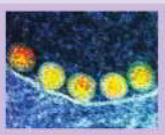
UNIT 1

Basic Cell Processes: Integration and Coordination

Unit 1 Core Concepts in Physiology

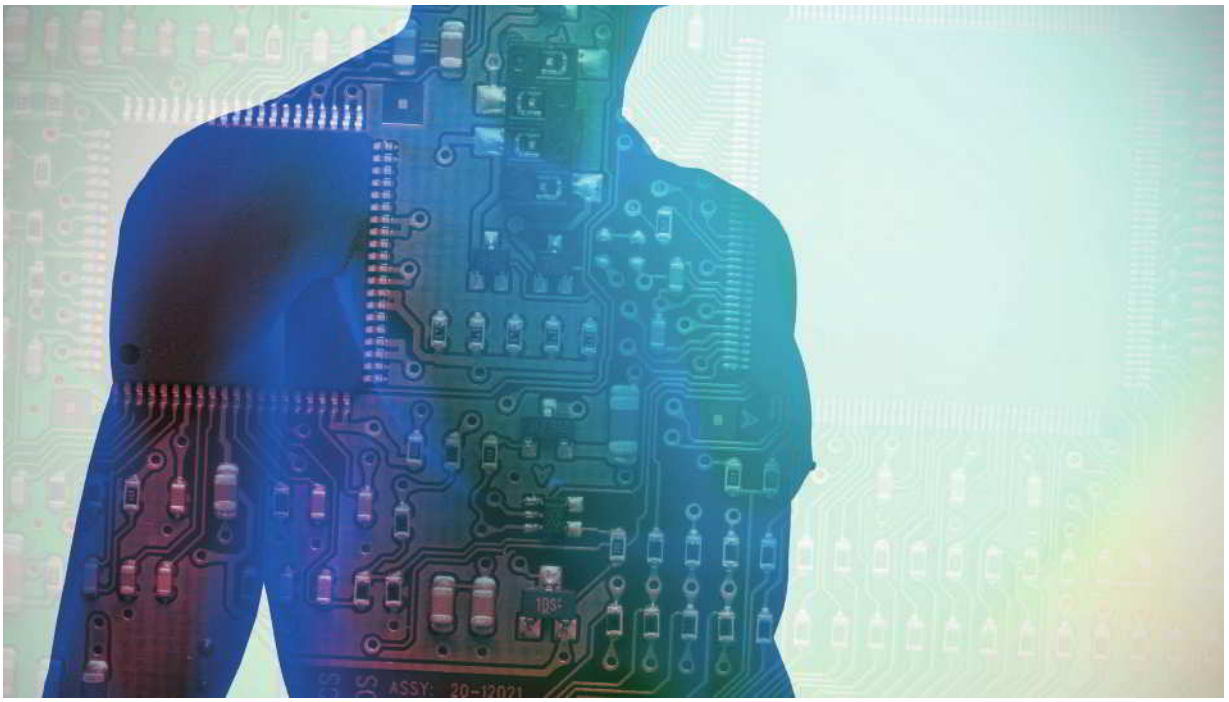
Welcome to the study of human physiology! In the first six chapters of this book you will learn about the core concepts of physiology – the general models or patterns that repeat over and over throughout the different body systems. Being able to recognize these patterns each time you encounter them will simplify learning physiology because you are seeing something familiar in a different context rather than learning a new concept. Pattern recognition is an important skill to acquire in your studies because it is a critical element in developing expertise. Studies have shown that when clinicians make a diagnosis, they are using rapid subconscious pattern recognition to help decide what might be going on.

To simplify learning the eight core concepts in this book, we have created icons that will appear at the start of each chapter to show the important core concepts discussed in that chapter. The icons and their descriptions appear next to the unit chapter titles where they are first discussed. Chapter 6 is the first chapter in Unit 2.

Chapter		Core Concepts	Icon
Chapter 1: Introduction to Physiology		Homeostasis	
		Mass Balance	
		Structure-Function Relationships	
		Communication	
Chapter 2: Molecular Interactions		Molecular Interactions	
Chapter 3: Compartmentation: Cells and Tissues		Compartmentation	
Chapter 4: Energy and Cellular Metabolism		Energy	
Chapter 5: Membrane Dynamics		Gradients	

1

Introduction to Physiology



The current tendency of physiological thought is clearly toward an increasing emphasis upon the unity of operation of the Human Body.

Ernest G. Martin, preface to The Human Body *10th edition, 1917*

Welcome to the study of human physiology! In this chapter you will be introduced to the core concepts of physiology—the general models or patterns that repeat over and over throughout the body systems of living organisms. Here are the core concepts featured in Chapter 1.

Homeostasis

A healthy body stays in homeostasis. Loss of homeostasis can result in illness.

Communication

The organ systems of the body must communicate with each other.

Mass Balance

Body stability requires that what comes in and what goes out remain balanced.

Structure-Function

The structure and function of body parts are closely related, from the tiniest subcellular fibers to the most complex organs.

Compartmentation

Compartments at all levels of organization separate functions.

Learning Outcomes

1.1 Physiology Is an Integrative Science
- **LO 1.1.1** Define physiology.
- **LO 1.1.2** List the levels of organization from atoms to the biosphere.
- **LO 1.1.3** Name the 10 physiological organ systems of the body and give their functions.

1.2 Function and Mechanism
- **LO 1.2.1** Distinguish between mechanistic explanations and teleological explanations.

1.3 Core Concepts in Physiology
- **LO 1.3.1** List and give examples of eight core concepts in physiology.

1.4 Homeostasis
- **LO 1.4.1** Define homeostasis. What happens when homeostasis fails?
- **LO 1.4.2** Name and describe the two major compartments of the human body.
- **LO 1.4.3** Explain the law of mass balance and how it applies to the body's load of a substance.
- **LO 1.4.4** Define mass flow using mathematical units and explain how it relates to mass balance.
- **LO 1.4.5** Define clearance and give an example.
- **LO 1.4.6** Distinguish between equilibrium and steady state.

1.5 Control Systems and Homeostasis
- **LO 1.5.1** List the three components of a control system and give an example.
- **LO 1.5.2** Explain the relationship between a regulated variable and its setpoint.
- **LO 1.5.3** Compare local control, long-distance control, and reflex control.
- **LO 1.5.4** Explain the relationship between a response loop and a feedback loop.
- **LO 1.5.5** Compare negative feedback, positive feedback, and feedforward control. Give an example of each.
- **LO 1.5.6** Explain what happens to setpoints in biological rhythms and give some examples.

1.6 The Science of Physiology
- **LO 1.6.1** Explain and give examples of the following components of scientific research: independent and dependent variables, experimental control, data, replication, variability.
- **LO 1.6.2** Compare and contrast the following types of experimental study designs: blind study, double-blind study, crossover study, prospective and retrospective studies, cross-sectional study, longitudinal study, meta-analysis.
- **LO 1.6.3** Define placebo and nocebo effects and explain how they may influence the outcome of experimental studies.

Welcome to the fascinating study of the human body! For most of recorded history, humans have been interested in how their bodies work. Early Egyptian, Indian, and Chinese writings describe attempts by physicians to treat various diseases and to restore health. Although some ancient remedies, such as camel dung and powdered sheep horn, may seem bizarre, we are still using others, such as blood-sucking leeches and chemicals derived from medicinal plants. The way we use these treatments has changed through the centuries as we have learned more about the human body.

There has never been a more exciting time in human physiology. **Physiology** is the study of the typical functioning of a living organism and its component parts, including all its chemical and physical processes. The term *physiology* literally means "knowledge of nature." Aristotle (384–322 BCE) used the word in this broad sense to describe the functioning of all living organisms, not just of the human body. However, Hippocrates (ca. 460–377 BCE), considered the father of medicine, used the word *physiology* to mean "the healing power of nature," and thereafter the field became closely associated with medicine. By the sixteenth century in Europe, physiology had been formalized as the study of the vital functions of the human body. Currently the term is again used to refer to the study of all living organisms.

Today, we benefit from centuries of work by physiologists who constructed a foundation of knowledge about how the human body functions. Since the 1970s, rapid advances in the fields of cellular and molecular biology have supplemented this work. A few decades ago, we thought that we would find the key to the secret of life by sequencing the human *genome*, which is the collective term for all the genetic information contained in the DNA of a species. However, this deconstructionist view of biology has proved to have its limitations, because living organisms are much more than the simple sum of their parts.

1.1 Physiology Is an Integrative Science

Many complex systems—including those of the human body—possess **emergent properties,** which are properties that cannot be predicted to exist based only on knowledge of the system's individual components. An emergent property is not a property of any single component of the system, and it is greater than the simple sum of the system's individual parts. Emergent properties result from complex, nonlinear interactions of the different components.

For example, suppose someone broke down a car into its nuts and bolts and pieces and laid them out on a floor. Could you predict that, properly assembled, these bits of metal and plastic would become a vehicle capable of converting the energy in gasoline into movement? Who could predict that the right combination of elements into molecules and assemblages of molecules would result in a living organism? Among the most complex emergent properties in humans are emotion, intelligence, and other aspects of brain function. None of these properties can be predicted from knowing the individual properties of nerve cells.

When the Human Genome Project began in 1990, scientists thought that by identifying and sequencing all the genes in human DNA, they would understand how the body worked. However, as research advanced, scientists had to revise their original idea that a given segment of DNA contained one gene that coded for one protein. It became clear that one DNA sequence could code for many proteins. The Human Genome Project ended in 2003, but before then researchers had moved beyond genomics to *proteomics*, the study of proteins in living organisms.

Now scientists have realized that knowing that a protein is made by a particular cell does not always tell us the significance of that protein to the cell, the tissue, or the functioning organism. The exciting new areas in biological research are using a *multiomics approach* that applies data from many fields of study to explain the integrated function of the human body.

Emerging Concepts

The Changing World of Omes

Contemporary research is now in an era of "omes" and "omics." What is an "ome"? The term apparently derives from the Latin word for a mass or tumor and refers to a collection of items that make up a whole, such as a genome. One of the earliest uses of the "ome" suffix in biology is the term *biome*, meaning all organisms living in a major ecological region, such as the marine biome. A *genome* is all the genetic material of an organism. Its *physiome* describes the organism's coordinated molecular, cellular, and physiological functioning. The related adjective "omics" describes the research related to studying an "ome."

New "omes" emerge every year. The human connectome project sponsored by the U.S. National Institutes of Health is a collaborative effort to map all the neural connections of the human brain. The human microbiome project is studying the influence of microbes that normally live on or in the human body. Long ignored for many years, these microbes have now been shown to have an influence on both health and disease.

1.2 Function and Mechanism

We define physiology as the typical functioning of the body, but physiologists are careful to distinguish between *function* and *mechanism*. The **function** of a physiological system or event is the "why" of the system or event: Why does a certain response help an animal survive in a particular situation? In other words, what is the *adaptive significance* of this event for this animal?

For example, humans are large, mobile, terrestrial animals, and our bodies maintain relatively constant water content despite living in a dry, highly variable external environment. Dehydration is a constant threat to our well-being. What processes have evolved in our anatomy and physiology that allow us to survive in this hostile environment? One is the production of highly concentrated urine by the kidney, which allows the body to conserve water. This statement tells us *why* we produce concentrated urine but does not tell us *how* the kidney accomplishes that task.

Thinking about a physiological event in terms of its adaptive significance is the **teleological approach** to science. For example, the teleological answer to the question of why red blood cells transport oxygen is "because cells need oxygen and red blood cells bring it to them." This answer explains *why* red blood cells transport oxygen—their function—but says nothing about *how* the cells transport oxygen.

In contrast, most physiologists study physiological processes, or **mechanisms**—the "how" of a system. The **mechanistic approach** to physiology examines process. The mechanistic answer to the question "How do red blood cells transport oxygen?" is "Oxygen binds to hemoglobin molecules in the red blood cells." This very concrete answer explains exactly how oxygen transport occurs but says nothing about the significance of oxygen transport to the animal.

Students often confuse these two approaches to thinking about physiology. Studies have shown that even medical students tend to answer questions with teleological explanations when the more appropriate response would be a mechanistic explanation.[1] Often they do so because instructors ask why a physiological event occurs when they really want to know how it occurs. Staying aware of the two approaches will help prevent confusion.

Although function and mechanism seem to be two sides of the same coin, it is possible to study mechanisms, particularly at the cellular and subcellular level, without understanding their function in the life of the organism. As biological knowledge becomes more complex, scientists sometimes become so involved in studying complex processes that they fail to step back and look at the adaptive significance of those processes to cells, organ systems, or the animal. Conversely, it is possible to use teleological thinking incorrectly by saying, "Oh, in this situation the body needs to do this." *This* may be a good solution, but if a mechanism for doing *this* doesn't exist, the situation cannot be corrected.

Applying the concept of integrated functions and mechanisms is the underlying principle in **translational research,** an approach sometimes described as "bench to bedside." Translational research uses the insights and results gained from basic biomedical research on mechanisms to develop treatments and strategies for preventing human diseases. For example, researchers working on rats found that a chemical from the pancreas named *amylin* reduced the rats' food intake. These findings led directly to a translational research study in which human volunteers injected a synthetic form of amylin and recorded their subsequent food intake, but without intentionally modifying their lifestyle.[2] The drug suppressed food intake in humans, and was later approved by the Food and Drug Administration for treatment of diabetes mellitus.

At the systems level, we know about most of the mechanics of body function from centuries of research. The unanswered questions today mostly involve integration and control of these mechanisms, particularly at the cellular and molecular levels. Nevertheless, explaining what happens in test tubes or isolated cells can only partially answer questions about function. For this reason, animal and human trials are essential steps in the process of applying basic research to treating or curing diseases.

Running Problem 1.1: What to Believe?

Hiro had just left his first physiology class when he saw a friend's social media link to a video claiming that everyone should take probiotics for gut health. He watched some of the video but he wasn't sure exactly what probiotics were and whether the information in the video was accurate. "I wonder if there is any scientific evidence supporting this claim," Hiro thought. "Let's see what I can find out."

1.3 Core Concepts in Physiology

"Physiology is not a science or a profession but a point of view."[3] Physiologists pride themselves on relating the mechanisms they study to the functioning of the organism as a whole. For students, being able to think about how multiple body systems integrate their function is one of the more difficult aspects of learning physiology. To develop expertise in physiology, you must do more than simply memorize facts and learn new terminology. Researchers have found that the ability to solve problems requires a conceptual framework, or "big picture," of the field.

This book will help you build a conceptual framework for physiology by explicitly emphasizing the basic biological themes, or **core concepts** that are common to all living organisms. These concepts form patterns that repeat over and over, and you will begin to recognize them when you encounter them in specific contexts. Pattern recognition is an important skill in healthcare professions, and it will also simplify learning physiology.

In the recent years, multiple organizations issued reports to encourage the teaching of biology using these fundamental concepts.[4] Although the descriptions vary from report to report, five major ideas emerge:

1. structure and function across all levels of organization
2. energy transfer, storage, and use
3. information flow, storage, and use within single organisms and within a species of organism
4. homeostasis and the control systems that maintain it
5. evolution

In addition, these reports emphasize the importance of understanding how science is done and of the quantitative nature of biology.

FIGURE 1.1 lists the eight core concepts we will focus on in this book. The major core concepts most related to physiology are structure-function relationships (anatomy and levels of organization, molecular interactions, compartmentation), biological energy use, gradients and flow, communication, and homeostasis, which includes mass balance. The first six chapters introduce the fundamentals of these core concepts, which you may already be familiar with from earlier biology or chemistry classes. The core concepts, with variations, then re-appear over and over in subsequent chapters of this book. Look for their icons throughout the chapters and in the summary material at the end of each chapter.

Core Concept 1: Structure and Function Are Closely Related

This overarching core concept subdivides into three major ideas: anatomy and levels of organization, molecular interactions, and compartmentation.

Anatomy and Levels of Organization

Anatomy is the study of body structures, and in all living organisms, structure and function are closely linked. The **integration of function** across many **levels of organization,** from the molecular level to the intact body, is a special focus of physiology. (To *integrate* means to bring varied elements together to create a unified whole.)

FIGURE 1.2 illustrates levels of organization ranging from the molecular level all the way up to populations of different species living together in *ecosystems* and in the *biosphere*. The levels of organization are shown along with the various subdisciplines of chemistry and biology related to the study of each organizational level. There is considerable overlap between the different fields of study, and these artificial divisions vary according to who is defining them. Notice, however, that physiology includes multiple levels, from molecular and cellular biology to the ecological physiology of populations.

Fig. 1.1 Core concepts and their icons

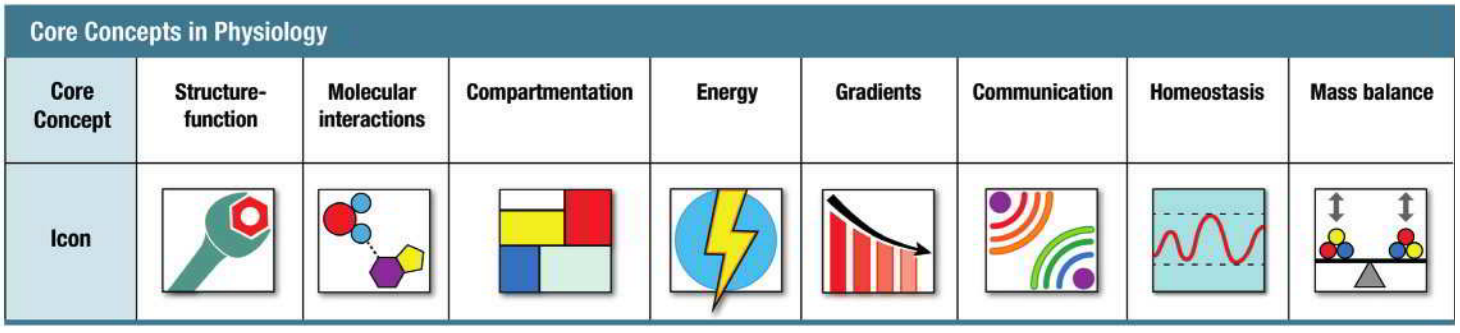
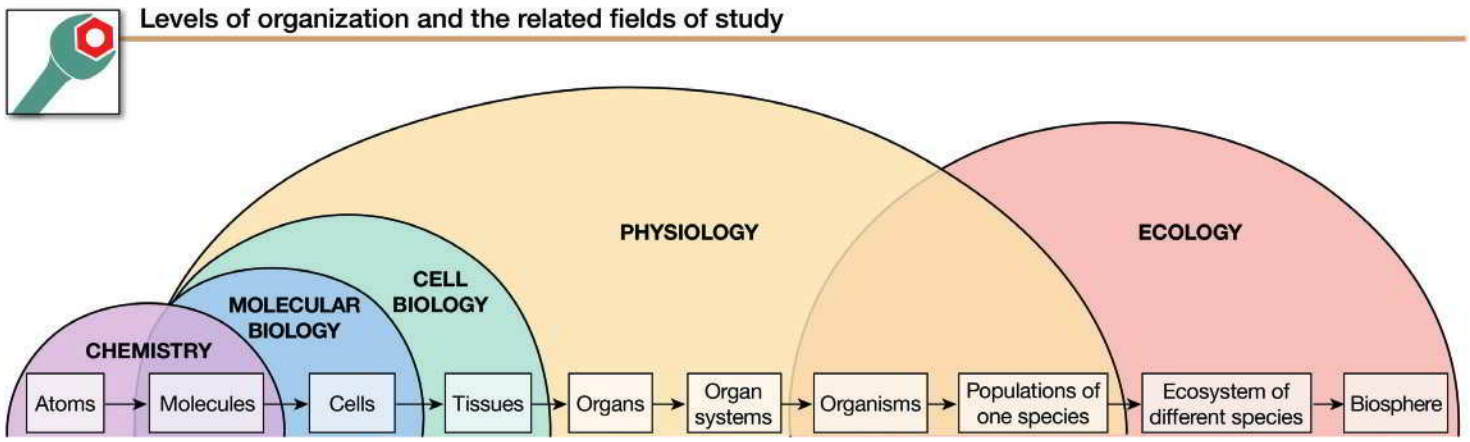


Fig. 1.2 Levels of organization



At the most basic level of organization shown in Figure 1.2, atoms of elements link together to form molecules. Collections of molecules in living organisms form **cells,** the smallest unit of structure capable of carrying out all life processes. A lipid and protein barrier called the **cell membrane** (also called the *plasma membrane*) separates cells from their external environment. Simple organisms are composed of only one cell, but complex organisms have many cells with different structural and functional specializations.

Collections of cells that carry out related functions are called **tissues** {*texere*, to weave}. Tissues form structural and functional units known as **organs** {*organon*, tool}, and groups of organs integrate their functions to create **organ systems**. Chapter 3 reviews the anatomy of cells, tissues, and organs.

The structure of a cell, tissue, or organ must provide an efficient physical base for its function. For this reason, it is nearly impossible to study the physiology of the body without understanding the underlying anatomy. Because of the interrelationship of anatomy and physiology, you will find Anatomy Summaries throughout the book. These special review features illustrate the basic anatomy of the physiological systems at different levels of organization.

Running Problem 1.2

When Hiro got back to his room, he sat down at his computer and googled *probiotics*. Almost instantly, he got back more than 244 million results. The first results were sponsored links from *seed.com*, *amazon.com*, and *ritual.com*. These were followed by pages from *mayoclinic.org*, *www.nccih.nih.gov*, *webmd.com*, *healthline.com*, *health.harvard.edu*, *en.wikipedia.org*, and *www.ods.od.nih.gov*. Hiro thought to himself, "Wow, there is a lot of information out there. What should I look at first?"

Q1: *Rank these 10 results from most to least likely to have good information and explain how you chose your rankings.*

The 10 physiological organ systems in the human body are illustrated in **FIGURE 1.3**. Several of the systems have alternate names, given in parentheses, that are based on the organs of the system rather than the function of the system. The **integumentary system** {*integumentum*, covering}, composed of the skin, forms a protective boundary that separates the body's internal environment from the external environment (the outside world). The **musculoskeletal system** provides support and body movement.

Four systems move material into and out of the body. The **respiratory system (pulmonary)** exchanges gases; the **digestive system (gastrointestinal)** takes up nutrients and water and eliminates wastes; the **urinary system (renal)** removes excess water and waste material; and the **reproductive system** produces eggs or sperm.

The remaining four systems extend throughout the body. The **circulatory system (cardiovascular)** distributes materials by pumping blood through vessels. The **nervous system** and **endocrine system** coordinate body functions. Note that the figure shows them as a continuum rather than as two distinct systems. Why? Because the lines between these two systems have blurred as we have learned more about the integrative nature of physiological function.

The one system not illustrated in Figure 1.3 is the diffuse **immune system,** which includes but is not limited to the anatomical structures known as the **lymphatic system**. The specialized cells of the immune system are scattered throughout the body. They protect the internal environment from foreign substances by intercepting material that enters through the intestines and lungs or through a break in the skin. In addition, immune tissues are closely associated with the circulatory system. Cells of the immune system secrete chemical messengers that communicate and coordinate with the nervous and endocrine systems.

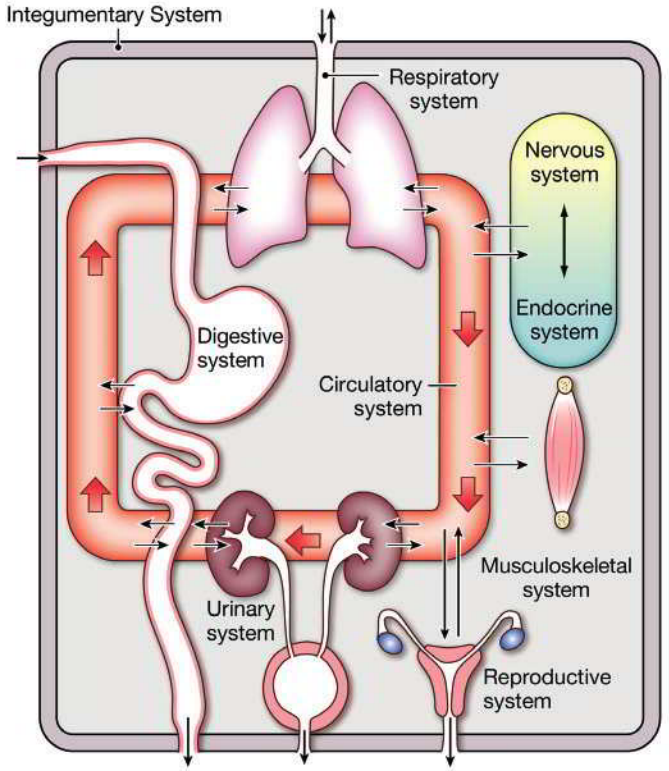
Traditionally, physiology courses and books are organized by organ system. Students study cardiovascular physiology and regulation of blood pressure in one chapter, and then study the kidneys and control of body fluid volume in a different chapter. In the functioning human, however, the cardiovascular and renal systems communicate with each other, so that a change in one is

Fig. 1.3 Organ systems of the human body and their integration

ESSENTIALS Organ Systems of the Human Body

System Name	Includes	Representative Functions
Circulatory	Heart, blood vessels, blood	Transport of materials between all cells of the body
Digestive	Stomach, intestine, liver, pancreas	Conversion of food into particles that can be transported into the body; elimination of some wastes
Endocrine	Thyroid gland, adrenal gland	Coordination of body function through synthesis and release of regulatory molecules
Immune	Thymus, spleen, lymph nodes	Defense against foreign invaders
Integumentary	Skin	Protection from external environment
Musculoskeletal	Skeletal muscles, bone	Support and movement
Nervous	Brain, spinal cord	Coordination of body function through electrical signals and release of regulatory molecules
Reproductive	Ovaries and uterus, testes	Perpetuation of the species
Respiratory	Lungs, airways	Exchange of oxygen and carbon dioxide between the internal and external environments
Urinary	Kidneys, bladder	Maintenance of water and solutes in the internal environment; waste removal

The Integration between Systems of the Body



This schematic figure indicates relationships between systems of the human body. The interiors of some hollow organs (shown in white) are part of the external environment.

likely to cause a reaction in the other. For example, body fluid volume influences blood pressure, while changes in blood pressure alter kidney function because the kidneys regulate fluid volume. In this book, each of the four units ends with an integrative physiology chapter that highlights the coordination of function across multiple organ systems.

Understanding how different organ systems work together is just as important as memorizing facts, but the complexity of interactions can be challenging. One way physiologists simplify and integrate information is by using visual representations of physiological processes called maps. The Focus on Mapping feature in this chapter will help you learn how to make maps. The first type of map, shown in **FIGURE 1.4**, is a schematic representation of structure or function. The second type of map diagrams a physiological process as it proceeds through time. These process maps are also called *flow charts*, and they are frequently used in health care. You will be able to practice creating maps with special end-of-chapter questions throughout the book. You will also find maps in the visual summary at the end of each chapter.

Molecular Interactions

The ability of individual molecules to bind to or react with other molecules is essential for biological function. A molecule's function depends on its structure and shape, and even a small change to the structure or shape may have significant effects on the function. The classic example of this phenomenon is the change in one amino acid of the hemoglobin protein. (Hemoglobin is the oxygen-carrying pigment of the blood.) This one small change in the protein converts normal hemoglobin to the form associated with sickle cell disease.

Many physiologically significant molecular interactions that you will learn about in this book involve the class of biological molecules called *proteins*. Functional groups of proteins include *enzymes* that speed up chemical reactions, *signal molecules* and the *receptor proteins* that bind signal molecules, and specialized proteins that function as biological pumps, filters, motors, or transporters. Chapter 2 describes molecular interactions involving proteins in more detail.

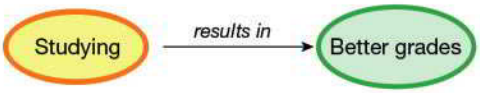
Fig. 1.4 Focus on . . . Mapping

Focus on . . . Mapping

Why use maps to study physiology? The answer is simple: maps will help you organize information you are learning in a way that makes sense to you and they will make that information easier to recall on a test. Creating a map requires higher-level thinking about the relationships among items on the map.

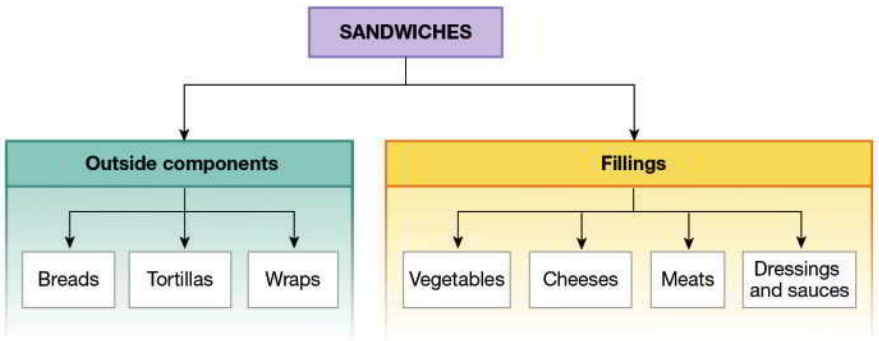
Mapping is not just a study technique. Scientists map out the steps in their experiments. Healthcare professionals create maps to guide them while diagnosing and treating patients. You can use mapping for almost every subject you study.

What is a map? Mapping is a nonlinear way of organizing material. A map can take a variety of forms but usually consists of terms (words or short phrases) linked by arrows to indicate associations. You can label the connecting arrows to describe the type of linkage between the terms (structure/function, cause/effect) or with explanatory phrases.

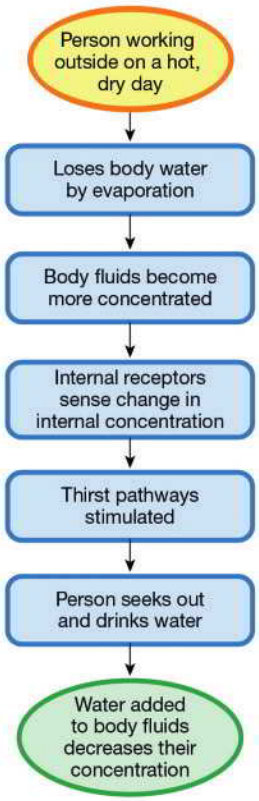


Here are two typical maps used in physiology.

Structure/function maps focus on the relationships between anatomical structures and their functions.



Process maps or **flow charts** follow normal homeostatic control pathways or the body's responses to abnormal (pathophysiological) events as they unfold over time.



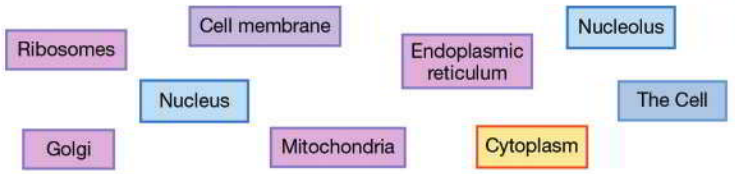
Practice making maps. Many maps appear in this textbook, and they can serve as the starting point for your own maps. However, the real benefit of mapping comes from preparing maps yourself rather than memorizing someone else's maps. Your instructor can help you get started.

HINTS

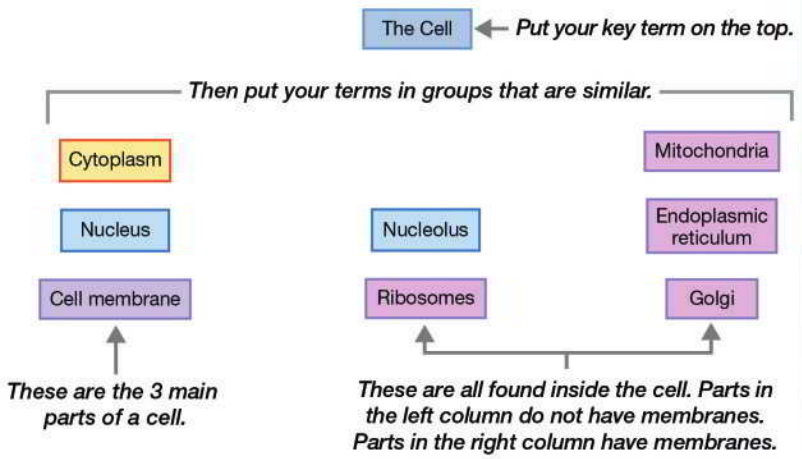
- To help you get started, the end-of-chapter questions in this book include at least one list of terms to map for each chapter.
- Write your terms on individual slips of paper or small sticky notes so that you can rearrange the map more easily.
- Some terms may seem to belong to more than one group. Do not duplicate the item but make a note of it, as this term will probably have several arrows pointing to it or leading away from it.
- If arrows crisscross, try rearranging the terms on the map.
- Use color to indicate similar items.
- Add pictures and graphs that are associated with specific terms in your map.

Electronic mapping. Some people do not like the messiness of hand-drawn maps. There are several electronic ways of making maps, including PowerPoint or free and commercial software programs. Free concept mapping software is available from IHMC CmapTools at https://cmap.ihmc.us.

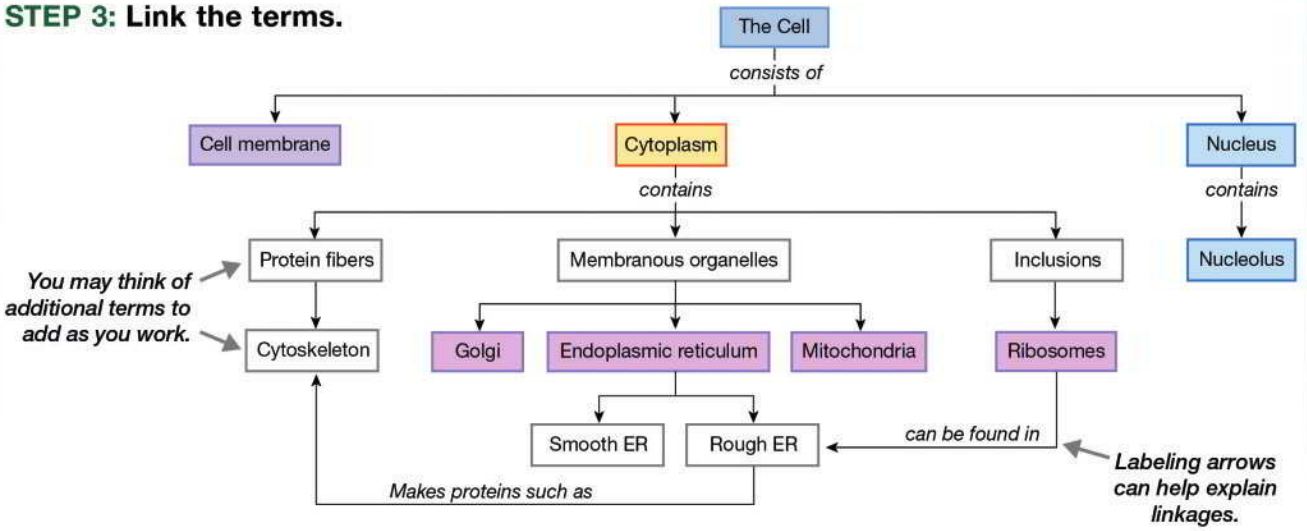
STEP 1: Write out the terms to map.
If you need help generating ideas for topics to map, the end-of-chapter mapping questions in each chapter have lists of terms to help you get started.



STEP 2: Organize the terms.



STEP 3: Link the terms.



Once you have created your map, sit back and think about it. Are all the items in the right place? You may want to move them around once you see the big picture. Add new concepts or correct wrong links. Review by recalling the main concept and then moving to the more specific details. Ask yourself questions like, What is the cause and what is the effect? What parts are involved? What are the main characteristics?

Science is a collaborative field. A useful way to study with a map is to **trade maps with a classmate** and try to understand each other's maps. Your maps will almost certainly not look the same! It's OK if they are different. Remember that your map reflects the way you think about the subject, which may be different from the way someone else thinks about it. Did one of you put in something the other forgot? Did one of you have an incorrect link between two items?

Interactions between proteins, water, and other molecules influence cell structure and the mechanical properties of cells and tissues. Mechanical properties you will encounter in your study of physiology include *compliance* (ability to stretch), *elastance* (stiffness or the ability to return to the unstretched state), strength, flexibility, and fluidity (*viscosity*).

Compartmentation

Compartmentation is the division of space into separate compartments, with or without obvious dividing walls. Compartments allow a cell, a tissue, or an organ to specialize and isolate functions. Each level of organization is associated with different types of compartments. At the macroscopic level, the tissues and organs of the body form discrete functional compartments, such as body cavities or the insides of hollow organs. At the microscopic level, cell membranes separate cells from the fluid surrounding them and also create tiny compartments within the cell called organelles. Compartmentation is the theme of Chapter 3.

Running Problem 1.3

Hiro looked at the results on the first page. He had heard of the NIH, and knew it was the U.S. National Institutes of Health, run by the federal government, so he clicked on *www.nccih.nih.gov*. This link went to a page for the NIH-Sponsored National Center for Complementary and Integrative Health (NCCIH). Hiro decided to learn more about NCCIH by using the ABOUT link. He used the SEARCH box to see what NCCIH said about probiotics.

Q2: *Go to www.nccih.nih.gov. What is the mission of NCCIH?*

Q3: *What does NCCIH say about whether probiotics are helpful and whether they are safe?*

Core Concept 2: Living Organisms Need Energy

Growth, reproduction, movement, homeostasis—these and all other processes that take place in an organism require the continuous input of energy. Where does this energy come from, and how is it stored? We will answer those questions and describe some of the ways that energy in the body is used for building and breaking down molecules in Chapter 4. In subsequent chapters, you will learn how energy is used to transport molecules across cell membranes and to create movement.

Core Concept 3: Gradients and Flow

A **gradient** {*gradiens*, to walk} is a gradual change in the value or magnitude of a function over distance or over time. In physiology, most of the gradients you will encounter represent a change in magnitude from one location to another, such as from the beginning to the end of a tube or between the inside and outside of a cell. The gradients icon (Fig. 1.1) shows two gradients moving from left to right: a decrease in size and a decrease in color intensity. Three types of gradients are particularly important in physiology: concentration (chemical) gradients, pressure gradients, and electrical gradients. You may also encounter other gradients, such as temperature gradients. Gradients are a form of stored (*potential*) energy, and substances will move or flow down a gradient unless there is a barrier blocking their movement.

Core Concept 4: Communication Coordinates Body Functions

Communication is the transmission of information within or between organisms. Information flow in living systems ranges from the transfer of information stored in DNA from generation to generation (genetics) to the flow of information within the body of a single organism. At the organismal level, information flow includes translation of DNA's genetic code into proteins responsible for cell structure and function as well as the communication signals between cells that coordinate function.

Cell-to-cell communication uses chemical signals, electrical signals, or a combination of both. Information may go from one cell to its neighbors (local communication) or from one part of the body to another (long-distance communication). Chapter 5 looks at the electrical gradients responsible for electrical signaling, while Chapter 6 discusses chemical communication in the body.

When chemical signals reach their target cells, they must get their information into the cell. Some molecules are able to pass through the barrier of the cell membrane, but signal molecules that cannot enter the cell must transfer their message across the cell membrane. How molecules cross biological membranes is the topic of Chapter 5, Chapter 6 looks at how chemical signals pass their information across the cell membrane.

Core Concept 5: Homeostasis Maintains Internal Stability

Organisms that survive in challenging habitats cope with external variability by keeping their internal environment relatively stable, an ability known as **homeostasis** {*homeo-*, similar + *-stasis*, condition}. Homeostasis and regulation of the internal environment are key principles of physiology and form an underlying core concept in each chapter of this book. The next section looks in detail at the key elements of this important core concept.

1.4 Homeostasis

The concept of a relatively stable internal environment is attributed to the French physician Claude Bernard in the mid-1800s. During his studies of experimental medicine, Bernard noted the stability of various physiological functions, such as body temperature, heart rate, and blood pressure. As the chair of physiology at the University of Paris, he wrote "La fixité du milieu intérieur est la condition de la vie libre, indépendante." (The constancy of the

internal environment is the condition for a free and independent life.)[5] This idea was applied to many of the experimental observations of his day, and it became the subject of discussion among physiologists and physicians.

In 1929, an American physiologist named **Walter B. Cannon** wrote a review for the American Physiological Society.[6] Using observations made by numerous physiologists and physicians during the nineteenth and early twentieth centuries, Cannon proposed a list of variables that are under homeostatic control. We now know that his list was both accurate and complete. Cannon divided his variables into what he described as environmental factors that affect cells (osmolarity, temperature, and pH) and "materials for cell needs" (nutrients, water, sodium, calcium, other inorganic ions, oxygen, as well as "internal secretions having general and continuous effects"). Cannon's "internal secretions" are the hormones and other chemicals that our cells use to communicate with one another.

In his essay, Cannon created the word *homeostasis* to describe the regulation of the body's internal environment. He explained that he selected the prefix *homeo-* (meaning *like* or *similar*) rather than the prefix *homo-* (meaning *same*) because the internal environment is maintained within a range of values rather than at an exact fixed value. He also pointed out that the suffix *-stasis* in this instance means a *condition*, not a state that is static and unchanging. Cannon's homeostasis, therefore, is a state of maintaining "a similar condition," similar to Claude Bernard's relatively constant internal environment.

Some physiologists contend that a literal interpretation of *stasis* {a state of standing} in the word *homeostasis* implies a static, unchanging state. They argue that we should use the word *homeodynamics* instead, to reflect the small changes constantly taking place in our internal environment {*dynamikos*, force or power}. Whether the process is called homeostasis or homeodynamics, the important concept to remember is that the body monitors its internal state and takes action to correct disruptions that threaten its normal function. Physiologists today generally recognize 10 variables (**TABLE 1.1**) that the body monitors and regulates to maintain homeostasis.

If the body fails to maintain homeostasis of the critical variables listed by Walter Cannon, then healthy function is disrupted and a disease state, or **pathological** condition {*pathos*, suffering}, may result. Diseases fall into two general groups according to their origin: those in which the problem arises from internal failure of some normal physiological process, and those that originate from some outside source. Internal causes of disease include the abnormal growth of cells, which may cause cancer or benign tumors; the production of antibodies by the body against its own tissues (autoimmune diseases); and the premature death of cells or the failure of cell processes. Inherited disorders are also considered to have internal causes. External causes of disease include toxic chemicals, physical trauma, and foreign invaders such as viruses and bacteria.

In both internally and externally caused diseases, when homeostasis is disturbed, the body attempts to compensate (**FIG. 1.5**). If the compensation is successful, homeostasis is restored. If compensation fails, illness or disease may result. The study of body functions in a disease state is known as **pathophysiology.** You will encounter many examples of pathophysiology as we study the various systems of the body.

One very common pathological condition in the United States is **diabetes mellitus,** a metabolic disorder characterized by abnormally high blood glucose concentrations. Although we speak of diabetes as if it were a single disease, it is actually a whole family of diseases with various causes and manifestations. You will learn more about diabetes in the focus boxes scattered throughout the chapters of this book. The influence of this one disorder on many systems of the body makes it an excellent example of the integrative nature of physiology.

What Is the Body's Internal Environment?

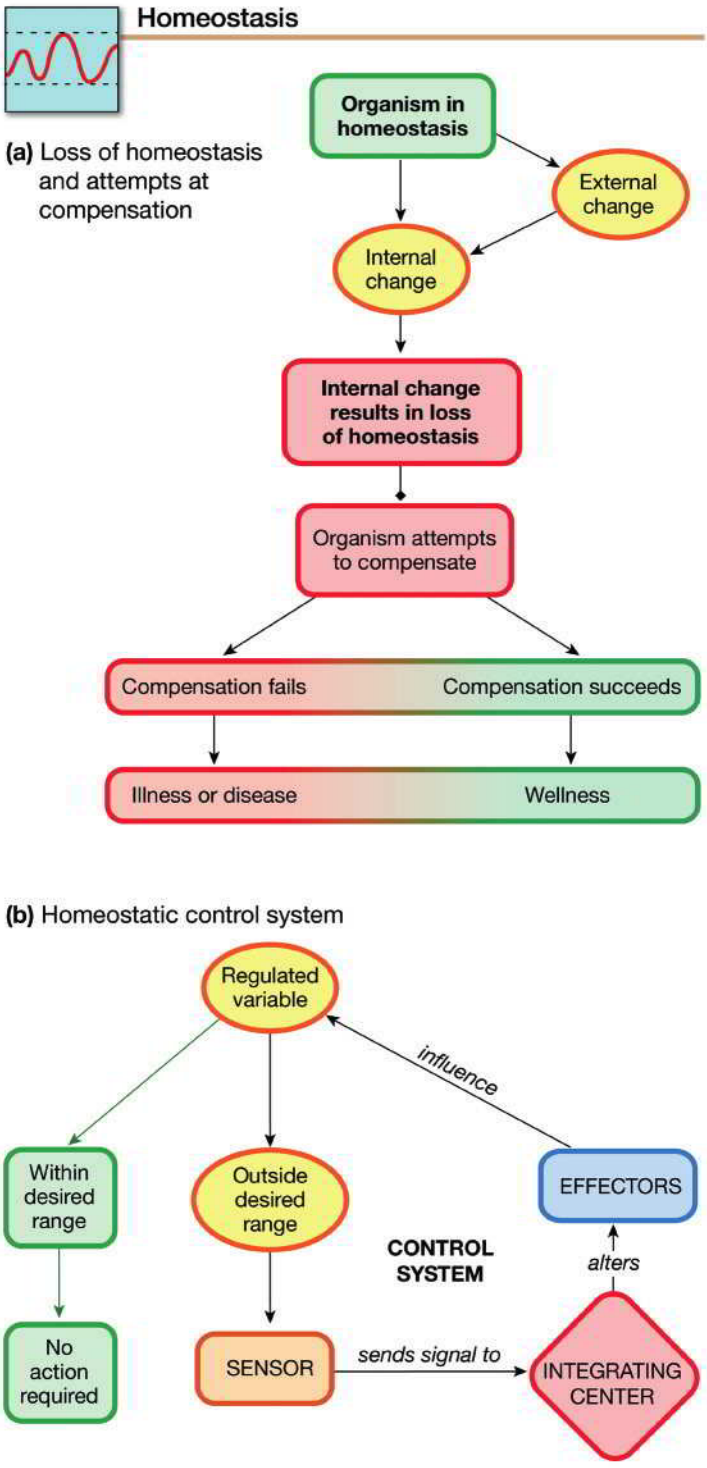
Claude Bernard wrote of the "constancy of the internal environment," but why is constancy so essential? As it turns out, most cells in our bodies are not very tolerant of changes in their surroundings. In this way they are similar to early organisms that lived in tropical seas, a stable environment where salinity, oxygen content, and pH vary little and where light and temperature cycle in predictable ways. The internal composition of these ancient creatures was almost identical to that of seawater. If environmental conditions changed, conditions inside the primitive organisms changed as well. Even today, marine invertebrates cannot tolerate significant changes in salinity and pH, as you know if you have ever maintained a saltwater aquarium.

In both ancient and modern times, many marine organisms relied on the constancy of their external environment to keep their internal environment in balance. In contrast, as organisms evolved and migrated from the ancient seas into estuaries, then into freshwater environments and onto the land, they encountered highly variable external environments. Rains dilute the salty water of estuaries, and organisms that live there must cope with the influx of water into their body fluids. Terrestrial organisms, including humans, face the challenge of dehydration—constantly losing internal water to the dry air around them. Keeping the internal environment stable means balancing water loss with appropriate water intake.

Table 1.1 Regulated Physiological Variables

Blood gases	Blood solutes	
• Oxygen • Carbon dioxide	• Potassium K^+ • Calcium Ca^{2+} • Hydrogen H^+ (pH) • Glucose	• Arterial blood pressure • Blood volume • Blood osmolarity • Body temperature (core)

Fig. 1.5 Homeostasis



But what exactly is the internal environment of the body? For multicellular animals, it is the watery internal environment that surrounds the cells, a "sea within" the body called the **extracellular fluid (ECF)** {*extra-*, outside of} (**FIG. 1.6**). Extracellular fluid serves as the transition between an organism's external environment and the **intracellular fluid (ICF)** inside cells {*intra-*, within}. Because extracellular fluid is a buffer zone between cells and the outside world, elaborate physiological processes have evolved to keep its composition relatively stable.

When the extracellular fluid composition varies outside its acceptable range of values, compensatory mechanisms are activated in an attempt to return the fluid to its usual state. For example, when you drink a large volume of water, the dilution of your extracellular fluid triggers a mechanism that causes your kidneys to remove excess water and protect your cells from swelling. Most cells of multicellular animals do not tolerate much change. They depend on the constancy of extracellular fluid to maintain their function.

Homeostasis Depends on Mass Balance

In the 1960s, a group of conspiracy theorists obtained a lock of Napoleon Bonaparte's hair and sent it for chemical analysis in an attempt to show that he died from arsenic poisoning. Today, a group of students sharing a pizza joke about the garlic odor on their breath. At first glance these two scenarios appear to have little in common, but in fact Napoleon's hair and "garlic breath" both demonstrate how the human body works to maintain the balance that we call *homeostasis*.

The human body is an open system that exchanges heat and materials with the outside environment. To maintain homeostasis, the body must maintain mass balance. We will consider mass balance to be another of our core concepts in physiology (Fig. 1.1).

The **law of mass balance** says that if the amount of a substance in the body is to remain constant, any gain must be offset by an equal loss (**FIG. 1.7a**). The amount of a substance in the body is also called the body's **load,** as in "sodium load."

For example, water loss to the external environment (output) in sweat and urine must be balanced by water intake from the external environment plus metabolic water production (input). The concentrations of other substances, such as oxygen and carbon dioxide, salts, and hydrogen ions (pH), are also maintained through mass balance. The following equation summarizes the law of mass balance:

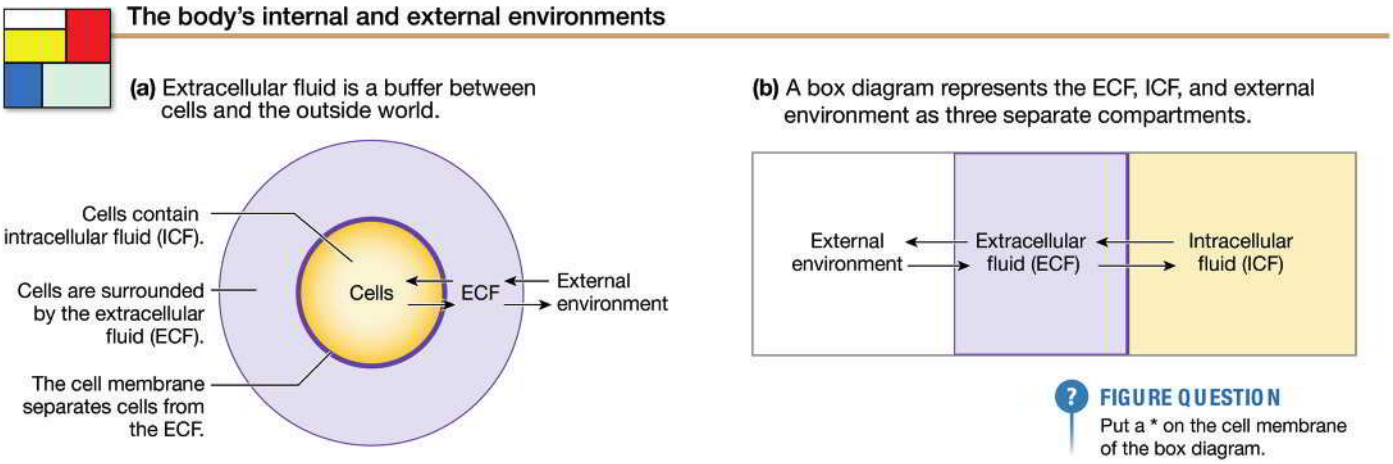
$$\text{Total amount of substance } x \text{ in the body} = \text{intake} + \text{production} - \text{excretion} - \text{metabolism}$$

Most substances enter the body from the outside environment, but some (such as carbon dioxide) are produced internally through metabolism (Fig. 1.7b). In general, water and nutrients enter the body as food and drink absorbed through the intestine. Oxygen and other gases and volatile molecules enter through the lungs. A few lipid-soluble chemicals make their way to the internal environment by penetrating the barrier of the skin.

To maintain mass balance, the body has two options for output. The simplest option is simply to excrete the material. **Excretion** is defined as the elimination of material from the body, usually through the urine, feces, lungs, or skin. For example, carbon dioxide (CO_2) produced during metabolism is excreted by the lungs. Many foreign substances that enter the body, such as drugs or artificial food additives, are excreted by the liver and kidneys. (Any foreign substance in the body is called a *xenobiotic,* from the Greek word *xenos,* a stranger.)

A second output option for maintaining mass balance is to convert the substance to a different substance through metabolism. Nutrients that enter the body become the starting point for

Fig. 1.6 Internal and external environments



metabolic pathways that convert the original nutrient to a different molecule. However, converting the original nutrient to something different then creates a new mass balance disturbance by adding more of the new substance, or *metabolite*, to the body. (*Metabolite* is the general term for any product created in a metabolic pathway.)

Mass Flow

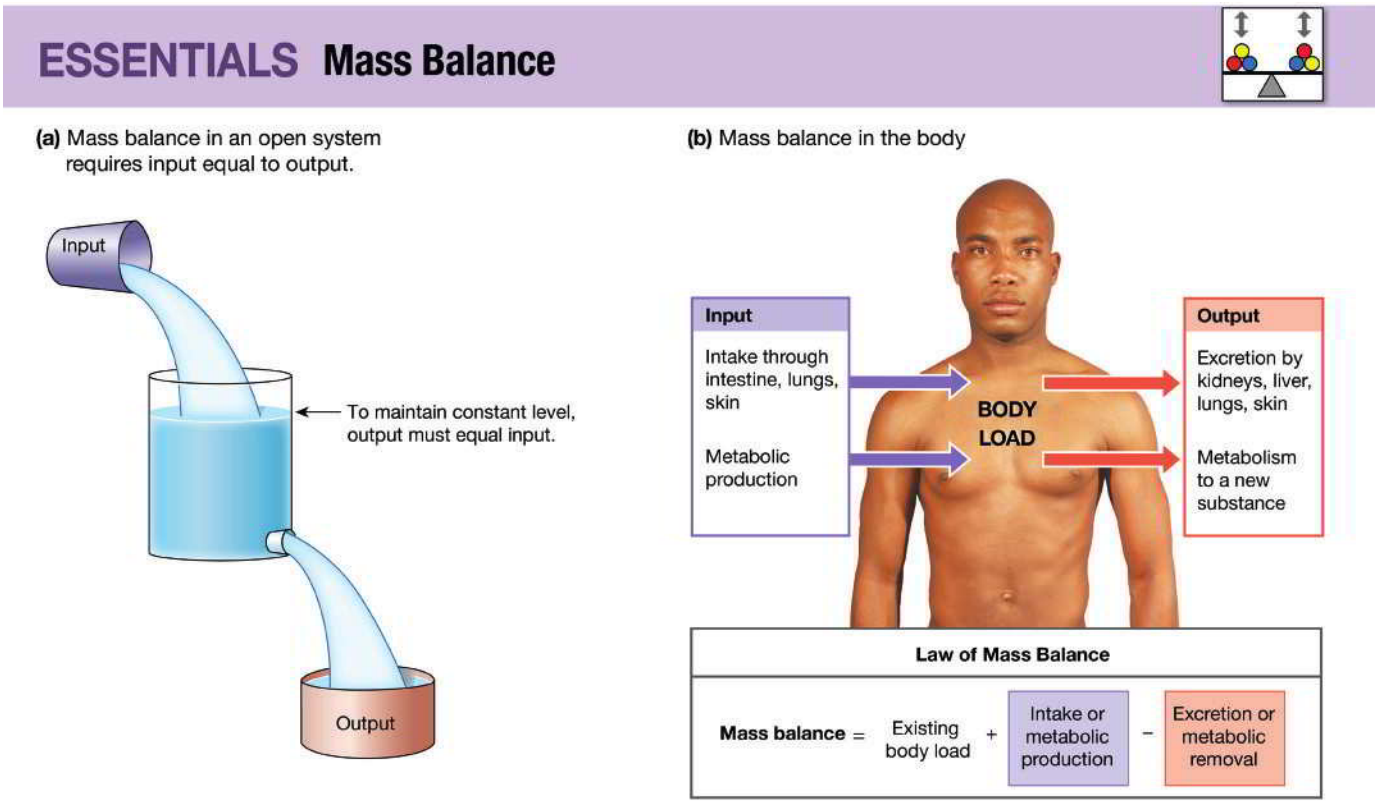
Scientists use **mass flow** to follow material throughout the body. Mass flow describes the rate of transport of a substance x as it moves through body fluids or into and out of the body. The equation for mass flow is

$$\text{Mass flow (amount } x/\text{min)} = \text{concentration of } x \text{ (amount } x/\text{vol)} \times \text{volume flow (vol/min)}$$

where volume flow describes the flow rate of a volume of blood, air, urine, and the like.

For example, suppose a person is given an intravenous (IV) infusion of glucose solution that has a concentration of 50 grams of glucose per liter of solution. If the infusion is given

Fig. 1.7 Mass balance



at a rate of 2 milliliters per minute, the mass flow of glucose into the body is:

$$\frac{50 \text{ g glucose}}{1000 \text{ mL solution}} \times 2 \text{ mL solution/min} = 0.1 \text{ g glucose/min}$$

The rate of glucose input into the body is 0.1 g glucose/min.

Mass flow applies not only to the entry, production, and removal of substances but also to the movement of substances from one compartment in the body to another. When materials enter the body, they first become part of the extracellular fluid. Where a substance goes after that depends on whether or not it can cross the barrier of the cell membrane and enter the cells.

Running Problem 1.4

Hiro wondered if there was another option for finding more information about probiotics, so he asked Jennifer, a friend who had just started graduate school in Public Health, how she would search. "I usually start with Google Scholar (scholar.google.com) rather than just googling. Google Scholar only shows you scholarly literature, so you won't get all the websites that are trying to sell you something. Or if you want to search the way scientists and healthcare professionals do, then try PubMed (www.pubmed.gov), the free database published by the U.S. National Library of Medicine." Hiro entered *probiotics* into Google Scholar and then repeated the same search in PubMed. "This is still way too much information," Hiro thought. "Surely there are ways to narrow this down."

Q4: *Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from the simple Google search.*

Q5: *One way to get fewer results is to limit the results to only recent papers. Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*

Excretion and Metabolism Clear Substances from the Body

It is relatively easy to monitor how much of a substance enters the body from the outside world, but it is more difficult to track molecules inside the body to monitor their excretion or metabolism. Instead of directly measuring the substance, we can follow the rate at which the substance disappears from the blood, a concept called **clearance.** Clearance is usually expressed as a volume of blood *cleared* of substance x per unit of time. For this reason, clearance is only an indirect measure of how substance x is handled by the body.

Clearance cannot tell you if the substance is disappearing by excretion or metabolism or by both. For example, urea is a normal metabolite produced from protein metabolism. A typical value for urea clearance is 70 mL plasma cleared of urea per minute, written as $urea\ clearance = 70\ mL\ plasma/min$. Knowing the rate at which urea disappears does not tell us anything about where urea is going. (It is being excreted by the kidneys.)

The kidney and the liver are the two primary organs that clear solutes from the body. *Hepatocytes* {*hepaticus*, pertaining to the liver + *cyte*, cell}, or liver cells, metabolize many different types of molecules, especially xenobiotics such as drugs. The resulting metabolites may be secreted into the intestine for excretion in the feces or released into the blood for removal by the kidneys. Pharmaceutical companies testing chemicals for their potential use as therapeutic drugs must know the clearance of the chemical before they can develop the proper dosing schedule.

Clearance also takes place in tissues other than the liver and kidneys. Saliva, sweat, breast milk, and hair all contain substances that have been cleared from the body. Salivary secretion of the hormone *cortisol* provides a simple noninvasive source of hormone for monitoring chronic stress.

An everyday example of clearance is "garlic breath," which occurs when volatile lipid-soluble garlic compounds in the blood pass into the airways and are exhaled. The lungs also clear ethanol in the blood: exhaled alcohol is the basis of the "breathalyzer" test used by law enforcement agencies. Drugs and alcohol secreted into breast milk are potentially dangerous because a breastfeeding infant will ingest these substances.

The 1960s analysis of Napoleon Bonaparte's hair tested it for arsenic because hair follicles help clear some compounds from the body. The test results showed significant concentrations of the poison in his hair, but the question remains whether Napoleon was murdered, poisoned accidentally, or died from stomach cancer.

Concept Check

1. If a person eats 12 milligrams (mg) of salt in a day and excretes 11 mg of it in the urine, what happened to the remaining 1 mg?
2. Glucose is metabolized to CO_2 and water. Explain the effect of glucose metabolism on mass balance in the body.

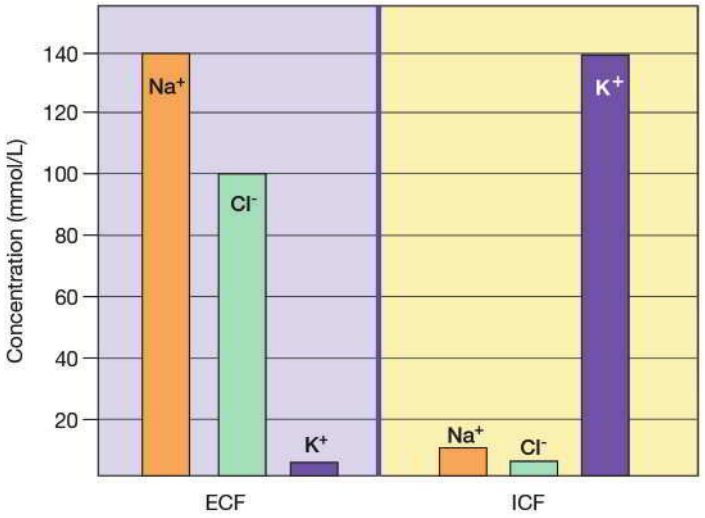
Homeostasis Does Not Mean Equilibrium

When physiologists talk about homeostasis, they are speaking of the stability of the body's **internal environment**—in other words, the stability of the extracellular fluid compartment (ECF). One reason for focusing on extracellular fluid homeostasis is that it is relatively easy to monitor by taking a blood sample. When you centrifuge blood, it separates into two parts: **plasma,** the fluid component, plus the heavier blood cells. Plasma is part of the extracellular fluid compartment, and its composition can be easily analyzed. It is much more difficult to follow what is taking place in the intracellular fluid compartment (ICF), although cells do maintain *cellular homeostasis*.

Fig. 1.8 Steady-state disequilibrium

Steady-state disequilibrium

The body compartments are in a dynamic steady state but are not at equilibrium. Ion concentrations are very different in the extracellular fluid compartment (ECF) and the intracellular fluid compartment (ICF).



In a state of homeostasis, the composition of both body compartments is relatively stable. This condition is a dynamic **steady state.** The modifier *dynamic* indicates that materials are constantly moving back and forth between the two compartments. In a steady state, there is no *net* movement of materials between the compartments.

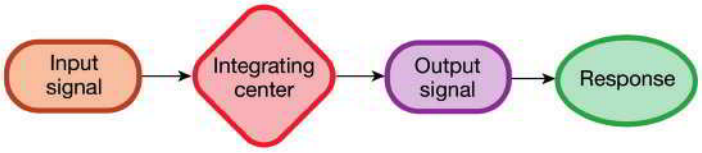
Steady state is not the same as **equilibrium** {*aequus*, equal + *libra*, balance}, however. Equilibrium implies that the composition of the body compartments is identical. If we examine the composition of the ECF and ICF, we find that the concentrations of many substances are different in the two compartments (**FIG. 1.8**). For example, sodium (Na^+) and chloride (Cl^-) are far more concentrated in the ECF than in the ICF, while potassium (K^+) is most concentrated in the ICF. Because of these concentration differences, the two fluid compartments are not at equilibrium. Instead the ECF and ICF exist in a state of relatively stable **disequilibrium** {*dis-* is a negative prefix indicating the opposite of the base noun}. For living organisms, the goal of homeostasis is to maintain the dynamic steady states of the body's compartments, not to make the compartments the same.

1.5 Control Systems and Homeostasis

In their simplest form, all **control systems** have three components (**FIG. 1.9**): (1) an input signal; (2) a controller, or **integrating center** {*integrare*, to restore}, that integrates incoming information and initiates an appropriate response; and (3) an output signal that creates a response. Long-distance reflex control systems are more complex than this simple model, however, as they may include input from multiple sources and have output that acts on multiple targets.

Fig. 1.9 A simple control system

A simple control system



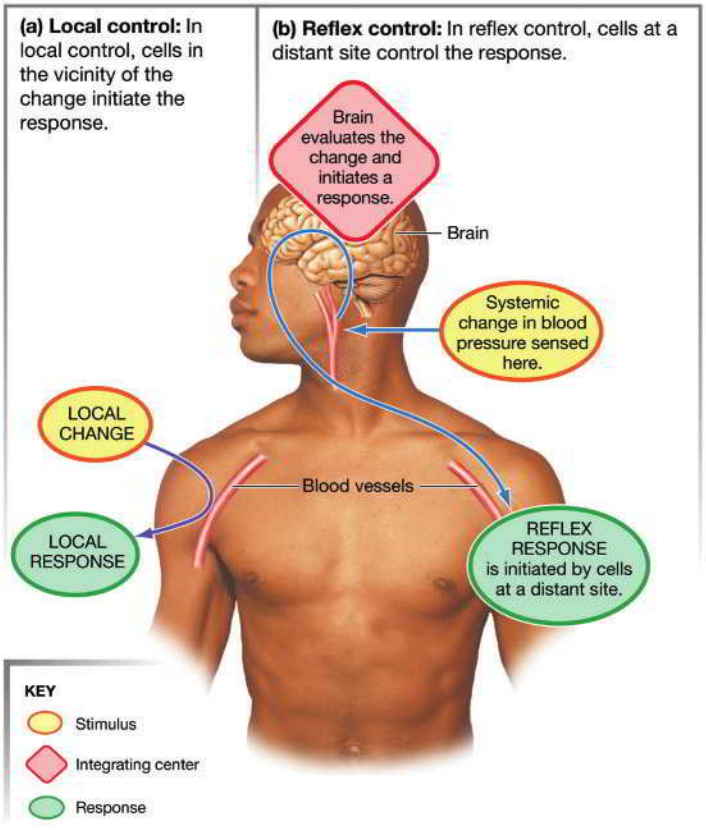
Local Control Is Restricted to a Tissue

The simplest form of control is **local control,** which is restricted to the tissue or cell involved (**FIG. 1.10**). In local control, a relatively isolated change occurs in a tissue. A nearby cell or group of cells senses the change in their immediate vicinity and responds, usually by releasing a chemical. The response is restricted to the region where the change took place—hence the term *local control*.

One example of local control can be observed when oxygen concentration in a tissue decreases. Cells lining the small blood vessels that bring blood to the area sense the lower oxygen concentration and respond by secreting a chemical signal. The signal molecule diffuses to nearby muscles in the blood vessel

Fig. 1.10 Local control and reflex control

A comparison of local control and reflex control



wall, bringing them a message to relax. Relaxation of the muscles widens (*dilates*) the blood vessel, which increases blood flow into the tissue and brings more oxygen to the area.

Reflex Control Uses Long-Distance Signaling

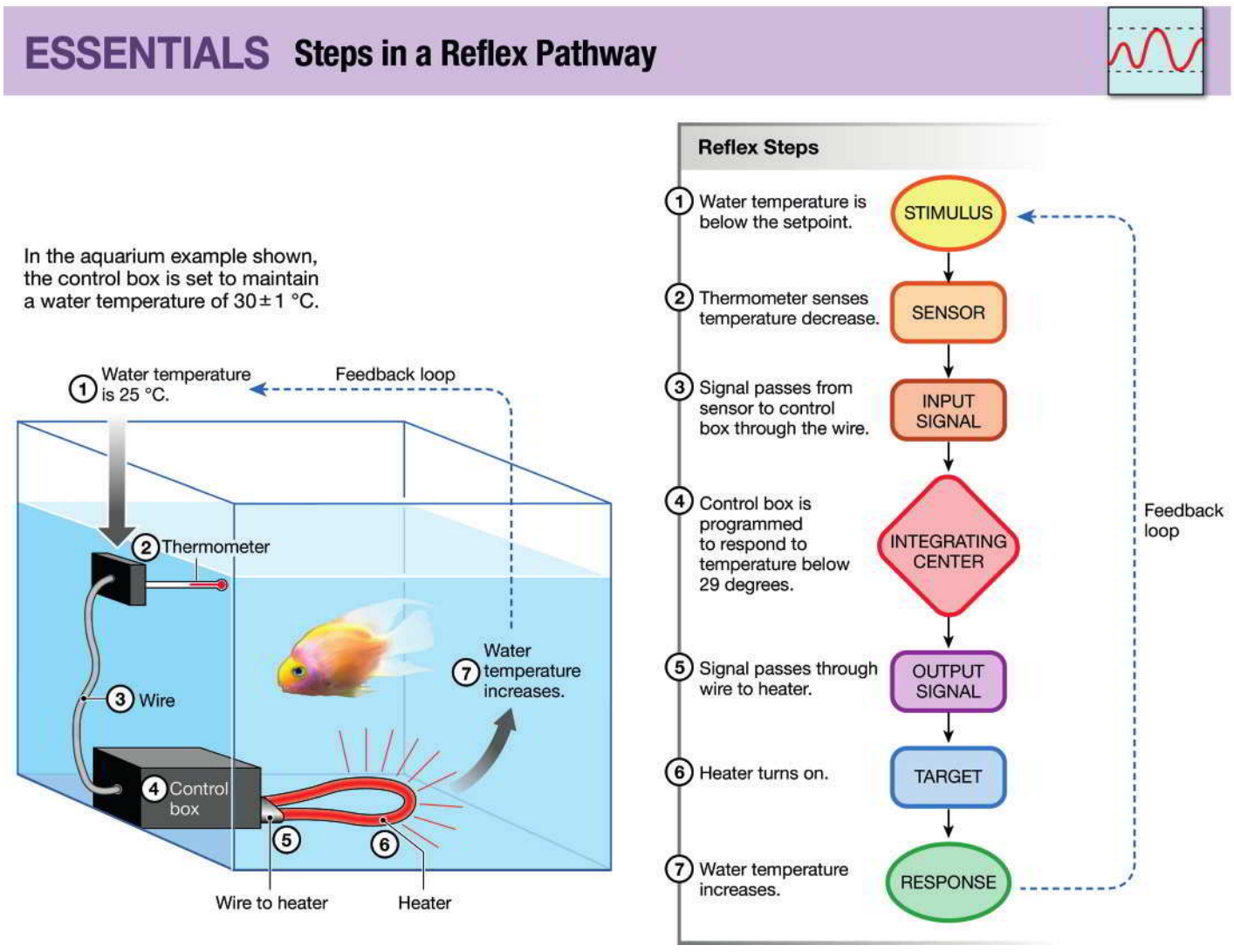
Changes that are widespread throughout the body, or *systemic* in nature, require more complex control systems. For example, maintaining blood pressure to drive blood flow throughout the body is a systemic issue rather than a local one. Because blood pressure is body-wide, maintaining it requires long-distance communication and coordination. We will use the term **reflex control** to mean any long-distance pathway that uses the nervous system, endocrine system, or both. Chapter 6 discusses different reflex pathways in more detail. It is important to note that not all reflexes are homeostatic! For example, the knee jerk reflex (patellar tendon reflex), where your lower leg kicks out after a tap just below the kneecap, is a reflex but it has nothing to do with homeostasis.

Physiological reflexes can be represented by response loops (**FIG. 1.11**). As with the simple control system just described, a **response loop** has three primary components: an *input signal*, an *integrating center* to integrate the signal, and an *output signal*. These three components can be expanded into the following sequence of seven steps to form a pattern that is found with slight variations in all reflex pathways:

Stimulus → sensor → input signal → integrating center → output signal → target → response

The input side of the response loop starts with a *stimulus*—the change that occurs when the regulated variable moves out of its desirable range. A specialized **sensor** monitors the variable. If the sensor is activated by the stimulus, it sends an input signal to the integrating center. The integrating center evaluates the information coming from the sensor and initiates an output signal. The output signal directs a target to carry out a response.

Fig. 1.11 The steps in a reflex pathway



In mammals, integrating centers are usually part of the nervous system or endocrine system. Output signals may be chemical signals, electrical signals, or a combination of both. The targets activated by output signals can be any cell of the body. If the reflex ends with the response, such as the knee-jerk reflex, the reflex is considered an **open-loop control system**. Open response loops are not homeostatic. A *closed-loop control system* has **feedback**, where the pathway's response "feeds back" to inform the sensor that a change has occurred. You will encounter both open and closed response loops as you study physiology, but homeostasis requires closed response loops with negative feedback.

Homeostasis Requires Monitored Variables

To maintain homeostasis, the human body monitors certain key functions, such as blood pressure and blood glucose concentration, that must stay within a particular operating range if the body is to remain healthy (Tbl. 1.1). These important **regulated variables** (monitored variables) are kept within their acceptable (normal) range by long-distance reflex control mechanisms that kick in if the variable ever strays too far from its **setpoint**, or preferred value.

To illustrate closed response loops and homeostasis, let's apply the concept to a simple nonbiological example. Think about an aquarium whose heater is programmed to maintain the water temperature (the regulated variable) at 30 °C (Fig. 1.11). The room temperature is 25 °C. The desired water temperature (30 °C) is the *setpoint* for the regulated variable.

Assume that initially the aquarium water is at room temperature, 25 °C. When you turn the control box on, you set the response loop in motion. The thermometer (sensor) registers a temperature of 25 °C. It sends this information through a wire (input signal) to the control box (integrating center). The control box is programmed to evaluate the incoming temperature signal, compare it with the setpoint for the system (30 °C), and "decide" whether a response is needed to bring the water temperature up to the setpoint. The control box sends a signal through another wire (output signal) to the heater (the target), which turns on and starts heating the water (response). This sequence—from stimulus to response—is the response loop.

This aquarium example involves a variable (temperature) controlled by a single control system (the heater). We can also describe a system that is under dual control. For example, think of a house that has both heating and air conditioning. The owner would like the house to remain at 70 °F (about 21 °C). On chilly autumn mornings, when the temperature in the house falls, the heater turns on to warm the house. Then, as the day warms up, the heater is no longer needed and turns off. When the sun heats the house above the setpoint, the air conditioner turns on to cool the house back to 70 °F. The heater and air conditioner have *antagonistic control* over house temperature because they work in opposition to each other. Similar situations occur in the human body when two branches of the nervous system or two different hormones have opposing effects on a single target.

Concept Check

3. What is the drawback of having only a single control system (a heater) for maintaining aquarium water temperature in some desired range?

Feedback Loops Modulate the Response Loop

The response loop is only the first part of many reflexes. For example, in the aquarium just described, the sensor sends temperature information to the control box, which recognizes that the water is too cold. The control box responds by turning on the heater to warm the water. Once the response starts, what keeps the heater from sending the temperature up to, say, 50 °C?

The answer is a **feedback loop,** where the response "feeds back" to influence the input portion of the pathway. In the aquarium example, turning on the heater increases the temperature of the water. The sensor continuously monitors the temperature and sends that information to the control box. When the control box gets feedback that the temperature has warmed up to the maximum acceptable value, it shuts off the heater, ending the reflex response.

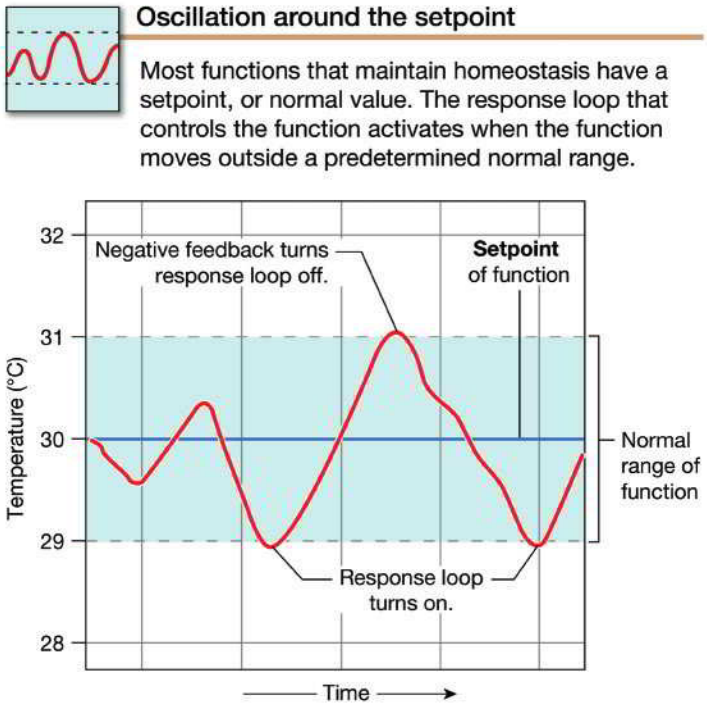
Negative Feedback Loops Are Homeostatic

For most reflexes, feedback loops are homeostatic—that is, designed to keep the system at or near a setpoint so that the regulated variable is relatively stable. How well an integrating center succeeds in maintaining stability depends on the *sensitivity* of the system. In the case of our aquarium, the control box is programmed to have a sensitivity of ±1 °C. If the water temperature drops from 30 °C to 29.5 °C, it is still within the acceptable range, and no response occurs. If the water temperature drops below 29 °C (30 − 1), the control box turns the heater on (**FIG. 1.12**). As the water heats up, the control box constantly receives information about the water temperature from the sensor. When the water reaches 31 °C (30 ± 1), the upper limit for the acceptable range, the feedback loop causes the control box to turn the heater off. The water then gradually cools off until the cycle starts all over again. The end result is a regulated variable that *oscillates* {*oscillare*, to swing} around the setpoint.

In physiological systems, some sensors are more sensitive than others. For example, the sensors that trigger reflexes to conserve water activate when blood concentration increases only 3% above the acceptable range, but the sensors for low oxygen in the blood will not respond until oxygen has decreased by 40%.

A pathway in which the response opposes or removes the signal is known as **negative feedback** (**FIG. 1.13a**). Negative feedback loops *stabilize* the regulated variable and thus aid the system in maintaining homeostasis. In the aquarium example, the heater warms the water (the response) and removes the

Fig. 1.12 Oscillation around the setpoint



stimulus (low water temperature). With loss of the stimulus for the pathway, the response loop shuts off. *Negative feedback loops can restore the usual state but cannot prevent the initial disturbance.*

Positive Feedback Loops Are Not Homeostatic

A few reflex pathways are not homeostatic. In a **positive feedback loop,** the response *reinforces* the stimulus rather than decreasing or removing it. In positive feedback, the response sends the regulated variable even farther from its usual value. This initiates a vicious cycle of ever-increasing response and sends the system temporarily out of control (Fig. 1.13b). Because positive feedback escalates the response, this type of feedback requires some intervention or event outside the loop to stop the response.

One example of a positive feedback loop involves the hormonal control of uterine contractions during childbirth (**FIG. 1.14**). When the baby is ready to be delivered, it drops lower in the uterus and begins to put pressure on the *cervix,* the opening of the uterus. Sensory signals from the cervix to the brain cause release of the hormone *oxytocin,* which causes the uterus to contract and push the baby's head even harder against the cervix, further stretching it. The increased stretch causes more oxytocin release, which causes more contractions that push the baby harder against the cervix. This cycle continues until finally the baby is delivered, releasing the stretch on the cervix and stopping the positive feedback loop.

Concept Check

4. Does the aquarium heating system in Figure 1.11 operate using positive feedback or negative feedback?

Feedforward Control Allows the Body to Anticipate Change

Negative feedback loops can stabilize a function and maintain it within an acceptable range but are unable to prevent the change that triggered the reflex in the first place. A few reflexes have evolved that enable the body to predict that a change is about to occur and start the response loop in anticipation of the change. These anticipatory responses are called **feedforward control.**

Fig. 1.13 Negative and positive feedback

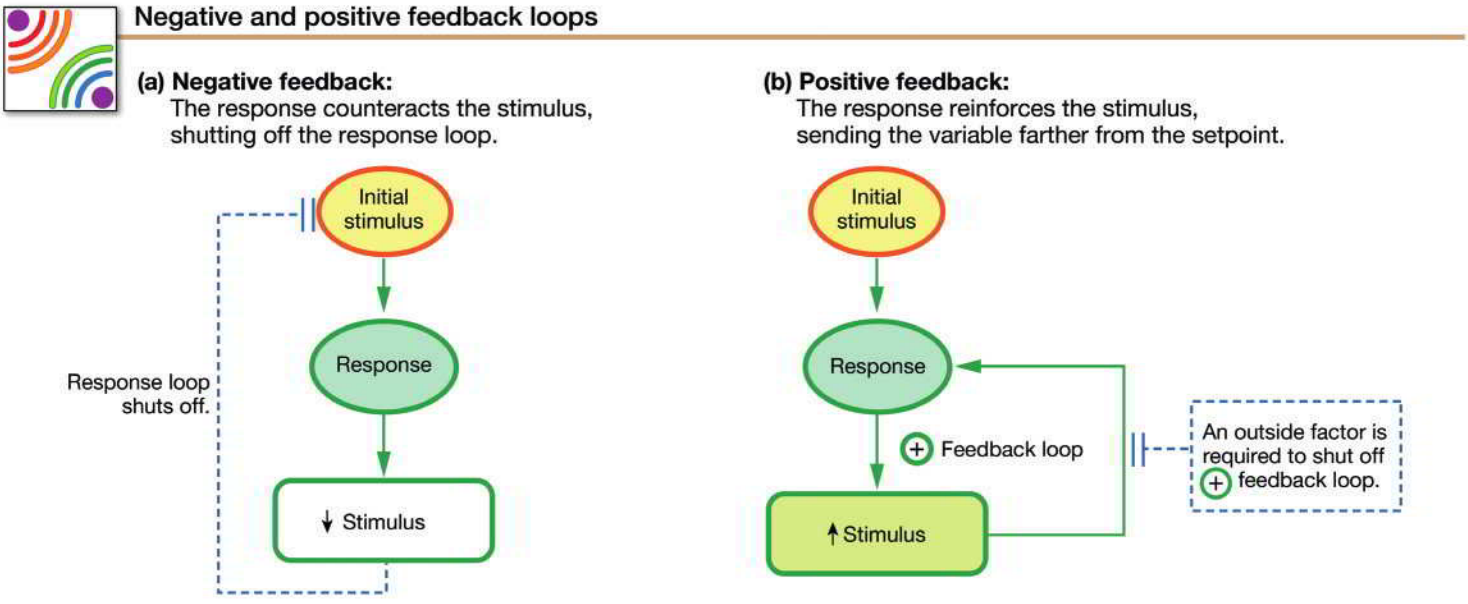
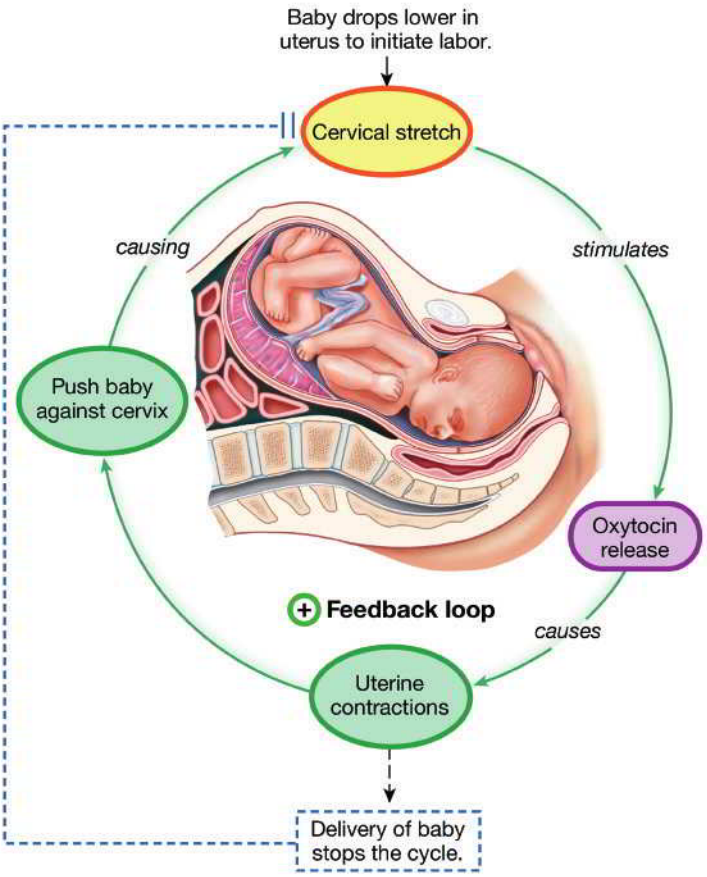


Fig. 1.14 A positive feedback loop



An easily understood physiological example of feedforward control is the salivation reflex. The sight, smell, or even the thought of food is enough to start our mouths watering in expectation of eating the food. This reflex extends even further, because the same stimuli can start the secretion of hydrochloric acid as the stomach anticipates food on the way. One of the most complex feedforward reflexes appears to be the body's response to exercise discussed in Chapter 25.

Biological Rhythms Result from Changes in a Setpoint

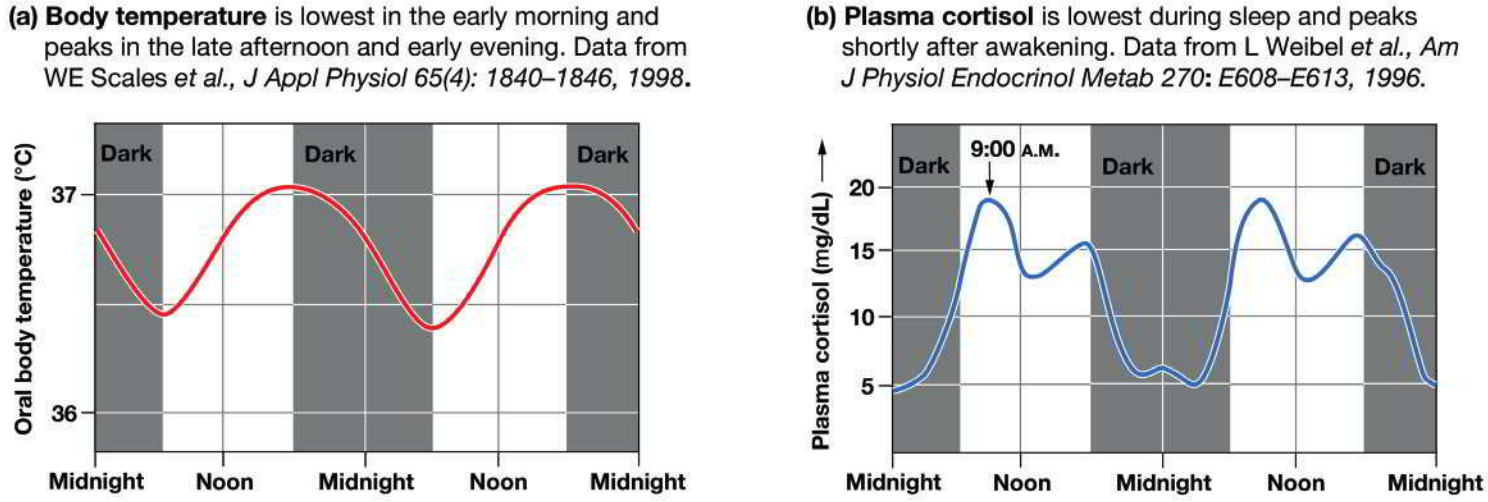
As discussed earlier, each regulated variable has an acceptable range within which it can vary without triggering a correction. In physiological systems, the setpoints for many regulated variables are different from person to person, or may change for the same individual over a period of time. Factors that influence an individual's setpoint for a given variable include normal biological rhythms, inheritance, and the conditions to which the person has become accustomed.

Regulated variables that change predictably and create repeating patterns or cycles of change are called **biological rhythms**, or *biorhythms*. The timing of many biorhythms coincides with a predictable environmental change, such as daily light–dark cycles or the seasons. Biological rhythms reflect changes in the setpoint of the regulated variable.

For example, all animals exhibit some form of daily biological rhythm, called a **circadian rhythm** {*circa*, about + *dies*, day}. Humans have circadian rhythms for many body functions, including blood pressure, body temperature, and metabolic processes. For example, body temperature peaks in the late afternoon and declines dramatically in the early hours of the morning (**FIG. 1.15a**). Have you ever been studying late at night and noticed that you feel cold? This is not because of a drop in environmental temperature but because your thermoregulatory reflex has turned down your internal thermostat.

One of the interesting correlations between circadian rhythms and behavior involves body temperature. Researchers found that self-described "morning people" have temperature rhythms that cause body temperature to climb before they wake

Fig. 1.15 Circadian rhythms in humans



up in the morning, so that they get out of bed prepared to face the world. On the other hand, "night people" may be forced by school and work schedules to get out of bed while their body temperature is still at its lowest point, before their bodies are prepared for activity. These night people are still going strong and working productively in the early hours of the morning, when the morning people's body temperatures are dropping and they are fast asleep.

Many hormones in humans have blood concentrations that fluctuate predictably in a 24-hour cycle. Cortisol, growth hormone, and the sex hormones are among the most noted examples. A cortisol concentration in a 9:00 AM sample might be nearly twice as high as one taken in the early afternoon (Fig. 1.15b).

If a patient has a suspected abnormality in hormone secretion, it is therefore important to know when hormone levels are measured. A concentration that is normal at 9:00 AM is high at 2:00 PM. One strategy for avoiding errors due to circadian fluctuations is to collect information for a full day and calculate an average value over 24 hours. For example, cortisol secretion is estimated indirectly by measuring all urinary cortisol metabolites excreted in 24 hours.

What is the adaptive significance of functions that vary with a circadian rhythm? Our best answer is that biological rhythms create an anticipatory response to a predictable environmental variable. There are seasonal rhythms of reproduction in many organisms. These rhythms are timed so that the offspring have food and other favorable conditions to maximize survival.

Circadian rhythms cued by the light–dark cycle may correspond to rest-activity cycles. These rhythms allow our bodies to anticipate behavior and coordinate body processes accordingly. You may hear people who are accustomed to eating dinner at 6:00 PM say that they cannot digest their food if they wait until 10:00 PM to eat because their digestive system has "shut down" in anticipation of going to bed.

Some variability in setpoints is associated with changing environmental conditions rather than biological rhythms. The adaptation of physiological processes to a given set of environmental conditions is known as **acclimatization** when it occurs naturally. If the process takes place artificially in a laboratory setting, it is called **acclimation**. Each winter, people in the upper latitudes of the northern hemisphere go south in February, hoping to escape the bitter subzero temperatures and snows of the northern climate. As the northerners walk around in 40 °F (about 4 °C) weather in short-sleeve shirts, the southerners, all bundled up in coats and gloves, cannot understand why: the weather is cold! The difference in behavior is due to different temperature acclimatization, a difference in the setpoint for body temperature regulation that is a result of prior conditioning.

Biorhythms and acclimatization are complex processes that scientists still do not completely understand. Some rhythms arise from special groups of cells in the brain and are reinforced by information about the light–dark cycle that comes in through the eyes. Some organs outside the nervous system generate their own rhythms of protein synthesis and breakdown. Research in simpler animals such as flies is helping explain the molecular basis for biological rhythms. We discuss the cellular and molecular basis for circadian rhythms in Chapter 10.

Running Problem 1.5

Most of the articles Hiro found in PubMed and Google Scholar seemed to be focused on detailed descriptions of experiments. "Is there any way to find papers that are not so complicated?" he asked Jennifer.

"Well, when I'm trying to learn about a new topic, I look for review articles, which are summaries of recent research. Both Google Scholar and PubMed have options that let you limit your results to show only review articles." Hiro went back to PubMed and Google Scholar to see if this would help him find the information he was looking for.

Jennifer had also mentioned using artificial intelligence to answer the question. "But you need to be cautious and always verify what an AI program tells you." Hiro went to ChatGPT (chat.openai.com) and typed "What does research say about taking probiotics?"

Q6: *On the Google Scholar and PubMed pages with results from the last 5 years, select the option for review articles. Now how many results are there?*

Q7: *Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*

1.6 The Science of Physiology

How do we know what we know about the physiology of the human body? The first descriptions of physiology came from simple observations. But physiology is an experimental science, one in which researchers generate **hypotheses** {*hypotithenai*, to assume; singular *hypothesis*}, or logical guesses, about how events take place. They test their hypotheses by designing experiments to collect evidence that supports or disproves their hypotheses, and they publish the results of their experiments in the scientific literature. Healthcare providers look in the scientific literature for evidence from these experiments to help guide their clinical decision-making. Critically evaluating the scientific evidence in this manner is a practice known as *evidence-based medicine*. Observation and experimentation are the key elements of **scientific inquiry.**

Good Scientific Experiments Must Be Carefully Designed

A common type of biological experiment either removes or alters some variable that the investigator thinks is an essential part of an observed phenomenon. That altered variable is the **independent variable.** For example, a biologist notices that birds at a feeder seem to eat more in the winter than in the summer. She generates a hypothesis that cold temperatures cause birds to increase their food intake. To test her hypothesis, she designs an experiment in

which she keeps birds at different temperatures and monitors how much food they eat. In her experiment, temperature, the manipulated element, is the independent variable. Food intake, which is hypothesized to be dependent on temperature, becomes the **dependent variable.**

Concept Check

5. Students in the laboratory run an experiment in which they drink different volumes of water and measure their urine output in the hour following drinking. What are the independent and dependent variables in this experiment?

An essential feature of any experiment is an experimental **control.** A control group is usually a duplicate of the experimental group in every respect except that the independent variable is not changed from its initial value. Ideally, all other conditions are kept identical in the control and experimental groups, and those factors are considered **controlled variables**. For example, in the bird-feeding experiment, the control group would be a set of birds maintained at a warm summer temperature but otherwise treated exactly like the birds held at cold temperatures. The purpose of the control group is to ensure that any observed changes are due to the manipulated variable and not to changes in some other variable. For example, suppose that in the bird-feeding experiment food intake increased after the investigator changed to a different food. Unless she had a control group that was also fed the new food, the investigator could not determine whether the increased food intake was due to temperature or to the fact that the new food was more palatable. The type of food fed to the birds would be a controlled variable.

During an experiment, the investigator carefully collects information, or **data** {plural; singular *datum*, a thing given}, about the effect that the manipulated (independent) variable has on the observed (dependent) variable. Once the investigator feels that she has sufficient information to draw a conclusion, she begins to analyze the data. Analysis can take many forms and usually includes statistical analysis to determine if apparent differences are statistically significant. A common format for presenting data is a graph (**FIG. 1.16**).

If one experiment supports the hypothesis that cold causes birds to eat more, then the experiment should be repeated to ensure that the results were not an unusual one-time event. This step is called **replication.** When the data support a hypothesis in multiple experiments, the hypothesis may become a working **model.** A model with substantial evidence from multiple investigators supporting it may become a **scientific theory.**

Most information presented in textbooks like this one is based on models that scientists have developed from the best available experimental evidence. On occasion, investigators publish new experimental evidence that does not support a current model. In that case, the model must be revised to fit the available evidence. For this reason, you may learn a physiological "fact" while using this textbook, but in 10 years that "fact" may be inaccurate because of what scientists have discovered in the interval.

For example, in 1970, students learned that the cell membrane was a "butter sandwich," a structure composed of a layer of fats sandwiched between two layers of proteins. In 1972, however, scientists presented a very different model of the membrane, in which globules of proteins float within a double layer of fats. As a result, students who had learned the butter sandwich model had to revise their mental model of the membrane.

Where do our scientific models for human physiology come from? We have learned much of what we know from experiments on animals ranging from fruit flies and squid to rats. In many instances, the physiological processes in such animals are either identical to those taking place in humans or else similar enough that we can extrapolate from the animal model to humans. It is important to use nonhuman models because experiments using human subjects can be difficult to perform.

However, not all studies done on animals can be applied to humans. For example, an antidepressant drug that Europeans had used safely for years was undergoing stringent testing required by the U.S. Food and Drug Administration before it could be sold in this country. When beagle dogs were given the drug for a period of months, the dogs started dying from heart problems. Scientists were alarmed until further research showed that beagles have a unique genetic makeup that causes them to break down the drug into a more toxic substance. The drug was perfectly safe in other breeds of dogs and in humans, and it was subsequently approved for human use.

The Results of Human Experiments Can Be Difficult to Interpret

Many reasons make it difficult to carry out physiological experiments in humans, including variability, psychological factors, and ethical considerations.

Variability

Human populations have tremendous genetic and environmental **variability.** It has been traditional in medicine to talk about "normal values" for body functions, but what is "normal" for one person may not be "normal" for someone else. When possible, it is better to use the word *typical* or *healthy* although you will still encounter *normal* in tables and discussions of variables that can be quantified, such as blood glucose concentrations. Physiology books usually present *average* values for many physiological variables, such as blood pressure, but these average values simply represent a number that falls somewhere near the middle of a wide range of values.

The variability found in human populations can make it difficult to show significant differences between experimental and control groups in a human experiment. Ideally, an investigator would have to include a large number of identical subjects in a study. However, getting two groups of people who are *identical* in every respect is impossible. Instead, the researcher must attempt to recruit subjects who are *similar* in as many aspects as possible. You may have seen newspaper advertisements requesting research volunteers: "Healthy males between 18 and 25,

Fig. 1.16 Focus on . . . Graphing

Focus on . . . Graphing

Graphs are pictorial representations of the relationship between two (or more) variables, plotted in a rectangular region. Graphs present a large amount of numerical data in a small space, emphasize comparisons between variables, or show trends over time.

A viewer can extract information much more rapidly from a graph than from a table of numbers or from a written description. A well-constructed graph should contain (in very abbreviated form) everything the reader needs to know about the data, including the purpose of the experiment, how the experiment was conducted, and the results.

All scientific graphs have common features.

The horizontal axis is called the **x-axis**.

The vertical axis is called the **y-axis**.

The intersection of the two axes is called the **origin**. The origin usually, but not always, has a value of zero for both axes.

The simplest way to know what most graphs mean is the substitute the labels on the X and Y axes into the following sentence:

The effect of [X] on [Y]

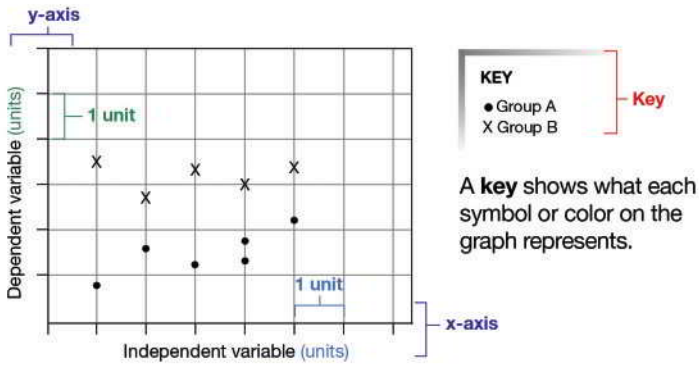
The x-axis shows values of the variable manipulated by the experimenter. This is called the **independent variable**.

The y-axis shows the variable measured by the experimenter. It is called the **dependent variable**.

If the experimental design is valid and the hypothesis is correct, changes in the independent variable (x-axis) will cause changes in the dependent variable (y-axis).

In other words, y is a function of x, or mathematically, y = f(x).

A graph should have a **title** (usually put above the graph) or **legend** below the graph. These describe what the graph represents.



A **key** shows what each symbol or color on the graph represents.

Each axis of a graph is divided into units represented by evenly spaced tick marks on the axis.

Each axis has a label that tells

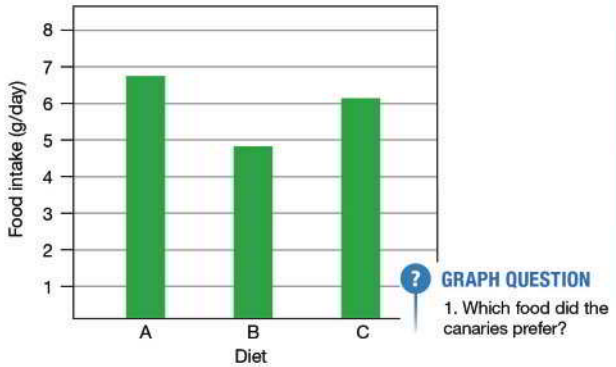
- what variable the axis represents (time, temperature, amount of food consumed)
- the units of the axis (days, degrees Celsius, grams per day).

Most graphs you will encounter in physiology display data either as bars (bar graphs or histograms), as lines (line graphs), or as dots (scatter plots). Some typical types of graphs are shown here.

Here's one approach to reading graphs:

1. Read the title and legend. These are a capsule summary of the graph's contents.
2. Read the axis labels and put them into the sentence
   The effect of [X] on [Y].
3. Look for trends in the graph. Are lines horizontal or do they have a slope? Are bars the same height or different heights?

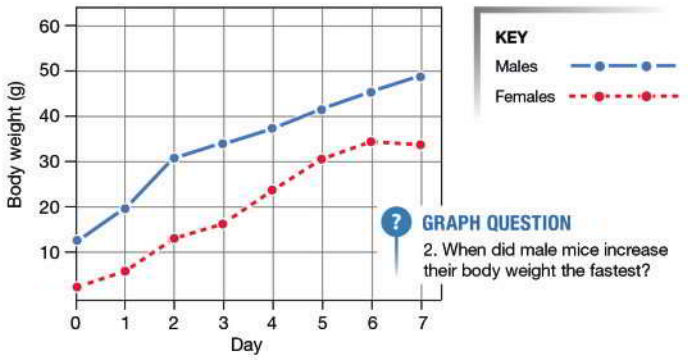
Bar graphs are used when the independent variables are distinct entities. Each bar represents a different variable. The bars are lined up side by side so that they can easily be compared with one another. Scientific bar graphs traditionally have vertical bars.



Canaries were fed one of three diets and their food intake was monitored for three weeks.

Line graphs are used when the independent variable on the x-axis is a continuous phenomenon, such as time, temperature, or weight.

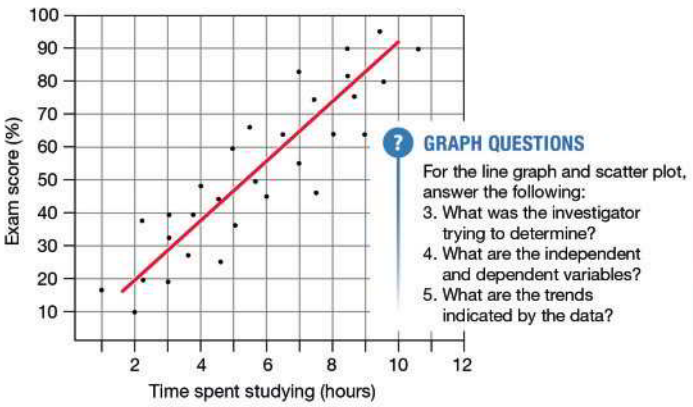
- Each point on the graph represents the average of a set of observations.
- Because the independent variable is a continuous function, the points can be connected with a line (point-to-point connections or a mathematically calculated "best fit" line or curve).
- The slope of the line between two points represents the rate at which the variable changed.
- Connecting the points with lines allows the reader to **interpolate**, or estimate values between the measured values.



Male and female mice were fed a standard diet and weighed daily.

Scatter plots show the relationship between two variables, such as time spent studying for an exam and performance on that exam.

- Usually each point on the plot represents one member of a test population.
- Individual points on a scatter plot are never connected by a line, but a "best fit" line or curve may indicate a trend in the data.



Student scores were directly related to the amount of time they spent studying.

Try It!

Graphing

Students in a physiology laboratory collected heart rate data on one another. In each case, heart rate was measured first for the subject at rest and again after the subject had exercised for 5 minutes using a step test.

Data from the experiment are shown in the table.

Subject	Sex	Age	Resting heart rate (beats/min)	Post exercise heart rate (beats/min)
1	M	20	58	90
2	M	21	62	110
3	F	19	70	111
4	M	20	64	95
5	F	20	85	120
6	F	19	72	98
7	F	21	73	101

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Describe two observations you can make from the data.

(c) Draw one graph that illustrates both findings you described in (b). Label each axis with the correct variable.

(*Hint:* Excel is a simple way to make graphs from data in tables. Excel calls graphs "charts.")

nonsmokers, within 10% of ideal body weight, to participate in a study. . . .” Researchers must take into account the variability inherent in even a select group of humans when doing experiments with human subjects. This variability may affect the researcher’s ability to interpret the significance of data collected on that group.

One way to reduce variability within a test population, whether human or animal, is to do a **crossover study.** In a crossover study, each individual acts both as experimental subject and as control. Thus, the individual’s responses to the treatment can be compared to the same subject's control value. This method is particularly effective when there is wide variability within a population.

For example, in a test of blood pressure medication, investigators might divide subjects into two groups. Group A takes an inactive substance called a **placebo** (from the Latin for “I shall be pleasing”) for the first half of the experiment, then changes to the experimental drug for the second half. Group B starts with the experimental drug, and then changes to the placebo. This scheme enables the researcher to assess the effect of the drug on each individual. In other words, subjects act as their own control. Statistically, the data analysis can use methods that look at the changes within each individual rather than at changes in the collective group data.

Psychological Factors

Another significant variable in human studies is the psychological aspect of administering a treatment. If you give someone a pill and tell the person that it will help alleviate some problem, there is a strong possibility that the pill will have exactly that effect, even if it contains only sugar or an inert substance. This well-documented phenomenon is called the **placebo effect.** Similarly, if you warn people that a drug they are taking may have specific adverse side effects, those people will report a higher incidence of the side effects than a similar group of people who were not warned. This phenomenon is called the **nocebo effect,** from the Latin *nocere,* to do harm. The placebo and nocebo effects show the ability of our minds to alter the physiological functioning of our bodies.

In setting up an experiment with human subjects, we must try to control for the placebo and nocebo effects. The simplest way to do this is with a **blind study,** in which the subjects do not know whether they are receiving the treatment or the placebo. Even this precaution can fail, however, if the researchers assessing the subjects know which type of treatment each subject is receiving. The researchers’ expectations of what the treatment will or will not do may color their measurements or interpretations.

To avoid this outcome, researchers often use **double-blind studies.** A third party, not involved in the experiment, is the only one who knows which group is receiving the experimental treatment and which group is receiving the control treatment. The most sophisticated experimental design for minimizing psychological effects is the **double-blind crossover study.** In this type of study, the control group in the first half of the experiment becomes the experimental group in the second half, and vice versa, but no one involved knows who is taking the active treatment.

Ethical Considerations

Ethical questions arise when humans are used as experimental subjects, particularly when the subjects are people suffering from a disease or other illness. Is it ethical to withhold a new and promising treatment from the control group? A noteworthy example occurred some years ago when researchers were testing the efficacy of a treatment for dissolving blood clots in heart attack victims. The survival rate among the treated patients was so much higher that testing was halted so that members of the control group could also be given the experimental drug.

In contrast, tests on some anticancer agents have shown that the experimental treatments were less effective in stopping the spread of cancer than were the standard treatments used by the controls. Was it ethical to undertreat patients in the experimental group by depriving them of the more effective current medical practice? Most studies now are evaluated continually over the course of the study to minimize the possibility that subjects will be harmed by their participation.

In 2002, a trial on hormone replacement therapy in postmenopausal women was halted early when investigators realized that women taking a pill containing two hormones were developing cardiovascular disease and breast cancer at a higher rate than women on placebo pills. On the other hand, the women receiving hormones also had *lower* rates of colon cancer and bone fractures. The investigators performed a *risk-benefit analysis* and decided that the risks associated with taking the hormones exceeded the potential benefits, so they stopped the study. To learn more about this clinical trial and the pros and cons of hormone replacement therapy, visit MedlinePlus, a website of the U.S. National Library of Medicine.

Human Studies Can Take Many Forms

Almost daily, the newspapers carry articles about clinical trials studying the efficacy of drugs or other medical treatments. Many different aspects of experimental design can affect the validity and applicability of the results of these trials. For example, some trials are carried out for only a limited time on a limited number of people, such as studies conducted for the U.S. Food and Drug Administration’s drug-approval process. In several instances in recent years, drugs approved as a result of such studies have later been withdrawn from the market when extended use of the drug by larger populations uncovered adverse side effects, including deaths.

Longitudinal studies are designed to be carried out for a long period of time. One of the most famous longitudinal studies is the Framingham Heart Study, started in 1948 and still ongoing. Framingham is a **prospective study** {*prospectus*, outlook, looking forward} that recruited healthy people and has been following them for years to identify factors that contribute to the development of cardiovascular disease. This study has already made important contributions to healthcare, and it continues today with the adult children and grandchildren of the original participants.

Additional study designs you may encounter in the literature include cross-sectional and retrospective studies. **Cross-sectional studies** survey a population for the prevalence of a disease or condition. Data from cross-sectional studies identify trends to be

investigated further, such as whether age group or socioeconomic status is associated with a higher risk of developing the condition being surveyed. **Retrospective studies** {*retro*, backward + *spectare*, to look} match groups of people who all have a particular disease to a similar but healthy control group. The goal of these studies is to determine whether development of the disease can be associated with a particular variable.

Often, the results of one or more published studies do not agree with the conclusions of other published studies. In some cases, the reason for the disagreement turns out to be a limitation of the experimental design, such as a small number of subjects who may not be representative of larger populations. In other cases, the disagreement may be due to small but potentially significant differences in the experimental designs of the different studies.

One way scientists attempt to resolve contradictory results is to perform a **meta-analysis** of the data {*meta-*, at a higher level}. A meta-analysis combines all the data from a group of similar studies and uses sophisticated statistical techniques to extract significant trends or findings from the combined data. For example, multiple studies have been done to assess whether glucosamine and chondroitin, two dietary supplements, can improve degenerative joint disease. However, the individual studies had small numbers of subjects (<50) and used different dosing regimens. A meta-analysis using statistical methods is one way to compare the results from these studies.[7]

The difficulty of using human subjects in experiments is one of the reasons scientists use animals to develop many of our scientific models. Since the 1970s, physiological research has increasingly augmented animal experimentation with techniques developed by cellular biologists and molecular geneticists. As we have come to understand the fundamentals of chemical signaling and communication in the body, we have unlocked the mysteries of many processes. In doing so, we also have come closer to being able to treat many diseases by correcting their cause rather than simply treating their symptoms.

More and more, medicine is turning to therapies based on interventions at the molecular level. A classic example is the treatment of cystic fibrosis (CF), an inherited disease in which the mucus of the lungs and digestive tract is unusually thick. For many years, patients with this condition had few treatment options, and most died at a young age. However, basic research into the mechanisms by which salt and water move across cell membranes provided clues to the underlying cause of cystic fibrosis: a defective protein in the membrane of certain cells. The newest treatments for CF now improve the function of the defective protein, and life expectancy of people with CF is close to that of the general population. Without the basic research into how cells and tissues carry out their usual tasks, however, this treatment would never have been developed. Some of the most exciting therapies coming to medicine are interventions targeting gene mutations that result in disease. In late 2023, the U.S. Food and Drug Administration approved two new treatments correcting the gene mutation that causes the abnormal hemoglobin associated with sickle cell disease.

As you read this book and learn what we know about how the human body works, keep in mind that many of the ideas presented are not hard facts – they simply describe models that represent our current understanding and therefore are subject to change. As we learned during the COVID-19 pandemic, scientific knowledge is constantly and rapidly changing. There are still many questions in physiology waiting for investigators to find the answers.

Running Problem 1.6 Conclusion: What to Believe?

After reading a few of the review articles Hiro found while searching, he called Jennifer back. "Hey! Those were great suggestions, but I just need something simple. Is there some place that a nonmedical person should go to learn about probiotics?"

"I send my friends to MedlinePlus (www.medlineplus.gov) when they need basic information," Jennifer answered. Hiro repeated his search once more in MedlinePlus and found himself back where he had started, with links to the probiotics articles on the NCCIH website. "All these sites are saying we don't have enough information yet to know whether probiotics are helpful," Hiro decided.

Most people today begin their quest for information by searching the internet. Be cautious! Anyone can make a website or video and publish it on the web. There is no screening process comparable to peer review in scientific journals, and the reader of a website must decide how valid the information on the site is. Websites published by recognized universities and nonprofit organizations are likely to have good information, but you should view an article about probiotics on a health food store web page with a skeptical eye unless the article cites published peer-reviewed research.

The best websites for health information are sponsored by organizations that are part of the scientific and healthcare communities, such as the National Institutes of Health (NIH), nonprofit groups dedicated to supporting research on a particular disease (e.g., The American Diabetes Association, diabetes.org), or clinics and universities where scientists and physicians are actively investigating causes and treatments for diseases. Treat commercial websites that end in **.com* with extra caution.

Check your answers to the questions against the information in the table below.

Question		Answer and Commentary
Q1:	*Rank these 10 results from most to likely to have good information, and explain how you chose your rankings.*	1. Best: The NIH websites that are written by scientists. *www.nccih.nih.gov, www.ods.od.nih.gov* 2. *mayoclinic.org* and *health.harvard.edu* are vetted by health professionals at medical schools 3. *webmd.com* and *healthline.com* are commercial sites with the potential for bias in favor of advertisers. 4. *en.wikipedia.org*: Wikipedia is a crowd-sourced website and sometimes contains information that is not accurate. 5. *seed.com, amazon.com,* and *ritual.com* are all commercial websites whose goal is to sell products.
Q2:	*What is the mission of NCCIH?*	The ABOUT page says the mission of NCCIH is to provide authoritative, science-based information on the use, safety, and efficacy of products used in complementary and integrative healthcare practices.
Q3:	*What does NCCIH say about whether probiotics are helpful and about whether they are safe?*	The "What you need to know" factsheet[8] on probiotics includes a warning about the risks of giving probiotics to premature infants. The section on effectiveness of probiotics says that although a lot is known, there are still unanswered questions about how probiotics work and when they might be unsafe.
Q4:	*Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from his simple Google search.*	The Google Scholar search returns over 860,000 results and the PubMed search yields more than 46,000 results.
Q5:	*Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*	For the last 5 years, the Google Scholar search returns more than 32,000 results and the PubMed search has more than 23,000 results.
Q6:	*On the Google Scholar and PubMed pages with results from the last 5 years, select the option for reviews. Now how many results are there?*	For reviews in the last 5 years, the Google Scholar search has more than 21,000 results and the PubMed search has about 5,000 results.
Q7:	*Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*	The responses of an AI program might differ slightly each time a question is asked, but in January 2024, ChatGPT returned the following answer: *As of my last knowledge update in January 2022, research on probiotics was ongoing, and findings were mixed regarding their overall benefits.* The answer continued to point out that the topic is complex and that there might be more recent information based on better evidence.

Citing Resources

Whenever you use someone else's material, even if it is just for a class project, you should cite your source. If you put a photo from the web into a PowerPoint slide, be sure to include the URL. If you paraphrase something written, acknowledge where you learned the information. Copying or paraphrasing material from another source without acknowledging that source is academic dishonesty.

There are many different citation format styles. PubMed allows you to choose between AMA (American Medical Association), APA (American Psychological Association), MLA (Modern Language Association), and NLM (National Library of Medicine) styles when downloading references. Two useful websites for learning about citation styles are *Scientific Style and Format*[9], published by the Council of Science Editors, and Purdue University's Online Writing Lab, Purdue OWL (owl.purdue.edu).

Citing Web Sources

Unlike formally published resources like scientific journals, web pages are not permanent and frequently disappear or move. Here is one suggested format for citing information from a website:

Author/Editor (if known). Revision or copyright date (if available). Title of web page [Publication medium]. Publisher of webpage. *URL* [Date accessed].

Example:

Patton G (editor). 2005. Biological Journals and Abbreviations. [Online]. National Cancer Institute. *http://home.ncifcrf.gov/research/bja* [accessed April 10, 2005].

Citing Publications

Citation formats for papers in research journals vary but will usually include the following elements (with the punctuation shown):

Author(s). Article title. *Journal Name* volume (issue): inclusive pages, year of publication. DOI.

Example:

Echevarria M, Ilundain AA. Aquaporins. *J Physiol Biochem* 54(2): 107–118, 1998.

Many articles now have a unique DOI (digital object identifier) number. These are alphanumeric codes that provide a permanent link to the article on the Internet, so that even if a website changes names, you will still be able to find the article.

Helpful Hints

- If you access a published journal on the web, you should give the print citation and DOI, not the URL of the website.

- Journal names are abbreviated using standard abbreviations that you can look up online[10]. One-word titles, such as *Science,* are never abbreviated. For example, the *American Journal of Physiology* is abbreviated as *Am J Physiol*.
- Journals group their publications into volumes that correspond to a certain period of time (a year, six months, etc.). The first publication of a given volume is designated issue 1, the second is issue 2, and so on. In the citation *J Physiol Biochem* 54(2): 107–118, 1998, you know that this was volume 54, issue 2.
- Word-for-word quotations placed within quotation marks are rarely used in scientific writing.
- When paraphrasing in written work, acknowledge the source this way:

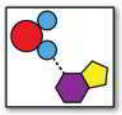
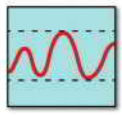
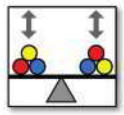
Some rare forms of epilepsy are known to be caused by mutations in ion channels (Mulley *et al*., 2003).

When a paper has three or more authors, we usually use the abbreviation *et al*.—from the Latin *et alii*, meaning "and others"—to save space in the body of the text. All authors' names are given in the full citation, which is usually included within a References section at the end of the paper.

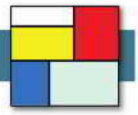
Chapter Summary

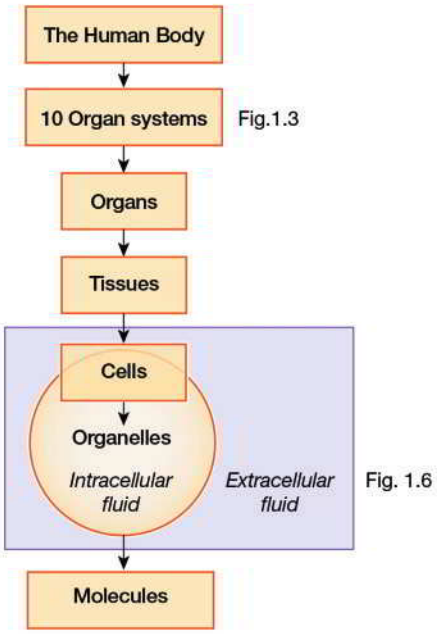
Chapter 1 has introduced you to the physiology you will be learning about as you continue through this book. The eight core concepts discussed here and in the other chapters in Unit 1 will provide you with a solid foundation for your studies.

Core Concepts in Physiology

Core Concept	Structure-function	Molecular interactions	Compartmentation	Energy	Gradients	Communication	Homeostasis	Mass balance
Icon								

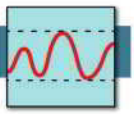
Levels of Organization





Homeostasis

Fig. 1.5

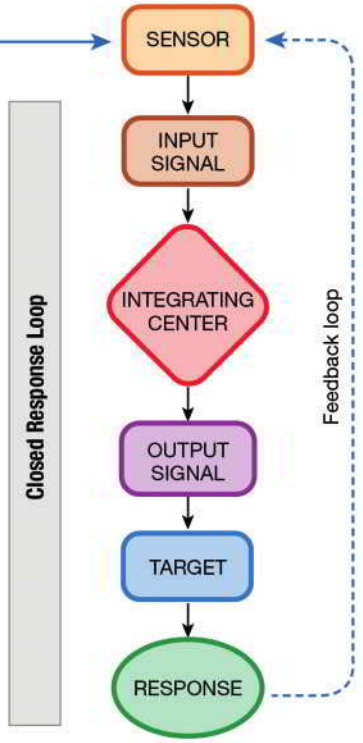


Maintenance of a relatively stable internal environment depends on

Table 1.1

10 Regulated Variables

- Some reflexes are not for homeostasis. Fig. 1.14
- Setpoints that initiate a response loop can vary. Fig. 1.15
- Negative feedback loops help maintain homeostasis. Fig. 1.11
- Positive feedback is not homeostatic. Fig. 1.13
- Feedforward reflexes anticipate a change.



Mass Balance

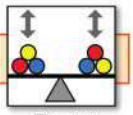
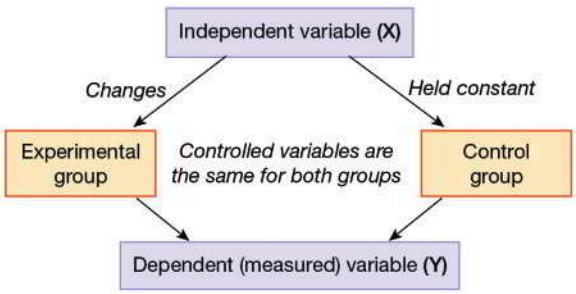


Fig. 1.7

- To maintain a steady state, input must equal output.
- Steady state is not the same as equilibrium.
- A disequilibrium can exist in a steady state. Fig. 1.8

The Science of Physiology

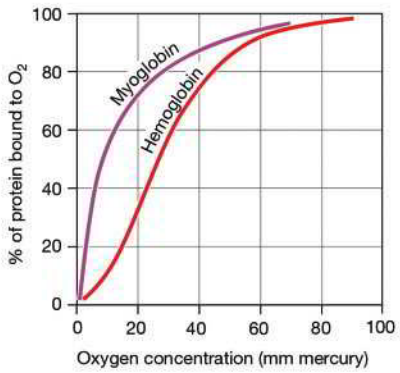
Scientific Experiments



Graphical display of data

Fig. 1.16

The effect of **X** on **Y**



Human Experiments

Complex because of

- Variability among individuals
  - What is "normal"?
- Psychological factors
  - Placebo and nocebo effects
- Ethical considerations
  - Risk-benefit analysis
  - Side effects
  - Undertreating

Types of Studies

- Blind and double-blind
- Crossover studies
- Prospective and retrospective
- Cross-sectional

Links to Resources

[1]DR Richardson. A survey of students' notions of body function as teleologic or mechanistic. *Advan Physiol Educ* 258: 8–10, Jun 1990. https://doi.org/10.1152/advances.1990.258.6.S8

[2]SR Smith et al. Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: a 6-wk translational research study. *Am J Physiol Endocrinol Metab* 293: E620–E627, 2007. https://doi.org/10.1152/ajpendo.00217.2007

[3]*Scientific Foundations for Future Physicians*. Howard Hughes Medical Institute (HHMI) and the Association of American Medical Colleges (AAMC), 2009. https://store.aamc.org/scientific-foundations-for-future-physicians-pdf.html

[4]*Vision and Change: A Call to Action*. National Science Foundation (NSF) and American Association for the Advancement of Science (AAAS). 2011.

[5]C Bernard. *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* (Vol. 1, p. 113), Paris: J.-B. Baillière, 1885. https://www.biodiversitylibrary.org/item/97313#page/151/mode/1up

[6]WB Cannon. Organization for physiological homeostasis. *Physiol Rev* 9: 399–443, 1929. nvc https://doi.org/10.1152/physrev.1929.9.3.399

[7]S Wandel et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *Br Med J* 341: c4675–c4676, 2010. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941572/

[8]*What you need to know* factsheet https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know#

[9]Scientific Style and Format https://www.scientificstyleandformat.org/Welcome.html

[10]https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/

[11]JB Moseley et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *The N Engl J Med* 347: 81–88, 2002. https://doi.org/10.1056/NEJMoa013259

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. Define physiology. Describe the relationship between physiology and anatomy.
2. Name the different levels of organization in the biosphere.
3. Name the 10 systems of the body and give their major function(s).
4. What does "Physiology is an integrative science" mean?
5. Define homeostasis. Name some regulated variables that are maintained through homeostasis.
6. Name eight core concepts in physiology.
7. Put the following parts of a reflex in the correct order for a physiological response loop: input signal, integrating center, output signal, response, sensor, stimulus, target.
8. The name for daily fluctuations of body functions such as blood pressure, temperature, and metabolic processes is a(n) _____.

Level Two Reviewing Concepts

9. **Mapping exercise:** Make a large map showing the organization of the human body. Show all levels of organization in the body (see Fig. 1.2) and all 10 organ systems. Try to include functions of all components on the map and remember that some structures may share functions. (*Hint:* Start with the human body as the most important term. You may also draw the outline of a body and make your map using it as the basis.)
10. Distinguish between the items in each group of terms.
    (a) tissues and organs
    (b) x-axis and y-axis on a graph
    (c) dependent and independent variables
    (d) teleological and mechanistic approaches
    (e) the internal and external environments for a human
    (f) blind, double-blind, and crossover studies
    (g) the target and the sensor in a control system
11. Name as many organs or body structures that connect directly with the external environment as you can.
12. Which organ systems are responsible for coordinating body function? For protecting the body from outside invaders? Which systems exchange material with the external environment, and what do they exchange?
13. Explain the differences among positive feedback, negative feedback, and feedforward mechanisms. Under what circumstances would each be advantageous?

Level Three Problem Solving

14. A group of biology majors went to a mall and asked passersby, "Why does blood flow?" These are some of the answers they received. Which answers are teleological and

which are mechanistic? (Not all answers are correct, but they can still be classified.)

(a) Because of gravity

(b) To bring oxygen and food to the cells

(c) Because if it didn't flow, we would die

(d) Because of the pumping action of the heart

15. Although dehydration is one of the most serious physiological obstacles that land animals must overcome, there are others. Think of as many as you can, and think of various strategies that different terrestrial animals have to overcome these obstacles. (*Hint:* Think of humans, insects, and amphibians; also think of as many different terrestrial habitats as you can.)

Level Four Quantitative Problems

16. A group of students wanted to see what effect a diet deficient in vitamin D would have on the growth of baby guppies. They fed the guppies a diet low in vitamin D and measured fish body length every third day for three weeks. Their data looked like this:

Day	0	3	6	9	12	15	18	21
Average body length (mm)	6	7	9	12	14	16	18	21

(a) What was the dependent variable and what was the independent variable in this experiment?

(b) What was the control in this experiment?

(c) Make a fully labeled graph with a legend, using the data in the table.

(d) During what time period was growth slowest? Most rapid? (Use your graph to answer this question.)

17. You performed an experiment in which you measured the volumes of nine slices of potato, then soaked the slices in solutions of different salinities for 30 minutes. At the end of 30 minutes, you again measured the volumes of the nine slices. The changes you found were:

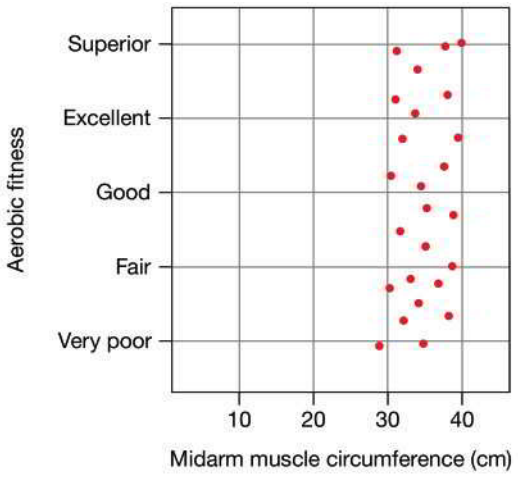
Percent Change in Volume after 30 Minutes			
Solution	**Sample 1**	**Sample 2**	**Sample 3**
Distilled water	10%	8%	11%
1% salt (NaCl)	0%	−0.5%	1%
9% salt (NaCl)	−8%	−12%	−11%

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Can you tell from the information given whether or not there was a control in this experiment? If there was a control, what was it?

(c) Graph the results of the experiment using the most appropriate type of graph.

18. At the end of the semester, researchers measured an intermediate-level class of 25 male weight lifters for aerobic fitness and midarm muscle circumference. The relationship between those two variables is graphed here.



(a) What kind of graph is this?

(b) What question were the investigators asking?

(c) In one sentence, summarize the relationship between the two variables plotted on the graph.

19. Answer the questions after the following article summary.

A study[11] was carried out on human volunteers to see whether two procedures performed during arthroscopic surgery {*arthro-*, joint + *scopium*, to look at} are effective in relieving knee pain associated with osteoarthritis, or degenerative joint disease {*osteon*, bone + *arthro* −, joint + *−itis*, inflammation}. The volunteers were up to 75 years old and were recruited from a Veterans Affairs Medical Center. They were 93% male and 60% white. One-third of the subjects had placebo operations—that is, they were given anesthesia and their knees were cut open, but the remainder of the treatment procedure was not done. The other two-thirds of the subjects had one of the two treatment procedures performed. Subjects were followed for two years. They answered questions about their knee pain and function and were given an objective walking and stair-climbing test. At the end of the study, the results showed no significant difference in knee function or perception of pain between subjects getting one of the standard treatments and those getting the placebo operation.

(a) Do you think it is ethical to perform placebo surgeries on humans who are suffering from a painful condition, even if the subjects are informed that they might receive the placebo operation and not the standard treatment?

(b) Give two possible explanations for the decreased pain reported by the placebo operation subjects.

(c) Analyze and critique the experimental design of this study. Are the results of this study applicable to everyone with knee pain?

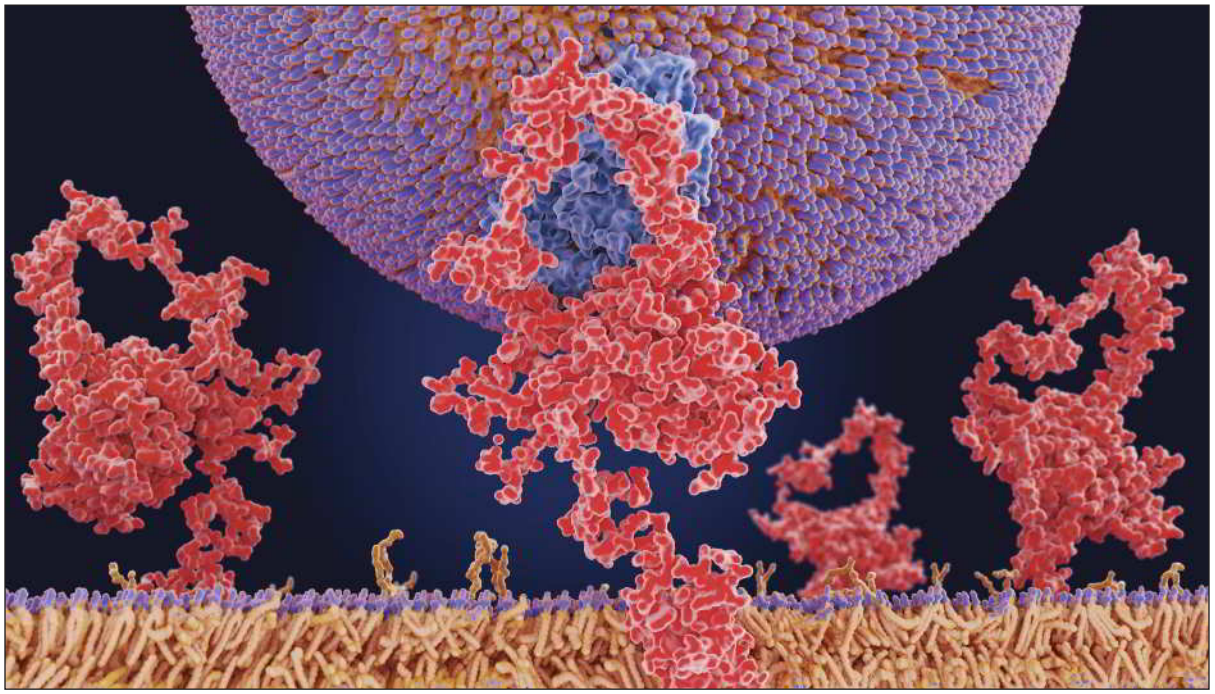
(d) Was this study a blind, double-blind, or double-blind crossover design?

(e) Why do you think the investigators felt it was necessary to include a placebo operation in this study?

Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

2

Molecular Interactions



LDL particle binding to the LDL receptor

Science regards man as an aggregation of atoms temporarily united by a mysterious force called the life-principle.

H. P. Blavatsky, 1877. In Isis Unveiled: A Master-Key to the Mysteries of Ancient and Modern Science and Theology, *Vol. I: Science*

Chapter 2 focuses on the core concept of Molecular Interactions, going from subatomic particles up to complex macromolecules that are responsible for many aspects of physiological function.

The first two sections of the chapter may be a review, depending on your background. Use the REVIEW figures to check your understanding of chemistry and biochemistry.

Section 2.3 focuses on protein binding, one of the key molecular interactions that govern physiological processes. The principles of protein binding apply to membrane transporters and signal receptors as well as to enzymes, so learning the basic patterns here is important.

Molecular Interactions

Learning Outcomes

2.1 Molecules and Bonds

- **LO 2.1.1** Compare and contrast the composition, structure, and functions of the four major groups of biomolecules.
- **LO 2.1.2** Describe four important biological roles of electrons.
- **LO 2.1.3** Describe and compare the different types of covalent and noncovalent bonds.

2.2 Noncovalent Interactions

- **LO 2.2.1** Contrast the structure and solubility of polar and nonpolar molecules.
- **LO 2.2.2** Describe the covalent and noncovalent interactions that contribute to molecular shape, and explain how molecular shape is related to molecular function.
- **LO 2.2.3** Define pH in words and mathematically, and explain the differences between acids, bases, and buffers.

2.3 Protein Interactions

- **LO 2.3.1** List nine important functions of proteins in the body.
- **LO 2.3.2** Explain the meanings of affinity, specificity, saturation, and competition in protein-ligand binding.
- **LO 2.3.3** Explain the different methods by which modulators alter protein binding or protein activity.

Nearly 100 years ago two scientists, Aleksander Oparin in Russia and John Haldane in England, speculated on how life might have arisen on a primitive Earth whose atmosphere consisted mainly of hydrogen, water, ammonia, and methane. Their theories were put to the test in 1953, when a 23-year-old scientist named Stanley Miller combined these molecules in a closed flask and boiled them for a week while periodically discharging flashes of electricity through them, simulating lightning. At the end of his test, Miller found amino acids had formed in the flask. With this simple experiment, he had shown that it was possible to create organic molecules, usually associated with living creatures, from nonliving inorganic precursors.

Miller's experiments were an early attempt to solve one of the biggest mysteries of biology: How did a collection of chemicals first acquire the complex properties that we associate with living creatures? We still do not have an answer to this question. Numerous scientific theories have been proposed, ranging from life arriving by meteor from outer space to molecules forming in deep ocean hydrothermal vents. No matter what their origin, the molecules associated with living organisms have the ability to organize themselves into compartments, replicate themselves, and act as *catalysts* to speed up reactions that would otherwise proceed too slowly to be useful.

The human body is far removed from the earliest life forms, but we are still a collection of chemicals—dilute solutions of dissolved and suspended molecules enclosed in compartments with lipid-protein walls. Strong links between atoms, known as **chemical bonds**, store and transfer energy to support life functions. Weaker interactions between and within molecules create distinctive molecular shapes and allow biological molecules to interact reversibly with each other.

This chapter introduces some of the fundamental principles of molecular interactions that you will encounter repeatedly in your study of physiology. The human body is more than 50% water, and because most of its molecules are dissolved in this water, we will review the properties of aqueous solutions. If you would like to refresh your understanding of the key features of **atoms**, chemical bonds, and biomolecules, you will find a series of one- and two-page review features that encapsulate biochemistry as it pertains to physiology. You can test your knowledge of basic chemistry and biochemistry with a special review quiz at the end of the chapter.

Running Problem 2.1: Chromium Supplements

"Lose weight while gaining muscle," the ads promise. "Prevent heart disease." "Stabilize blood sugar." What is this miracle substance? It's chromium picolinate, a nutritional supplement being marketed to consumers looking for a quick fix. Does it work, though, and is it safe? Some athletes, like Malik—the star running back on the college football team—swear by it. Malik takes 500 micrograms of chromium picolinate daily. Many researchers, however, are skeptical and feel that the necessity for and safety of chromium supplements have not been established.

2.1 Molecules and Bonds

There are more than 100 known elements on Earth, but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are considered *major* **essential elements**. Some additional *minor essential elements* (trace elements) are required in minute amounts, but there is no universal agreement on which trace elements are essential for cell function in humans. The **periodic table** shows the major and commonly accepted minor essential elements.

Most Biomolecules Contain Carbon, Hydrogen, and Oxygen

Molecules that contain carbon are known as **organic molecules,** because it was once thought that they all existed in or were derived from plants and animals. Organic molecules associated with living organisms are also called **biomolecules.** There are four major groups of biomolecules: carbohydrates, lipids, proteins, and nucleotides.

The body uses carbohydrates, lipids, and proteins for energy and as the building blocks of cellular components. The fourth group, the **nucleotides**, includes DNA, **RNA**, ATP, and cyclic AMP. DNA and RNA are the structural components of genetic

material. **ATP** (adenosine triphosphate) and related molecules carry energy, while **cyclic AMP** (adenosine monophosphate; cAMP) and related compounds regulate metabolism.

Each group of biomolecules has a characteristic composition and molecular structure. **Lipids** are mostly carbon and hydrogen (**FIG. 2.1**). **Carbohydrates** are primarily carbon, hydrogen, and oxygen, in the ratio CH_2O (**FIG. 2.2**). **Proteins** and nucleotides contain nitrogen in addition to carbon, hydrogen, and oxygen (**FIGS. 2.3** and **2.4**). Two **amino acids**, the building blocks of proteins, also contain sulfur.

Fig. 2.1 REVIEW Biochemistry of Lipids

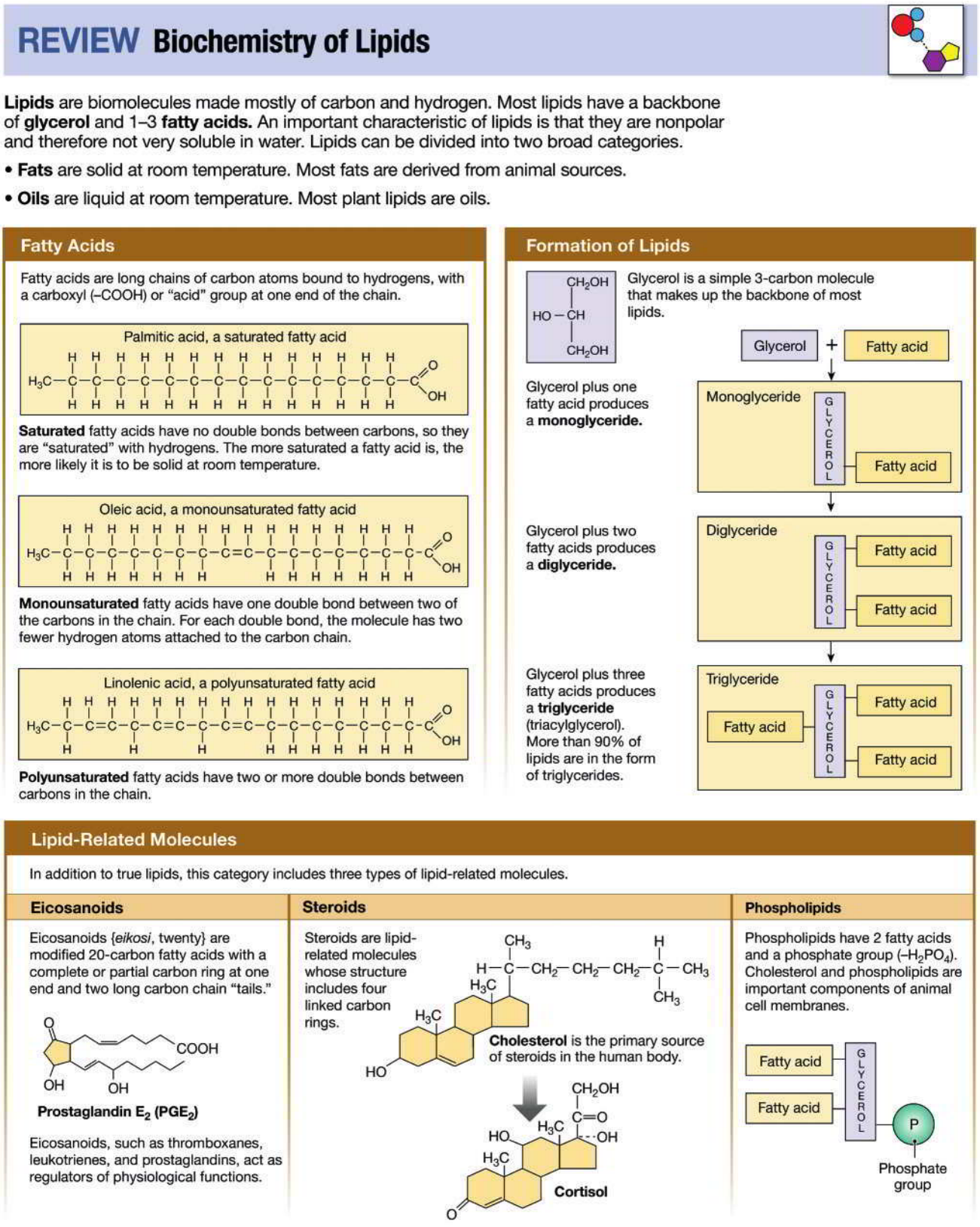


Fig. 2.2 REVIEW Biochemistry of Carbohydrates

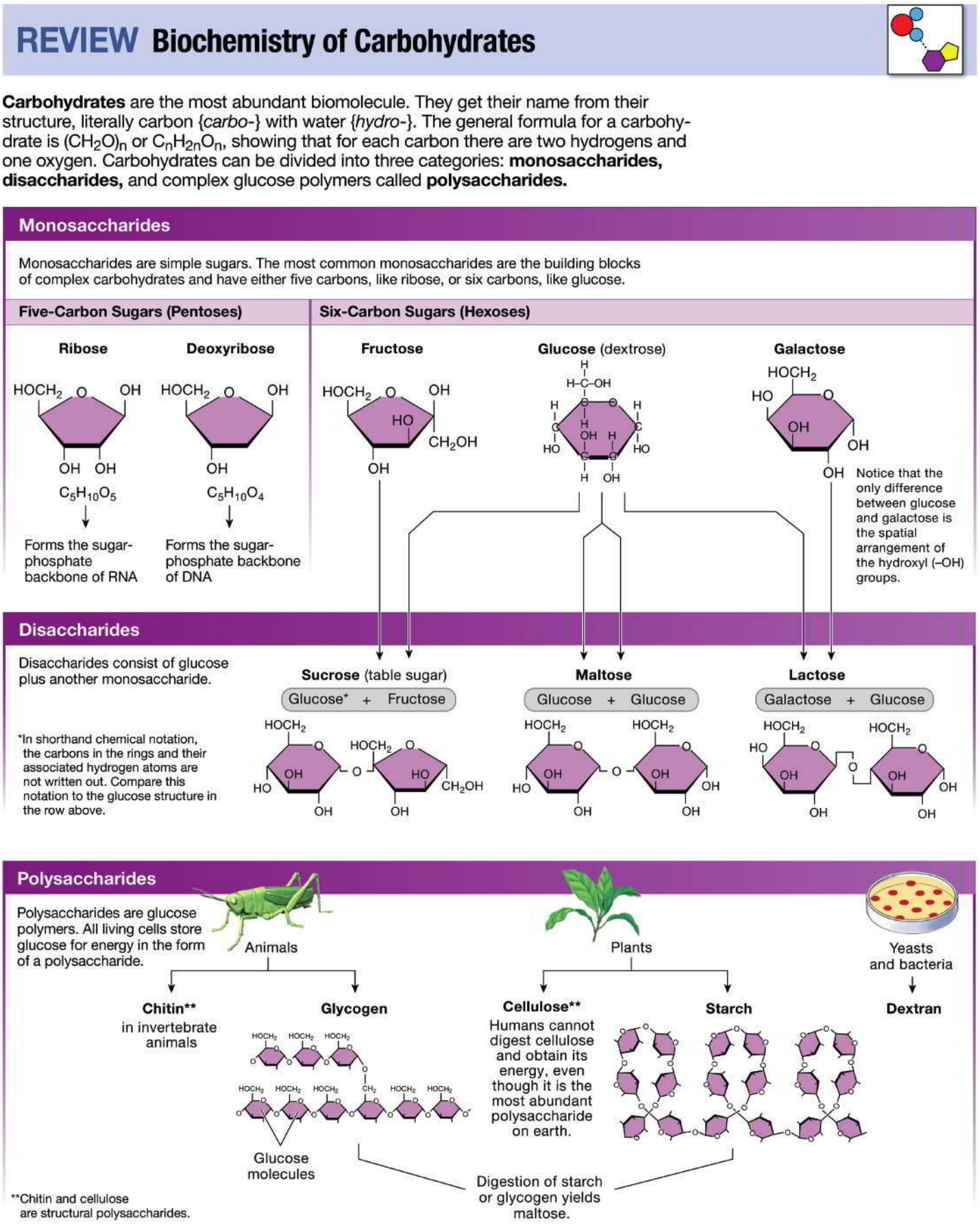


Fig. 2.3 REVIEW Biochemistry of Proteins

REVIEW Biochemistry of Proteins

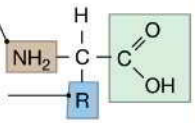
Proteins are polymers of smaller building-block molecules called **amino acids.**

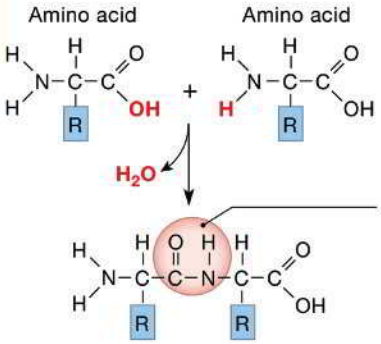
Amino Acids

All amino acids have a carboxyl group (–COOH), an amino group ($–NH_2$), and a hydrogen attached to the same carbon. The fourth bond of the carbon attaches to a variable "R" group.

The nitrogen (N) in the amino group makes proteins our major dietary source of nitrogen.

The R groups differ in their size, shape, and ability to form hydrogen bonds or ions. Because of the different R groups, each amino acid reacts with other molecules in a unique way.





In a **peptide bond,** the amino group of one amino acid joins the carboxyl group of the other, with the loss of water.

Amino Acids in Natural Proteins

Twenty different amino acids commonly occur in natural proteins. The human body can synthesize most of them, but at different stages of life some amino acids must be obtained from diet and are therefore considered *essential amino acids*. Some physiologically important amino acids are listed below.

Amino Acid	Three-Letter Abbreviation	One-Letter Symbol
Arginine	Arg	R
Aspartic acid (aspartate)*	Asp	D
Cysteine	Cys	C
Glutamic acid (glutamate)*	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Tryptophan	Trp	W
Tyrosine	Tyr	Y

*The suffix -ate indicates the anion form of the acid.

Note:

A few amino acids do not occur in proteins but have important physiological functions.

- *Homocysteine*: a sulfur-containing amino acid that in excess is associated with heart disease
- *γ-amino butyric acid* (gamma-amino butyric acid) or *GABA*: a chemical made by nerve cells
- *Creatine*: a molecule that stores energy when it binds to a phosphate group

Structure of Peptides and Proteins

Primary Structure

The 20 protein-forming amino acids assemble into polymers called peptides. The sequence of amino acids in a peptide chain is called the **primary structure.** Just as the 26 letters of our alphabet combine to create different words, the 20 amino acids can create an almost infinite number of combinations.

Peptides range in length from two to two million amino acids:

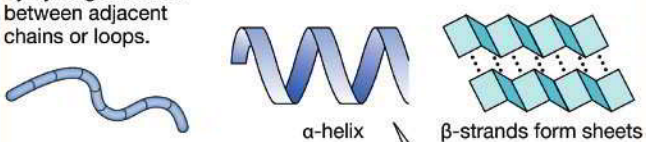
- **Oligopeptide** {*oligo-*, few}: 2–9 amino acids
- **Polypeptide:** 10–100 amino acids
- **Proteins:** >100 amino acids

Sequence of amino acids

Secondary Structure

Secondary structure is created primarily by hydrogen bonds between adjacent chains or loops.

Covalent bond angles between amino acids determine secondary structure.



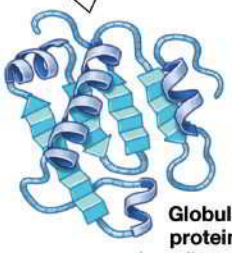
α-helix

β-strands form sheets

Tertiary Structure

Tertiary structure is the protein's three-dimensional shape.

Fibrous proteins
(usually insoluble)
Collagen

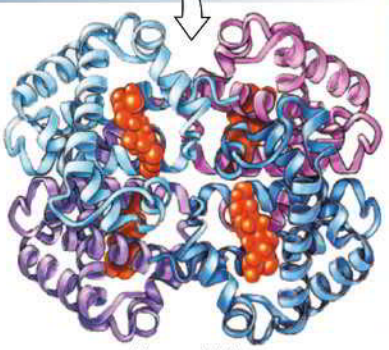


Globular proteins
(usually soluble)

Tertiary structures can be a mix of secondary structures. Beta-sheets are shown as flat ribbon arrows and alpha helices are shown as ribbon coils.

Quaternary Structure

Multiple subunits combine with noncovalent bonds. Hemoglobin molecules are made from four globular protein subunits.



Hemoglobin

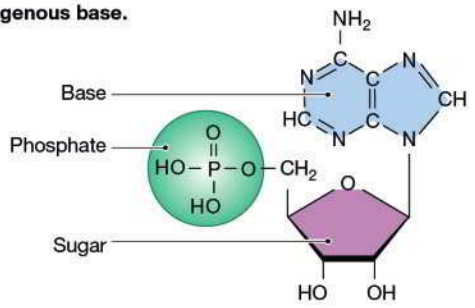
Fig. 2.4 REVIEW Nucleotides and Nucleic Acids

REVIEW Nucleotides and Nucleic Acids

Nucleotides are biomolecules that play an important role in energy and information transfer. Single nucleotides include the energy-transferring compounds **ATP** (adenosine triphosphate) and **ADP** (adenosine diphosphate), as well as **cyclic AMP,** a molecule important in the transfer of signals between cells. **Nucleic acids** (or nucleotide polymers) such as **RNA** and **DNA** store and transmit genetic information.

Nucleotide

A nucleotide consists of (1) one or more phosphate groups, (2) a 5-carbon sugar, and (3) a carbon-nitrogen ring structure called a **nitrogenous base.**



consists of

Nitrogenous Bases

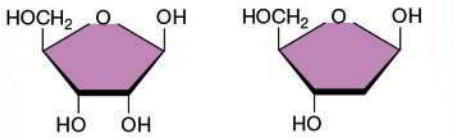
Purines have a double ring structure.

Pyrimidines have a single ring.

Adenine (A) | Guanine (G) | Cytosine (C) | Thymine (T) | Uracil (U)

Five-Carbon Sugars

Ribose | **Deoxyribose** {*de-*, without; *oxy-*, oxygen}



Phosphate

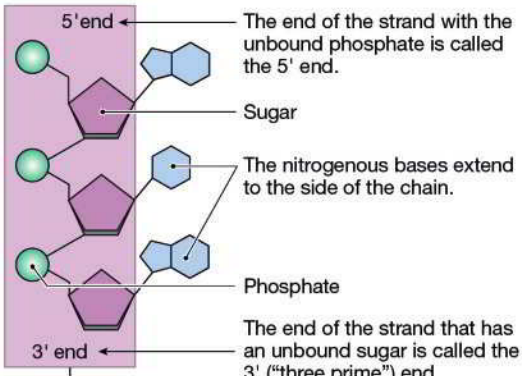
Adenine + Ribose → Adenosine

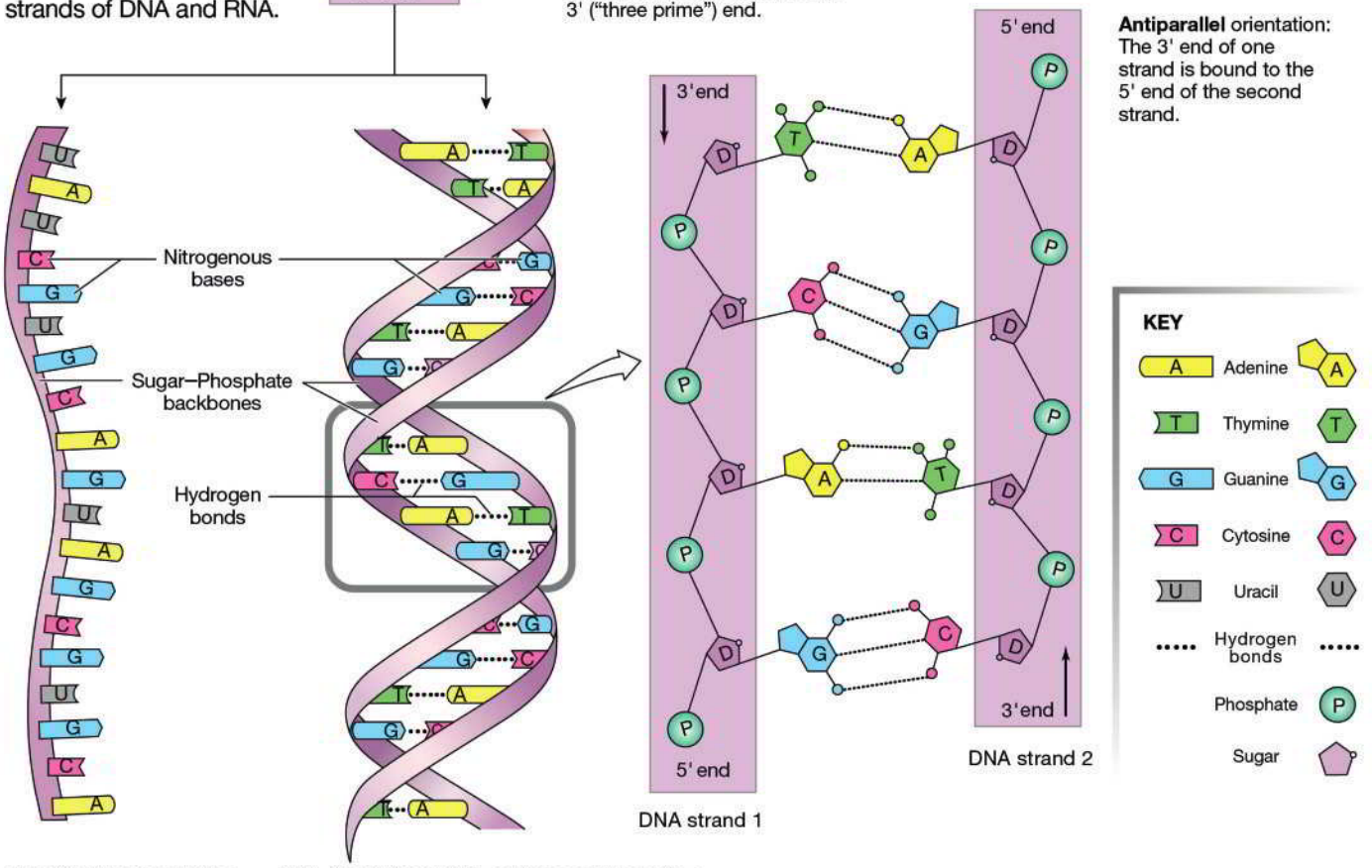
Single Nucleotide Molecules

Single nucleotide molecules have two critical functions in the human body: (1) Capture and transfer energy in high-energy electrons or phosphate bonds, and (2) aid in cell-to-cell communication.

Nucleotide	*consists of*	Base	+	Sugar	+	Phosphate Groups	+	Other Component	Function
ATP	=	Adenine	+	Ribose	+	3 phosphate groups			Energy capture and transfer
ADP	=	Adenine	+	Ribose	+	2 phosphate groups			
NAD	=	Adenine	+	2 Ribose	+	2 phosphate groups	+	Nicotinamide	
FAD	=	Adenine	+	Ribose	+	2 phosphate groups	+	Riboflavin	
cAMP	=	Adenine	+	Ribose	+	1 phosphate group			Cell-to-cell communication

Nucleic acids (nucleotide polymers) function in information storage and transmission. The sugar of one nucleotide links to the phosphate of the next, creating a chain of alternating sugar–phosphate groups. The sugar–phosphate chains, or backbone, are the same for every nucleic acid molecule. Nucleotide chains form strands of DNA and RNA.





RNA (ribonucleic acid) is a single-strand nucleic acid with ribose as the sugar in the backbone, and four bases—adenine, guanine, cytosine, and uracil.

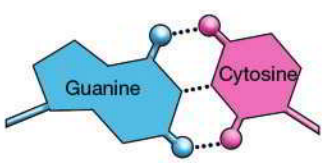
DNA (deoxyribonucleic acid) is a double helix, a three-dimensional structure that forms when two DNA strands link through hydrogen bonds between complementary base pairs. Deoxyribose is the sugar in the backbone, and the four bases are adenine, guanine, cytosine, and thymine.

Base-Pairing

Bases on one strand form hydrogen bonds with bases on the adjoining strand. This bonding follows very specific rules:

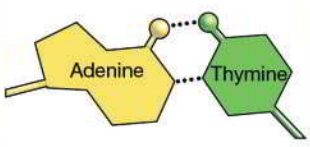
- Because purines are larger than pyrimidines, space limitations always pair a purine with a pyrimidine.
- Guanine (G) forms three hydrogen bonds with cytosine (C).
- Adenine (A) forms two hydrogen bonds with thymine (T) or uracil (U).

Guanine-Cytosine Base Pair



More energy is required to break the triple hydrogen bonds of G≡C than the double bonds of A=T or A=U.

Adenine-Thymine Base Pair



Not all biomolecules are pure protein, pure carbohydrate, or pure lipid, however. **Conjugated proteins** are protein molecules combined with another kind of biomolecule. For example, proteins combine with lipids to form **lipoproteins.** Lipoproteins are found in cell membranes and in the blood, where they act as carriers for less soluble molecules, such as cholesterol.

Glycosylated molecules are molecules to which a carbohydrate has been attached. Proteins combined with carbohydrates form **glycoproteins.** Lipids bound to carbohydrates become **glycolipids.** Glycoproteins and glycolipids, like lipoproteins, are important components of cell membranes [Fig. 3.2].

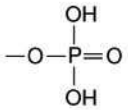
Many biomolecules are **polymers,** large molecules made up of repeating units {*poly-*, many + *-mer*, a part}. For example, **glycogen** and **starch** are both **glucose** polymers. They differ in the way the glucose molecules attach to each other, as you can see at the bottom of Figure 2.2.

Some combinations of elements, known as **functional groups,** occur repeatedly in biological molecules. The atoms in a functional group tend to move from molecule to molecule as a single unit. For example, *hydroxyl groups*, –OH, common in many biological molecules, are added and removed as a group rather than as single hydrogen or oxygen atoms. **Amino groups**, $-NH_2$, are the signature of amino acids. The phosphate group, $-H_2PO_4$, plays a role in many important cell processes, such as energy transfer and protein regulation. Addition of a phosphate group is called *phosphorylation*; removal of a phosphate group is **dephosphorylation**.

The most common functional groups are listed in **TABLE 2.1**.

Table 2.1 Common Functional Groups

Notice that oxygen, with two electrons to share, sometimes forms a double bond with another atom.

	Shorthand	Bond Structure
Amino	$-NH_2$	
Carboxyl (acid)	—COOH	
Hydroxyl	—OH	—O—H
Phosphate	$-H_2PO_4$	

Concept Check

1. List three major essential elements found in the human body.
2. What is the general formula of a carbohydrate?
3. What is the chemical formula of an amino group? Of a carboxyl group?

Electrons Have Four Important Biological Roles

An atom of any element has a unique combination of protons and electrons that determines the element's properties (**FIG. 2.5**). We are particularly interested in the electrons because they play four important roles in physiology:

1. **Covalent bonds.** The arrangement of electrons in the outer energy level (*shell*) of an atom determines an element's ability to bind with other elements. Electrons shared between atoms form strong covalent bonds that bind atoms together to form molecules
2. **Ions.** If an atom or molecule gains or loses one or more electrons, it acquires an electrical charge and becomes an **ion.** Ions are the basis for electrical signaling in the body. Ions may be single atoms, like the sodium ion Na^+ and chloride ion Cl^-. Other ions are combinations of atoms, such as the bicarbonate ion HCO_3^-. Important ions of the body are listed in **TABLE 2.2**.
3. **High-energy electrons.** The electrons in certain atoms can capture energy from their environment and transfer it to other atoms. This allows the energy to be used for synthesis, movement, and other life processes. The released energy may also be emitted as radiation. For example, bioluminescence in fireflies is visible light emitted by high-energy electrons returning to their normal low-energy state.
4. **Free radicals.** Free radicals are unstable molecules with an unpaired electron. They are thought to contribute to aging and to the development of certain diseases, such as some cancers. Free radicals and high-energy electrons are discussed in Chapter 23.

The role of electrons in molecular bond formation is discussed in the next section. There are four common bond types, two strong and two weak. Covalent and ionic bonds are strong bonds because they require significant amounts of energy to make or break. Hydrogen bonds and van der Waals forces are weaker bonds that require much less energy to break. Interactions between molecules with different bond types are responsible for energy use and transfer in metabolic reactions as well as a variety of other reversible interactions.

Table 2.2 Important Ions of the Body

Cations		Anions	
Na^+	Sodium	Cl^-	Chloride
K^+	Potassium	HCO_3^-	Bicarbonate
Ca^{2+}	Calcium	HPO_4^{2-}	Phosphate
H^+	Hydrogen	SO_4^{2-}	Sulfate
Mg^{2+}	Magnesium		

Covalent Bonds between Atoms Create Molecules

Molecules form when atoms share pairs of electrons, one electron from each atom, to create **covalent bonds.** These strong bonds require the input of energy to break them apart. It is possible to predict how many covalent bonds an atom can form by knowing how many unpaired electrons are in its outer shell, because an atom is most stable when all of its electrons are paired (**FIG. 2.6**).

For example, a hydrogen atom has one unpaired electron and one empty electron place in its outer shell. Because hydrogen has only one electron to share, it always forms one covalent bond, represented by a single line (—) between atoms. Oxygen has six electrons in an outer shell that can hold eight. That means oxygen can form two covalent bonds and fill its outer shell with electrons. If adjacent atoms share two pairs of electrons rather than just one pair, a **double bond,** represented by a double line (=), results. If two atoms share three pairs of electrons, they form a triple bond.

Running Problem 2.2

What is chromium picolinate? Chromium (Cr) is an essential element that has been linked to normal glucose metabolism. In the diet, chromium is found in brewer's yeast, broccoli, mushrooms, and apples. Because chromium in food and in chromium chloride supplements is poorly absorbed from the digestive tract, a scientist developed and patented the compound chromium picolinate. Picolinate, derived from amino acids, enhances chromium uptake at the intestine. The recommended adequate intake (AI) of chromium for men ages 19–50 is 35 μg/day. (For women, it is 25 μg/day.) As we've seen, Malik takes more than 10 times this amount.

Q1: *Locate chromium on the periodic table of the elements. What is chromium's atomic number?* ***Atomic mass****? How many electrons does one atom of chromium have?*

Q2: *Which elements close to chromium are also essential elements?*

Polar and Nonpolar Molecules

Some molecules develop regions of partial positive and negative charge when the electron pairs in their covalent bonds are not evenly shared between the linked atoms. When electrons are shared unevenly, the atom(s) with the stronger attraction for electrons develops a slight negative charge (indicated by δ^-), and the atom(s) with the weaker attraction for electrons develops a slight positive charge (δ^+). These molecules are called **polar molecules** because they can be said to have positive and negative ends, or poles. Certain elements, particularly nitrogen and oxygen, have a strong attraction for electrons and are often found in polar molecules.

A good example of a polar molecule is water (H_2O). The larger and stronger oxygen atom pulls the hydrogen electrons toward itself (Fig. 2.6b). This pull leaves the two hydrogen atoms of the molecule with a partial positive charge, and the single oxygen atom with a partial negative charge from the unevenly shared electrons. Note that the net charge for the entire water molecule is zero. The polarity of water makes it a good solvent, and all life as we know it is based on **aqueous solutions**, with water as the solvent.

A **nonpolar molecule** is one whose shared electrons are distributed so evenly that there are no regions of partial positive or negative charge. For example, molecules composed mostly of carbon and hydrogen, such as the **fatty acid** shown in Figure 2.6a, tend to be nonpolar. This is because carbon does not attract electrons as strongly as oxygen does. As a result, the carbons and hydrogens share electrons evenly, and the molecule has no regions of partial charge.

Noncovalent Bonds Facilitate Reversible Interactions

Ionic bonds, hydrogen bonds, and van der Waals forces are noncovalent bonds. They play important roles in many physiological processes, including pH, molecular shape, and the reversible binding of molecules to each other.

Ionic Bonds

Ions form when one atom has such a strong attraction for electrons that it pulls one or more electrons completely away from another atom. For example, a chlorine atom needs only one electron to fill the last of eight places in its outer shell, so it pulls an electron from a sodium atom, which has only one weakly held electron in its outer shell (Fig. 2.6c). The atom that gains electrons acquires one negative charge (−1) for each electron added, so the chlorine atom becomes a chloride ion Cl^-. Negatively charged ions are called **anions**.

An atom that gives up electrons has one positive charge (+1) for each electron lost. For example, the sodium atom becomes a sodium ion Na^+. Positively charged ions are called **cations**.

Ionic bonds, also known as *electrostatic attractions*, result from the attraction between ions with opposite charges. (Remember the basic principle of electricity that says that opposite charges attract and like charges repel.) In a crystal of table salt, the solid form of ionized NaCl, ionic bonds between alternating Na^+ and Cl^- ions hold the ions in a neatly ordered structure.

Hydrogen Bonds

A **hydrogen bond** is a weak attractive force between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. No electrons are gained, lost, or shared in a hydrogen bond. Instead, the oppositely charged regions in polar molecules are attracted to each other. Hydrogen bonds may occur between atoms in neighboring molecules or between atoms in different parts of the same molecule. For example, one water molecule may hydrogen-bond with as many as four other water molecules. As a result, the molecules line up with their neighbors in a somewhat ordered fashion (Fig. 2.6d).

Hydrogen bonding between molecules is responsible for the **surface tension** of water. Surface tension is the attractive force between water molecules that causes water to form spherical

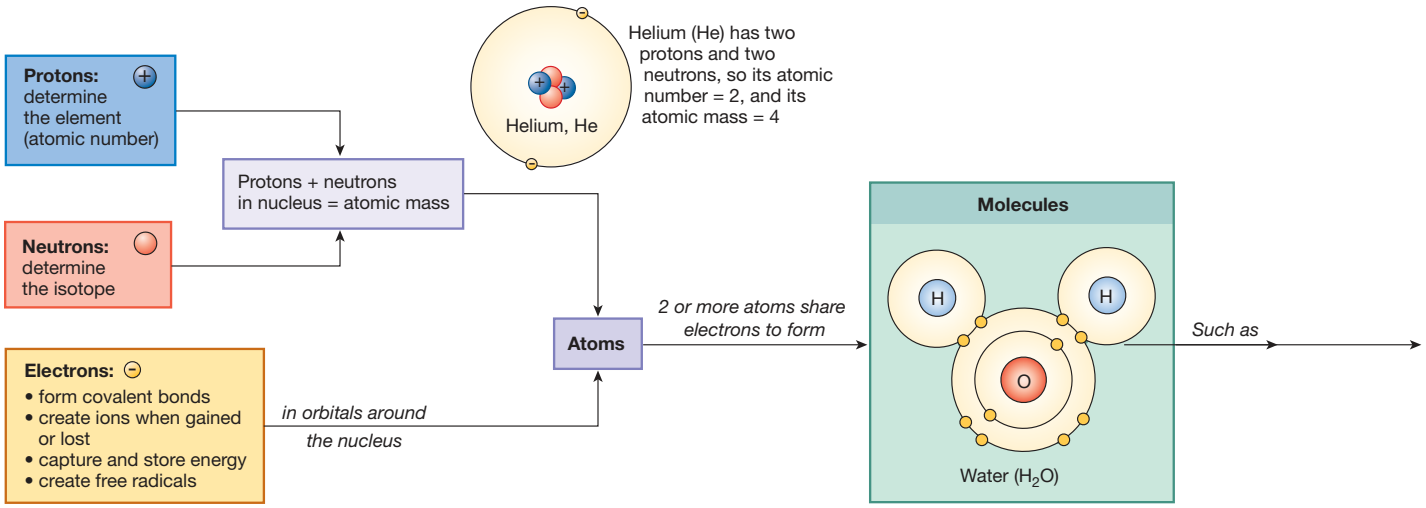
Fig. 2.5 REVIEW Atoms and Molecules

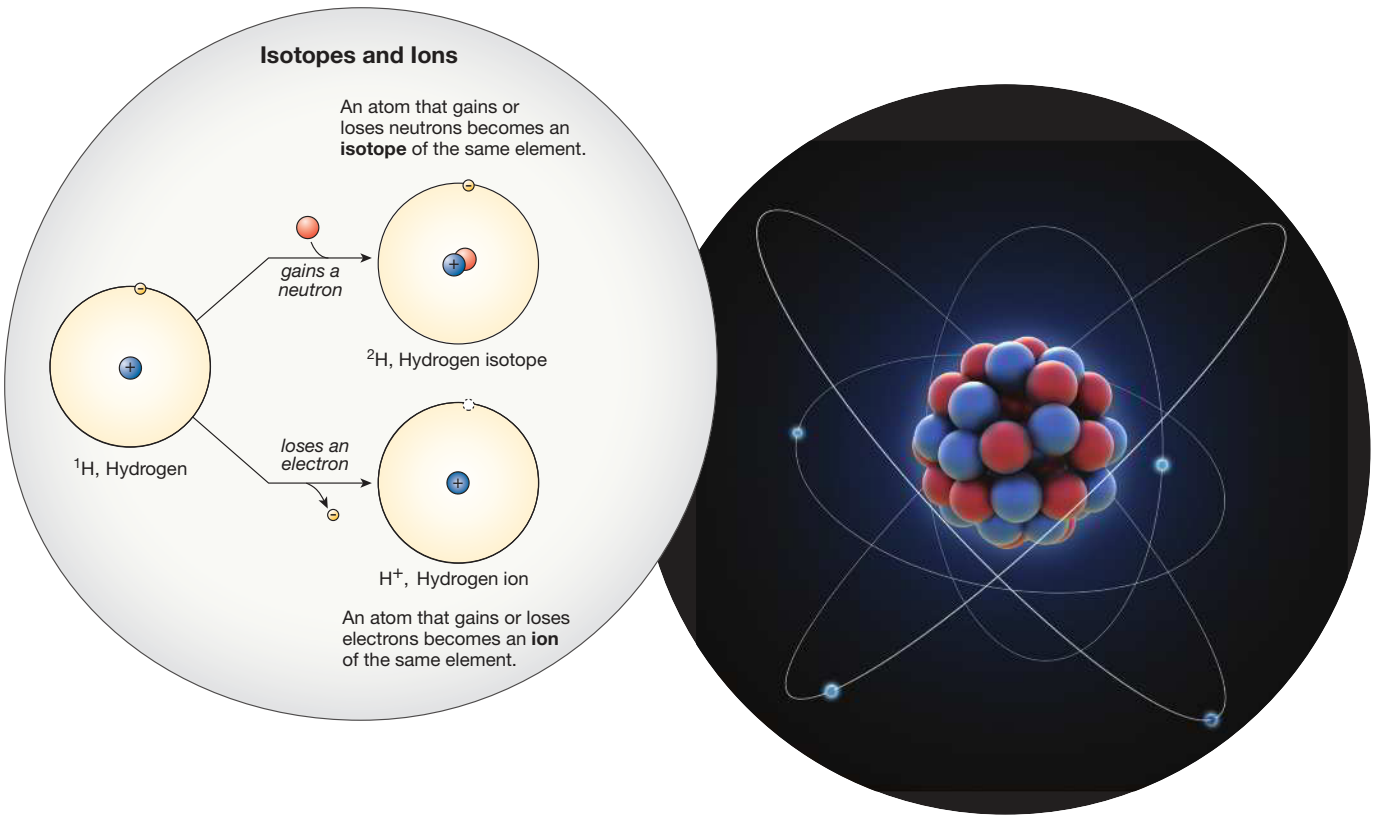
REVIEW Atoms and Molecules

Elements are the simplest type of matter. There are over 100 known elements,* but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are *major essential elements*. An additional 19 *minor essential elements* are required in trace amounts. The smallest particle of any element is an **atom** {*atomos*, indivisible}. Atoms link by sharing electrons to form molecules.

Major Essential Elements	Minor Essential Elements
H, C, O, N, Na, Mg, K, Ca, P, S, Cl	Li, F, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Y, I, Zr, Nb, Mo, Tc, Ru, Rh, La

* A periodic table of the elements can be found inside the back cover of the book.





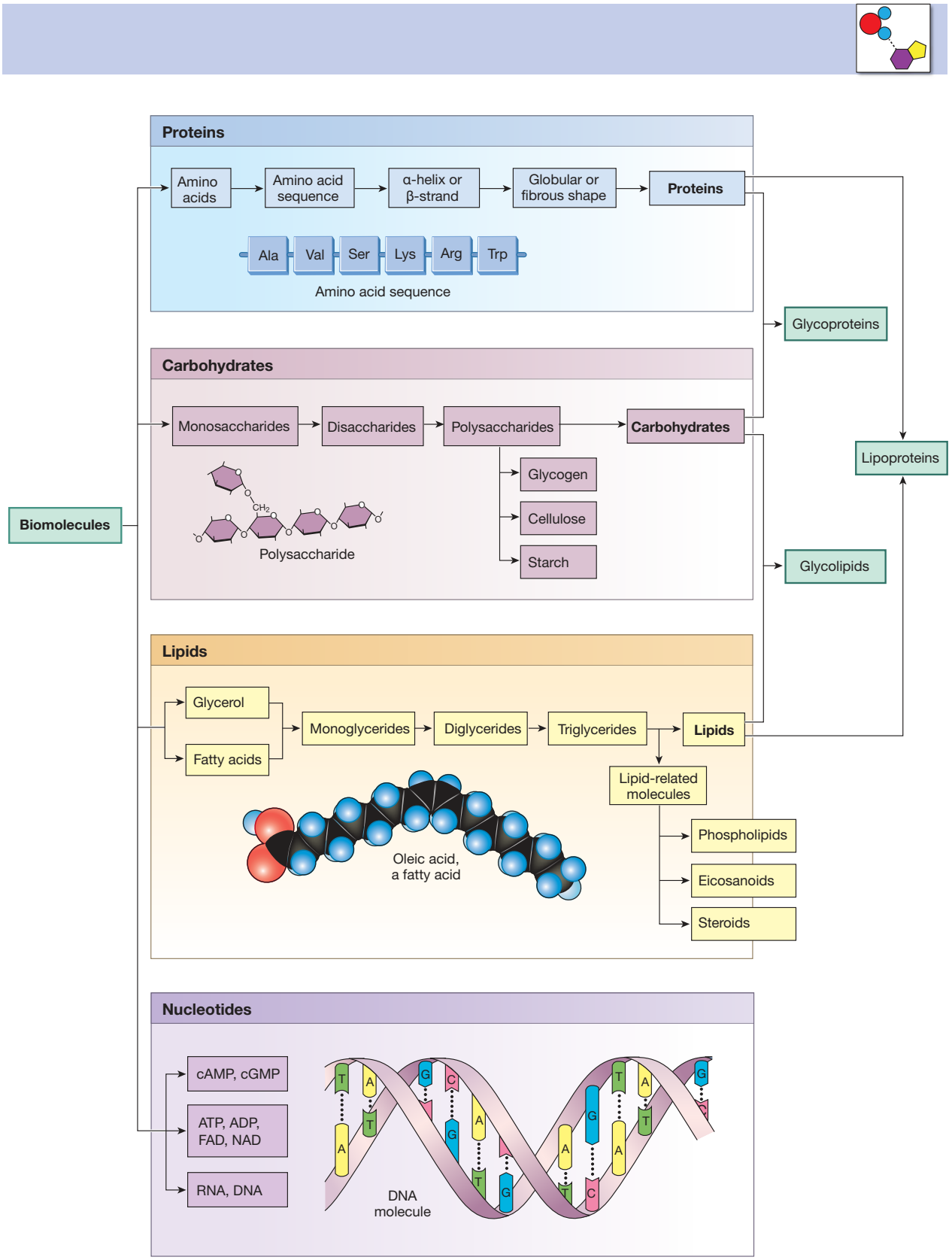
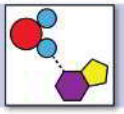


Fig. 2.6 REVIEW Molecular Bonds

REVIEW Molecular Bonds



When two or more atoms link by sharing electrons, they make units known as **molecules.** The transfer of electrons from one atom to another or the sharing of electrons by two atoms is a critical part of forming **bonds,** the links between atoms.

Bonds

Covalent Bonds

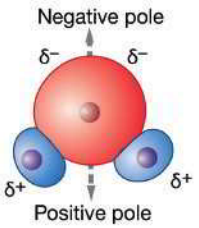
Covalent bonds result when atoms share electrons. These bonds require the most energy to make or break.

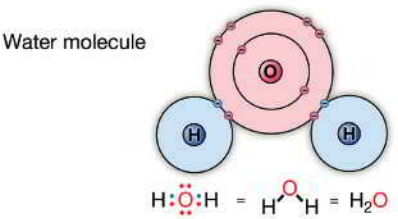
(a) Nonpolar Molecules

Nonpolar molecules have an even distribution of electrons. For example, molecules composed mostly of carbon and hydrogen tend to be nonpolar.

(b) Polar Molecules

Polar molecules have regions of partial charge (δ+ or δ−). The most important example of a polar molecule is water.

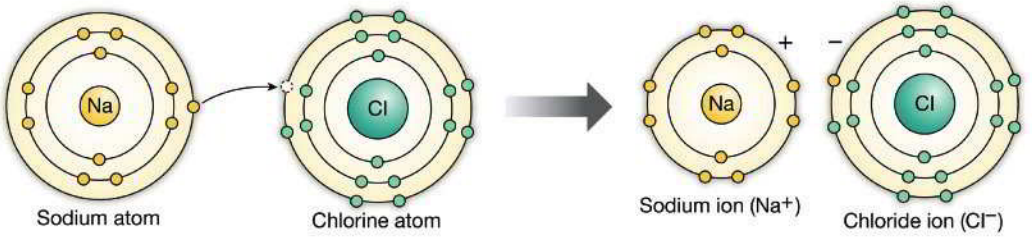




Noncovalent Bonds

(c) Ionic Bonds

Ionic bonds are electrostatic attractions between ions. A common example is sodium chloride.

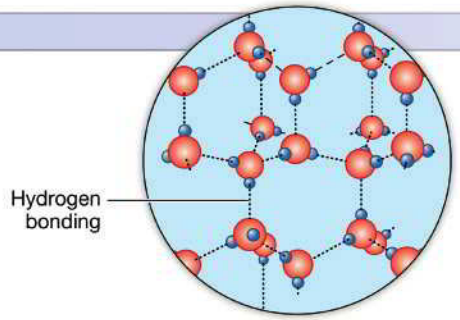


Sodium gives up its one weakly held electron to chlorine, creating sodium and chloride ions, Na^+ and Cl^-.

The sodium and chloride ions both have stable outer shells that are filled with electrons. Because of their opposite charges, they are attracted to each other and, in the solid state, the ionic bonds form a sodium chloride (NaCl) crystal.

(d) Hydrogen Bonds

Hydrogen bonds form between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. So, for example, the polar regions of adjacent water molecules allow them to form hydrogen bonds with one another.



Hydrogen bonding between water molecules is responsible for the surface tension of water.

(e) Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between atoms.

droplets when falling or to bead up when spilled onto a nonabsorbent surface (Fig. 2.6d). The high cohesiveness {*cohaesus*, to cling together} of water is due to hydrogen bonding and makes it difficult to stretch or deform, as you may have noticed in trying to pick up a wet glass that is "stuck" to a slick table top by a thin film of water. The surface tension of water influences lung function (described in Chapter18).

Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between the nucleus of any atom and the electrons of nearby atoms. Two atoms that are weakly attracted to each other by van der Waals forces move closer together until they are so close that their electrons begin to repel one another. Consequently, van der Waals forces allow atoms to pack closely together and occupy a minimum amount of space. A single van der Waals attraction between atoms is very weak.

Running Problem 2.3

One advertising claim for chromium is that it improves the transfer of glucose—the simple sugar that cells use to fuel all their activities—from the bloodstream into cells. In people with diabetes mellitus, cells are unable to take up glucose from the blood efficiently. It seemed logical, therefore, to test whether the addition of chromium to the diet would enhance glucose uptake in people with diabetes. In one Chinese study, diabetic patients receiving 500 micrograms (μg) of chromium picolinate twice a day showed significant improvement in their glucose uptake, but patients receiving 100 micrograms or a placebo did not.

Q3: *If people have a chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*

Q4: *From the results of the Chinese study, can you conclude that all people with diabetes suffer from a chromium deficiency?*

Concept Check

4. Are electrons in an atom or molecule most stable when they are paired or unpaired?
5. When an atom of an element gains or loses one or more electrons, it is called a(n) _____ of that element.
6. Match each type of bond with its description:

(a) covalent bond	1. weak attractive force between hydrogen and oxygen or nitrogen
(b) ionic bond	2. formed when two atoms share one or more pairs of electrons
(c) hydrogen bond	3. weak attractive force between atoms
(d) van der Waals force	4. formed when one atom loses one or more electrons to a second atom

2.2 Noncovalent Interactions

Many different kinds of noncovalent interactions can take place between and within molecules as a result of the four different types of bonds. For example, the charged, uncharged, or partially charged nature of a molecule determines whether that molecule can dissolve in water. Covalent and noncovalent bonds determine molecular shape and function. Finally, noncovalent interactions allow proteins to associate reversibly with other molecules, creating functional pairings such as enzymes and substrates, or signal receptors and molecules.

Hydrophilic Interactions Create Biological Solutions

Life as we know it is established on water-based, or *aqueous*, **solutions** that resemble dilute seawater in their ionic composition. The adult human body is about 60% water. Na^+, K^+, and Cl^- are the main ions in body fluids, with other ions making up a lesser proportion. All molecules and cell components are either dissolved or suspended in these solutions. For these reasons, it is useful to understand the properties of solutions, which are reviewed in **FIGURE 2.7**.

The degree to which a molecule is able to dissolve in a **solvent** is the molecule's **solubility:** the more easily a molecule dissolves, the higher its solubility. Water, the biological solvent, is polar, so molecules that dissolve readily in water are polar or ionic molecules whose positive and negative regions readily interact with water. For example, if NaCl crystals are placed in water, polar regions of the water molecules disrupt the ionic bonds between sodium and chloride, which causes the crystals to dissolve (**FIG. 2.8a**). Molecules that are soluble in water are said to be **hydrophilic** {*hydro-*, water + *-philic*, loving}.

In contrast, molecules such as oils that do not dissolve well in water are said to be **hydrophobic** {*-phobic*, hating}. Hydrophobic substances are usually nonpolar molecules that cannot form hydrogen bonds with water molecules. The lipids (fats and oils) are the most hydrophobic group of biological molecules.

When placed in an aqueous solution, lipids do not dissolve. Instead they separate into distinct layers. One familiar example is salad oil floating on vinegar in a bottle of salad dressing. Before hydrophobic molecules can dissolve in body fluids, they must combine with a hydrophilic molecule that will carry them into solution.

For example, **cholesterol**, a common animal fat, is a hydrophobic molecule. Fat from a piece of meat dropped into a glass of warm water will float to the top, undissolved. In the blood, cholesterol will not dissolve unless it binds to special water-soluble carrier molecules. You may know the combination of cholesterol with its hydrophilic carriers as **HDL-cholesterol** and LDL-cholesterol, the "good" and "bad" forms of cholesterol associated with heart disease.

Some molecules, such as the **phospholipids**, have both polar and nonpolar regions (Fig. 2.8b). This dual nature allows them to associate both with each other (hydrophobic interactions) and

Fig. 2.7 REVIEW Solutions

REVIEW Solutions

Life as we know it is established on water-based, or aqueous, solutions that resemble dilute seawater in their ionic composition. The human body is 60% water. Sodium, potassium, and chloride are the main ions in body fluids. All molecules and cell components are either dissolved or suspended in these saline solutions. For these reasons, the properties of solutions play a key role in the functioning of the human body.

Terminology

A **solute** is any substance that dissolves in a liquid. The degree to which a molecule is able to dissolve in a solvent is the molecule's solubility. The more easily a solute dissolves, the higher its **solubility**.

A **solvent** is the liquid into which solutes dissolve. In biological solutions, water is the universal solvent.

A **solution** is the combination of solutes dissolved in a solvent. The **concentration** of a solution is the amount of solute per unit volume of solution.

Concentration = solute amount/volume of solution

Expressions of Solute Amount

- **Mass** (weight) of the solute before it dissolves. Usually given in grams (g) or milligrams (mg).
- **Molecular mass** is calculated from the chemical formula of a molecule. This is the mass of one molecule, expressed in atomic mass units (amu) or, more often, in daltons (Da), where 1 amu = 1 Da.

Molecular mass = SUM [atomic mass of each element × the number of atoms of each element]

Example

What is the molecular mass of glucose, $C_6H_{12}O_6$?

Answer

Element	# of Atoms	Atomic Mass of Element
Carbon	6	12.0 amu × 6 = 72
Hydrogen	12	1.0 amu × 12 = 12
Oxygen	6	16.0 amu × 6 = 96

Molecular mass of glucose = 180 amu (or Da)

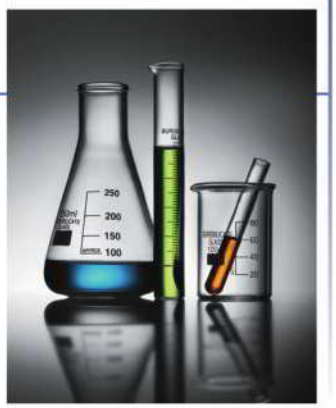
- **Moles** (mol) are an expression of the number of solute molecules, without regard for their weight. One mole = 6.02×10^{23} atoms, ions, or molecules of a substance. One mole of a substance has the same number of particles as one mole of any other substance, just as a dozen eggs has the same number of items as a dozen roses.
- **Gram molecular weight.** In the laboratory, we use the molecular mass of a substance to measure out moles. For example, one mole of glucose (with 6.02×10^{23} glucose molecules) has a molecular mass of 180 Da and weighs 180 grams. The molecular mass of a substance expressed in grams is called the gram molecular weight.
- **Equivalents** (Eq) are a unit used for ions, where 1 equivalent = molarity of the ion × the number of charges the ion carries. The sodium ion, with its charge of +1, has one equivalent per mole. The hydrogen phosphate ion (HPO_4^{2-}) has two equivalents per mole. Concentrations of ions in the blood are often reported in milliequivalents per liter (mEq/L).

FIGURE QUESTIONS

1. What are the two components of a solution?
2. The concentration of a solution is expressed as:
   (a) amount of solvent/volume of solute
   (b) amount of solute/volume of solvent
   (c) amount of solvent/volume of solution
   (d) amount of solute/volume of solution
3. Calculate the molecular mass of water, H_2O.
4. How much does a mole of KCl weigh?

Expressions of Volume

Volume is usually expressed as liters (L) or milliliters (mL) {*milli-*, 1/1000}. A volume convention common in medicine is the deciliter (dL), which is 1/10 of a liter, or 100 mL.



Prefixes

deci- (d)	1/10	1×10^{-1}
milli- (m)	1/1000	1×10^{-3}
micro- (μ)	1/1,000,000	1×10^{-6}
nano- (n)	1/1,000,000,000	1×10^{-9}
pico- (p)	1/1,000,000,000,000	1×10^{-12}

Useful Conversions

- 1 liter of water weighs 1 kilogram (kg) {*kilo-*, 1000}
- 1 kilogram = 2.2 pounds

Expressions of Concentration

- **Percent solutions.** In a laboratory or pharmacy, scientists cannot measure out solutes by the mole. Instead, they use the more conventional measurement of weight. The solute concentration may then be expressed as a percentage of the total solution, or percent solution. A 10% solution means 10 parts of a solute per 100 parts of total solution. Weight/volume solutions, used for solutes that are solids, are usually expressed as g/100 mL solution or mg/dL. An out-of-date way of expressing mg/dL is mg% where % means per 100 parts or 100 mL. A concentration of 20 mg/dL could also be expressed as 20 mg%.

Example

Solutions used for intravenous (IV) infusions are often expressed as percent solutions. How would you make 500 mL of a 5% dextrose (glucose) solution?

Answer

5% solution = 5 g glucose dissolved in water to make a final volume of 100 mL solution.

5 g glucose/100 mL = ? g/500 mL

25 g glucose with water added to give a final volume of 500 mL

- **Molarity** is the number of moles of solute in a liter of solution, and is abbreviated as either mol/L or M. A one molar solution of glucose (1 mol/L, 1 M) contains 6.02×10^{23} molecules of glucose per liter of solution. It is made by dissolving one mole (180 grams) of glucose in enough water to make one liter of solution. Typical biological solutions are so dilute that solute concentrations are usually expressed as **millimoles** per liter (mmol/L or mM).

Example

What is the molarity of a 5% dextrose solution?

Answer

5 g glucose/100 mL = 50 g glucose/1000 mL (or 1 L)

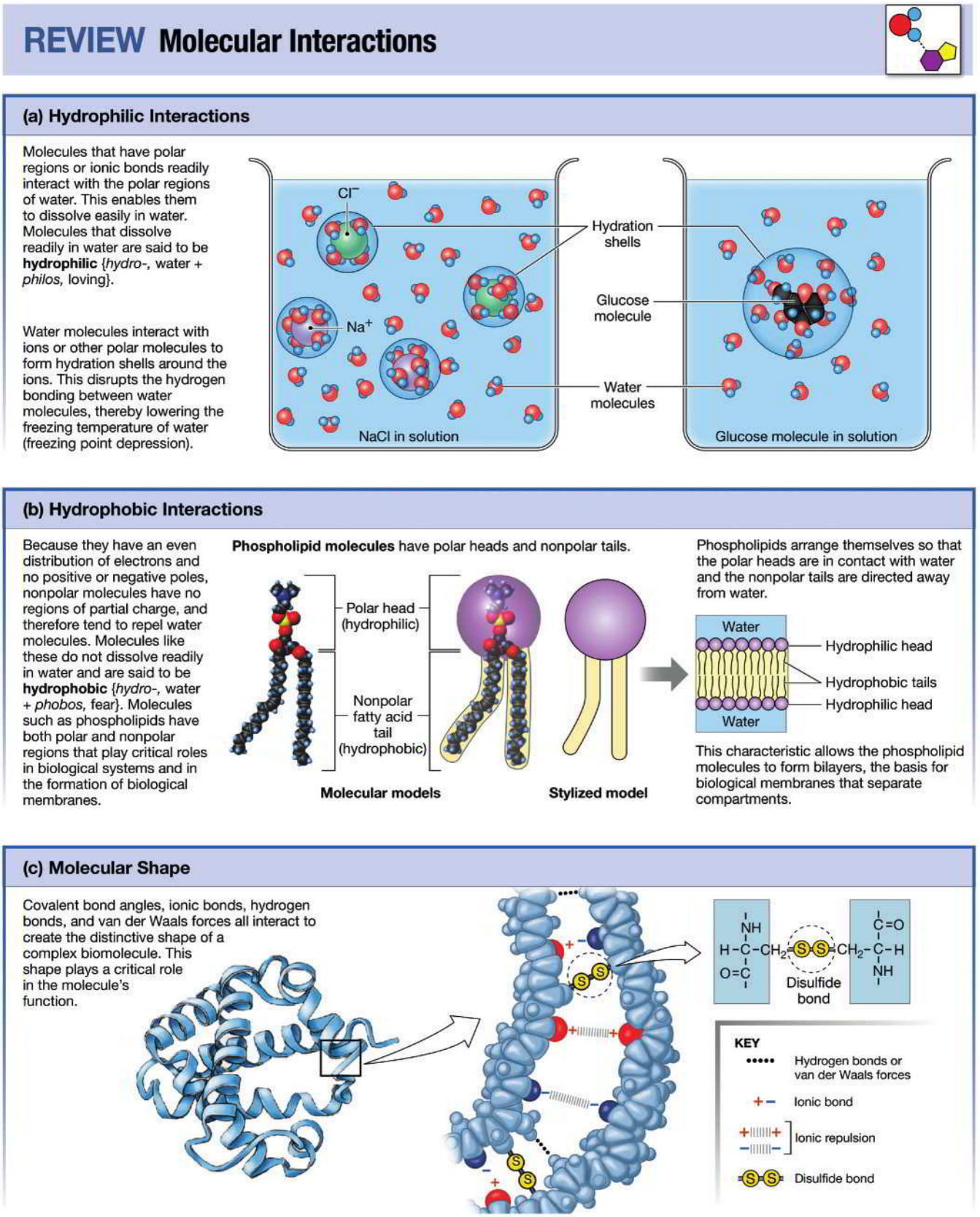
1 mole glucose = 180 g glucose

50 g/L × 1 mole/180 g = 0.278 moles/L or 278 mM

FIGURE QUESTIONS

5. Which solution is more concentrated: a 100 mM solution of glucose or a 0.1 M solution of glucose?
6. When making a 5% solution of glucose, why don't you measure out 5 grams of glucose and add it to 100 mL of water?

Fig. 2.8 REVIEW Molecular Interactions



with polar water molecules (hydrophilic interactions). Phospholipids are the primary component of biological membranes.

Concept Check

7. Which dissolve more easily in water, polar molecules or nonpolar molecules?
8. A molecule that dissolves easily is said to be hydro__ic.
9. Why does table salt (NaCl) dissolve in water?

Molecular Shape Is Related to Molecular Function

A molecule's shape is closely related to its function. Molecular bonds—both covalent bonds and weak bonds—play a critical role in determining molecular shape. The three-dimensional shape of a molecule is difficult to show on paper, but many molecules have characteristic shapes due to the angles of covalent bonds between the atoms. For example, the two hydrogen atoms of the water molecule shown in Figure 2.6b are attached to the oxygen with a bond angle of 104.5°. Double bonds in long carbon chain fatty acids cause the chains to kink or bend, as shown by the three-dimensional model of oleic acid in Figure 2.5.

Weak noncovalent bonds also contribute to molecular shape. The complex double helix of a **DNA** molecule, shown in Figure 2.4, results both from covalent bonds between adjacent **nitrogenous bases** in each strand and the hydrogen bonds connecting the two strands of the helix.

Proteins have the most complex and varied shapes of all the biomolecules. Their shapes are determined both by the sequence of amino acids in the protein chain (the **primary structure of a protein**) plus varied noncovalent interactions as long **polypeptide** chains loop and fold back on themselves. The stable **secondary structures** of proteins are formed by covalent bond angles between amino acids in the polypeptide chain.

The two common protein **secondary structures** are the **α – helix (alpha-helix)** spiral and the zigzag shape of **β – sheets (beta-sheet)** (Fig. 2.3). Adjacent β-*strands* in the polypeptide chain associate into sheetlike structures held together by hydrogen bonding, shown as dotted lines (. . .) in Figure 2.3. The sheet configuration is very stable and occurs in many proteins destined for structural uses. Proteins with other functions may have a mix of β-strands and α-helices. Protein secondary structure is illustrated by ribbon diagrams (or Richardson diagrams), with beta-sheets shown as flat arrows and α-helices as ribbon spirals (Fig. 2.3).

The **tertiary structure** of a protein is its three-dimensional shape, created through spontaneous folding as the result of covalent bonds and noncovalent interactions. Proteins are categorized into two large groups based on their shape: globular and fibrous (see Fig. 2.3). **Globular proteins** can be a mix of α-helices, β-sheets, and amino acid chains that fold back on themselves. The result is a complex tertiary structure that may contain pockets, channels, or protruding knobs. The tertiary structure of globular proteins arises partly from the angles of covalent bonds between amino acids and partly from hydrogen bonds, van der Waals forces, and ionic bonds that stabilize the molecule's shape.

In addition to covalent bonds between adjacent amino acids, covalent **disulfide bonds** (S–S) play an important role in the shape of many globular proteins (Fig. 2.8c). The amino acid *cysteine* contains sulfur as part of a *sulfhydryl group* (–SH). Two cysteines in different parts of the polypeptide chain can bond to each other with a disulfide bond that pulls the sections of chain together.

Fibrous proteins can be β-strands or long chains of α-helices. Fibrous proteins are usually insoluble in water and form important structural components of cells and tissues. Examples of fibrous proteins include *collagen*, found in many types of connective tissue, such as skin, and *keratin*, found in hair and nails.

Hydrogen Ions in Solution Can Alter Molecular Shape

Hydrogen bonding is an important part of molecular shape. However, free hydrogen ions, H^+, in solution can also participate in hydrogen bonding and van der Waals forces. If free H^+ disrupts a molecule's noncovalent bonds, the molecule's shape, or *conformation*, can change. A change in shape may alter or destroy the molecule's ability to function.

Running Problem 2.4

Chromium is found in several ionic forms. The chromium usually found in biological systems and in dietary supplements is the cation Cr^{3+}. This ion is called trivalent because it has a net charge of $+3$. The hexavalent cation, Cr^{6+}, with a charge of $+6$, is used in industry, such as in the manufacturing of stainless steel and the chrome plating of metal parts.

Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*

The concentration of free H^+ in body fluids, or *acidity*, is measured in terms of **pH. FIGURE 2.9** reviews the chemistry of pH and shows a pH scale with the pH values of various substances. The typical pH of blood in the human body is 7.40, slightly alkaline. Regulation of the body's pH within a narrow range is critical because a blood pH more acidic than 7.00 ($pH < 7.00$) or more alkaline than 7.70 ($pH > 7.70$) is incompatible with life.

Where do hydrogen ions in body fluids come from? Some of them come from the separation of water molecules (H_2O) into H^+ and OH^- ions. Others come from **acids,** molecules that release H^+ when they dissolve in water (Fig. 2.9). Many of the molecules made during metabolism are acids. For example, acid is made in the body from CO_2 (carbon dioxide) and water.

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

Note that when the hydrogen is part of the water molecule, it does not contribute to acidity. *Only free H^+ contributes to the hydrogen ion concentration.*

We are constantly adding acid to the body through metabolism, so how does the body maintain an acceptable pH? One

Fig. 2.9 REVIEW pH

REVIEW pH

Acids and Bases

An **acid** is a molecule that contributes H^+ to a solution.

- The carboxyl group, –COOH, is an acid because in solution it tends to lose its H^+:

$$R\text{–}COOH \longrightarrow R\text{–}COO^- + H^+$$

A **base** is a molecule that decreases the H^+ concentration of a solution by combining with free H^+.

- Molecules that produce hydroxide ions, OH^-, in solution are bases because the hydroxide combines with H^+ to form water:

$$R\text{–}OH \longrightarrow R^+ + OH^- \longrightarrow OH^- + H^+ \longrightarrow H_2O$$

- Another molecule that acts as a base is ammonia, NH_3. It reacts with a free H^+ to form an ammonium ion:

$$NH_3 + H^+ \longrightarrow NH_4^+$$

pH

The concentration of H^+ in body fluids is measured in terms of **pH.**

- The expression pH stands for "power of hydrogen."

(1) $pH = -\log [H^+]$

This equation is read as "pH is equal to the negative log of the hydrogen ion concentration." Square brackets are shorthand notation for "concentration" and by convention, concentration is expressed in Eq/L.

- Using the rule of logarithms that says $-\log x = \log(1/x)$, pH equation (1) can be rewritten as:

(2) $pH = \log (1/[H^+])$

This equation shows that pH is inversely related to H^+ concentration. In other words, as the H^+ concentration goes up, the pH goes down.

Example

What is the pH of a solution whose hydrogen ion concentration $[H^+]$ is 10^{-7} Eq/L?

Answer

$pH = -\log [H^+]$
$pH = -\log [10^{-7}]$

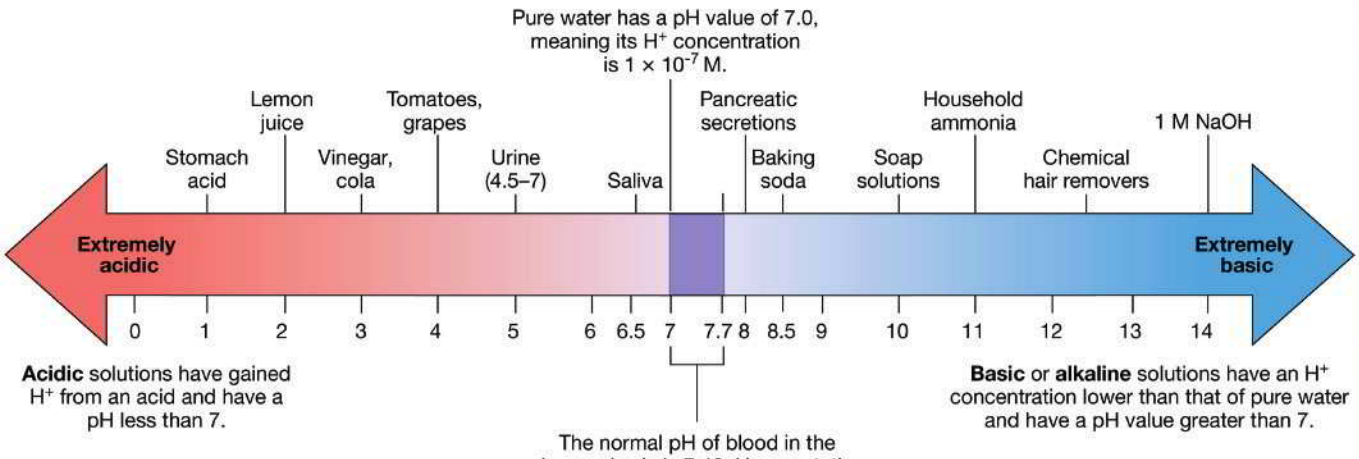
Using the rule of logs, this can be rewritten as

$pH = \log (1/10^{-7})$

Using the rule of exponents that says $1/10^x = 10^{-x}$

$pH = \log 10^7$

the log of 10^7 is 7, so the solution has a pH of 7.



The pH of a solution is measured on a numeric scale between 0 and 14. The pH scale is logarithmic, meaning that a change in pH value of 1 unit indicates a 10-fold change in $[H^+]$. For example, if a solution changes from pH 8 to pH 6, there has been a 100-fold (10^2 or 10 × 10) increase in $[H^+]$.

FIGURE QUESTIONS

1. When the body becomes more acidic, does pH increase or decrease?
2. How can urine, stomach acid, and saliva have pH values outside the pH range that is compatible with life and yet be part of the living body?

answer is buffers. A **buffer** is any substance that moderates changes in pH. Many buffers contain anions that have a strong attraction for H^+ molecules. When free H^+ is added to a buffer solution, the buffer's anions bond to the H^+, thereby minimizing any change in pH.

The bicarbonate anion, HCO_3^-, is an important buffer in the human body. The following equation shows how a sodium bicarbonate solution acts as a buffer when hydrochloric acid (HCl) is added. When placed in plain water, hydrochloric acid separates, or dissociates, into H^+ and Cl^- and creates a high H^+ concentration (low pH). When HCl dissociates in a sodium bicarbonate solution, however, some of the bicarbonate ions combine with some of the H^+ to form undissociated carbonic acid. "Tying up" the added H^+ in this way keeps the free H^+ concentration of the solution from changing significantly and minimizes the pH change.

$$\underset{\text{Hydrochloric acid}}{H^+ + Cl^-} + \underset{\text{Sodium bicarbonate}}{HCO_3^- + Na^+} \rightleftharpoons \underset{\text{Carbonic acid}}{H_2CO_3} + \underset{\text{Sodium chloride (table salt)}}{Cl^- + Na^+}$$

Concept Check

10. To be classified as an acid, a molecule must do what when dissolved in water?
11. pH is an expression of the concentration of what in a solution?
12. When pH goes up, acidity goes _____.

2.3 Protein Binding Interactions

Noncovalent molecular interactions occur between proteins and many different biomolecules. For example, biological membranes are formed by the noncovalent associations of proteins and phospholipids. And glycoproteins join glycolipids in cell membranes to create a "sugar coat" on cell surfaces that assists cell **aggregation** {*aggregare*, to join together} and adhesion {*adhaerere*, to stick}.

Proteins play important roles in so many cell functions that we can consider them the "workhorses" of the body. Most proteins fall into nine broad categories:

1. **Enzymes.** Some proteins act as **enzymes,** biological catalysts that speed up chemical reactions. Enzymes are crucial players in metabolism and you will learn more about their properties in Chapter 4.
2. **Membrane transporters.** Proteins in cell membranes help substances move between the intracellular and extracellular compartments. These proteins may form channels in the cell membrane, or they may bind to ions and molecules and carry them through the membrane. Membrane transporters are discussed in detail in Chapter 5.
3. **Signal molecules.** Some proteins and smaller **peptides** act as hormones and other signal molecules. Signal molecules are described in Chapters 6 and 8.
4. **Receptors.** Proteins that bind signal molecules and initiate cellular responses are called *receptors*. Receptors are discussed along with signal molecules in Chapter 6.
5. **Binding proteins.** These proteins, found mostly in the extracellular fluid, bind to and transport molecules throughout the body. Examples you may be familiar with include cholesterol-binding lipoproteins such as LDL (low-density lipoprotein) and the oxygen-transporting protein *hemoglobin* found inside red blood cells.
6. **Immunoglobulins.** These extracellular immune proteins, also called *antibodies*, help protect the body from foreign invaders and substances. Immune functions are discussed in Chapter 7.
7. **Motor proteins.** Motor proteins use energy from ATP to create movement. Examples include *myosin* that plays a role in muscle contraction, proteins that propel cilia and flagella, and protein fibers inside cells that move organelles and help in cell division.
8. **Structural proteins.** Fibrous proteins play an important role in creating the shape and structure of cells, tissues, and organs, as you will learn in Chapter 3. Some of the key structural proteins include *collagen*, *keratin*, and *elastin*.
9. **Regulatory proteins.** Regulatory proteins turn cell processes on and off or up and down. For example, the regulatory proteins known as *transcription factors* bind to DNA and alter gene expression and protein synthesis. The details of regulatory proteins can be found in cell biology textbooks.

Although proteins are quite diverse in shape and function, they share one common feature: they all bind to other molecules through noncovalent interactions. The interaction takes place at a location on the protein molecule called the **binding site.** The binding site depends on the three-dimensional shape of the protein, and its properties can be altered or *modulated* by factors that affect protein structure. The unique shapes of different binding sites give rise to three important properties of protein binding that are discussed below: specificity, affinity, and competition.

Running Problem 2.5

The hexavalent form of chromium used in industry is known to be toxic to humans. In 1992, officials at California's Hazard Evaluation System and Information Service warned that inhaling chromium dust, mist, or fumes placed chrome and stainless steel workers at increased risk for lung cancer. Officials found no risk to the public from normal contact with chrome surfaces or stainless steel. In 1995 and 2002, a possible link between the biological trivalent form of chromium (Cr^{3+}) and cancer came from *in vitro* studies {*vitrum*, glass—that is, a test tube} in which mammalian cells were kept alive in tissue culture. In these experiments, cells exposed to moderately high levels of chromium picolinate developed potentially cancerous changes.[1, 2]

Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*

Any molecule or ion that binds to another molecule is called a **ligand** {*ligare*, to bind or tie}. Ligands that bind to enzymes and membrane transporters are usually called **substrates** {*sub-*, below + *stratum*, a layer}. Proteins can also be ligands. Protein signal molecules bind to receptors, and protein transcription factors bind to DNA. Immunoglobulins bind ligands called *antigens*, but the immunoglobulin-antigen complex itself can then become a ligand [Fig. 7.8].

Proteins Are Selective about the Molecules They Bind

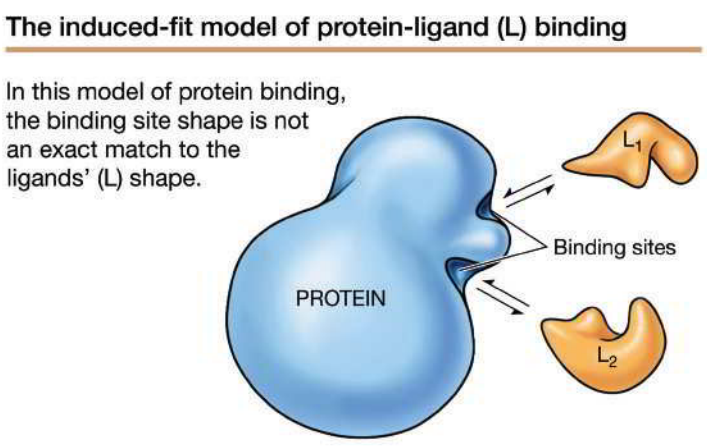
The ability of a protein to bind to a particular ligand or a group of related ligands is called **specificity.** Some proteins are very specific about the ligands they bind, while others bind to whole groups of molecules. For example, the enzymes known as **peptidases** bind to polypeptide ligands and break apart their **peptide bonds**, no matter which two amino acids are joined by those bonds. For this reason the action of peptidases is not very specific. In contrast, **aminopeptidases** also break peptide bonds but are more specific. They will bind to only one end of a protein chain (the end with an unbound amino group) and can act only on the last peptide bond in the chain.

Ligand binding requires **molecular complementarity**. In other words, the ligand and the protein binding site must be complementary, or compatible. In protein binding, when the ligand and protein come close to each other, noncovalent interactions between the ligand and the protein's binding site allow the two molecules to bind. From studies of enzymes and other binding proteins, scientists have discovered that a protein's binding site and the shape of its ligand do not need to fit one another exactly. When the binding site and the ligand come close to each other, they begin to interact through hydrogen and ionic bonds and van der Waals forces. The protein's binding site then changes shape (*conformation*) to fit more closely to the ligand. This is known as the **induced-fit model of protein-ligand interaction** and is shown in **FIGURE 2.10**.

When one protein binds to several related ligands, the related ligands that compete for the binding sites are said to be **competitors.** Competition between ligands is a universal property of protein binding. Competing ligands that mimic each other's actions are called **agonists** {*agonist*, contestant}. Agonists may occur in nature, such as *nicotine*, the chemical found in tobacco, which mimics the activity of the neurotransmitter *acetylcholine* by binding to the same receptor protein. Agonists can also be synthesized using what scientists learn from the study of protein–ligand binding sites.

Competing ligands that bind to the protein and block the binding site without causing a response are **antagonists**, also called inhibitors. Antagonists act like someone slipping into the front of a box office line to chat with their friend, the cashier. They are not interested in buying a ticket, but prevent the people waiting in line from getting their tickets. The ability of agonist and antagonist molecules to mimic or decrease the activity of naturally occurring ligands has led to the development of many drugs.

Fig. 2.10 The induced-fit model of protein-ligand (L) binding



Isoforms

Closely related proteins whose function is similar but whose affinity for ligands differs are called **isoforms** of one another. For example, the oxygen-transporting protein *hemoglobin* has multiple isoforms. One hemoglobin molecule has a **quaternary structure** consisting of four subunits (see Fig. 2.3). In the developing fetus, the hemoglobin isoform has two α (alpha) chains and two γ (gamma) chains that make up the four subunits. Shortly after birth, fetal hemoglobin molecules are broken down and replaced by adult hemoglobin. The adult hemoglobin isoform retains the two α chain isoforms but has two β (beta) chains in place of the γ chains. Both adult and fetal isoforms of hemoglobin bind oxygen, but the fetal isoform has a higher affinity for oxygen. This makes it more efficient at picking up oxygen across the placenta.

Protein-Binding Reactions Are Reversible

The degree to which a protein is attracted to a particular ligand is called the protein's **affinity** for the ligand. If a protein has a high affinity for a given ligand, the protein is more likely to bind to that ligand than to other ligands for which the protein has lower affinity.

Protein binding to a ligand can be written using the same notation that we use to represent chemical reactions:

$$P + L \rightleftharpoons PL$$

where P is the protein, L is the ligand, and PL is the bound protein-ligand complex. The double arrow indicates that binding is reversible.

Reversible binding reactions reach a state of **equilibrium**, where the rate of binding ($P + L \rightarrow PL$) is exactly equal to the rate of unbinding, or *dissociation* ($P + L \leftarrow PL$) When a reaction is at equilibrium, the ratio of the product concentration, or protein-ligand complex [PL], to the reactant concentrations [P][L] is always the same. This ratio is called the **equilibrium constant** K_{eq}, and it applies to all reversible chemical reactions:

$$K_{eq} = \frac{[PL]}{[P][L]}$$

The square brackets [ ] around the letters indicate concentrations of the protein, ligand, and protein-ligand complex.

In protein-binding reactions, the equilibrium constant K_{eq} is a quantitative representation of the protein's binding affinity for the ligand: high affinity for the ligand means a larger K_{eq}.[3] If one protein binds to several related ligands, a comparison of their K_{eq} values tells us which ligand is more likely to bind to the protein.

Binding Reactions Obey the Law of Mass Action

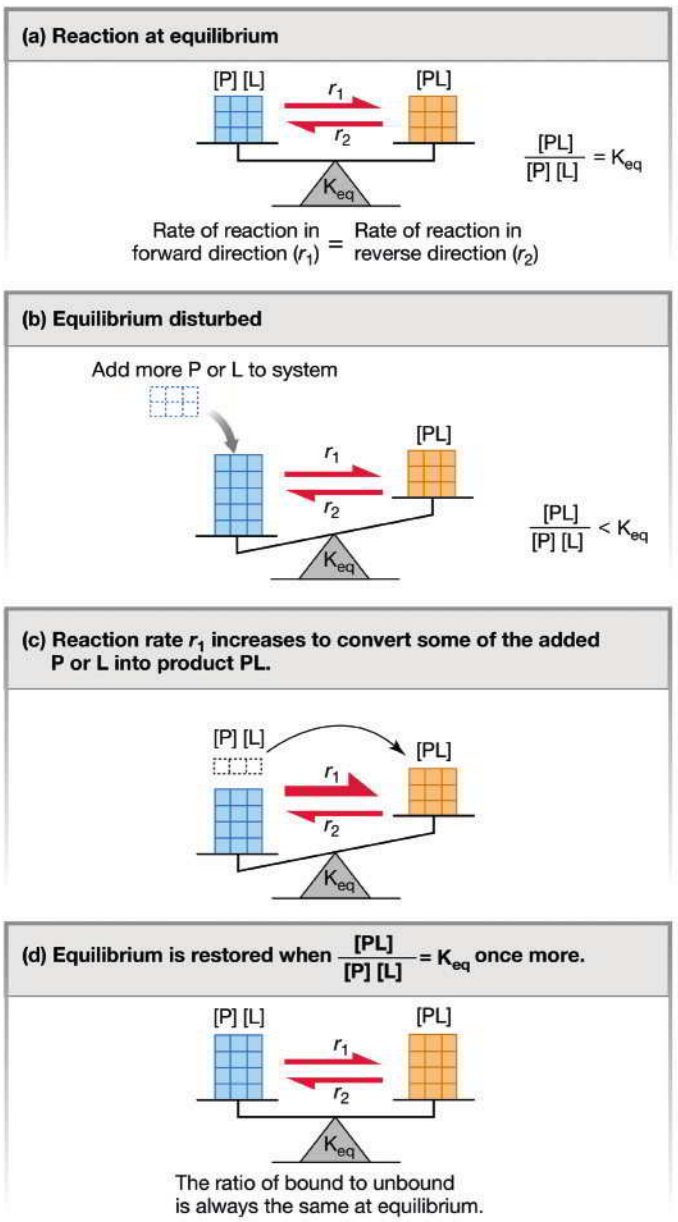
Reversible reactions at equilibrium have a constant ratio of bound protein to free protein and ligand. However, equilibrium is not a static state. In the living body, concentrations of protein or ligand change constantly through synthesis, breakdown, or movement from one compartment to another. So what restores equilibrium when it is disturbed?

When the concentration of protein or ligand changes, the reaction follows the **law of mass action**, which you may have learned in chemistry as *Le Châtelier's principle*. The law of mass action says that reaction rates are proportional to the concentration of the reactants. If the concentration of one of the participants changes, the reaction rates will increase or decrease to restore the equilibrium condition.

An example of this is shown in **FIGURE. 2.11**, which begins with a reaction at equilibrium (Fig 2.11a). The equilibrium is disturbed when more protein or ligand is added to the system (Fig. 2.11b). Now the ratio of [PL] to [P][L] differs from the K_{eq}. In response, the rate of the binding reaction increases to convert some of the added P or L into the bound protein-ligand complex (Fig. 2.11c). As the ratio approaches its equilibrium value again, the rate of the forward reaction slows until finally the system reaches the equilibrium ratio once more (Fig. 2.11d). [P], [L], and [PL] have all increased over their initial values, but the equilibrium ratio has been restored.

One example of this principle at work is the transport of **steroid** hormones in the blood. Steroids are hydrophobic, so more than 99% of steroid hormone in the blood is bound to carrier proteins. The equilibrium ratio [PL]/[P][L] is 99% bound:1% unbound hormone. However, only the unbound or "free" hormone can cross the cell membrane and enter cells. As unbound hormone leaves the blood, the equilibrium ratio is disturbed. The binding proteins then release some of the bound hormone until the 99:1 ratio is again restored. The same principle applies to enzymes and metabolic reactions. Changing the concentration of one participant in a chemical reaction has a chain-reaction effect that alters the concentrations of other participants in the reaction.

Fig. 2.11 The law of mass action



Concept Check

13. Consider the carbonic acid reaction, which is reversible:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

If the concentration of carbon dioxide in the body increases, what happens to the pH?

14. A researcher is trying to design a drug to bind to a particular cell receptor protein. Candidate molecule A has a K_{eq} of 0.9 for the receptor. Molecule B has a K_{eq} of 4.3. Which molecule has the most potential to be successful as the drug?

Running Problem 2.6

Malik has been taking chromium picolinate because he heard that it would increase his strength and muscle mass. Then a friend told him that the Food and Drug Administration (FDA) said there was no evidence to show that chromium would help build muscle. In one study,[4] a group of researchers gave high daily doses of chromium picolinate to football players during a two-month training period. By the end of the study, the players who took chromium supplements had not increased muscle mass or strength any more than players who did not take the supplement.

Use Google Scholar (*http://scholar.google.com*) and search for *chromium picolinate AND muscle*. Look for articles on body composition or muscle strength in humans before you answer the next question.

Q7: *Based on the papers you found, the Hallmark et al. study (which did not support enhanced muscle development from chromium supplements), and the studies that suggest that chromium picolinate might cause cancer, do you think that Malik should continue taking chromium picolinate?*

Multiple Factors Alter Protein Binding

A protein's affinity for a ligand is not always constant. Chemical and physical factors can alter, or *modulate*, binding affinity or can even eliminate it totally. Some proteins must be activated before they have a functional binding site. In this section we discuss some of the processes that have evolved to allow activation, modulation, and inactivation of protein binding. **TABLE 2.3** summarizes the different types of activation and modulation.

Activation

Some proteins are synthesized in the cell in an inactive state. Before these proteins can become active, enzymes must chop off one or more portions of the protein molecule (**FIG. 2.12a**). Protein hormones (a type of signal molecule) and enzymes are two groups that commonly undergo such *proteolytic activation* {*lysis*, to release}. The inactive forms of these proteins are often identified with the prefix *pro-* {before}: prohormone, proenzyme, proinsulin, for example. Some inactive enzymes have the suffix *-ogen* added to the name of the active enzyme instead, as in **trypsinogen**, the inactive form of trypsin.

The activation of some proteins requires the presence of a **cofactor,** which is an ion or small organic functional group. Cofactors must attach to the protein before the binding site is able to bind to a ligand (Fig. 2.12b). Ionic cofactors include Ca^{2+}, Mg^{2+}, and Fe^{2+}. Many enzymes do not function without their cofactors.

Table 2.3 Factors That Affect Protein Binding

Essential for Binding Activity	
Cofactors	Required for ligand binding at binding site
Proteolytic activation	Converts inactive to active form by removing part of molecule. Examples: digestive enzymes, protein hormones
Modulators and Factors That Alter Binding or Activity	
Competitive inhibitor	Competes directly with ligand by binding reversibly to active site
Irreversible inhibitor	Binds to binding site and cannot be displaced by competition
Allosteric modulator	Binds to protein away from binding site and changes activity; may be inhibitors or activators
Covalent modulator	Binds covalently to protein and changes its activity. Example: phosphate groups
pH and temperature	Alter three-dimensional shape of protein by disrupting hydrogen or S–S bonds; may be irreversible if protein becomes denatured

Modulation

The ability of a protein to bind a ligand and initiate a response can be altered by various factors, including temperature, pH, and molecules that interact with the protein. **Chemical modulators** are molecules that bind to proteins and alter their binding ability or their activity. Chemical modulators can be classified in several ways:

- By whether they enhance or inhibit the protein's activity,
- By whether their effect is reversible or irreversible,
- By where they bind to the protein (at the binding site or to another part of the protein), and
- By how they bind to the protein (noncovalent interactions or covalent bonds).

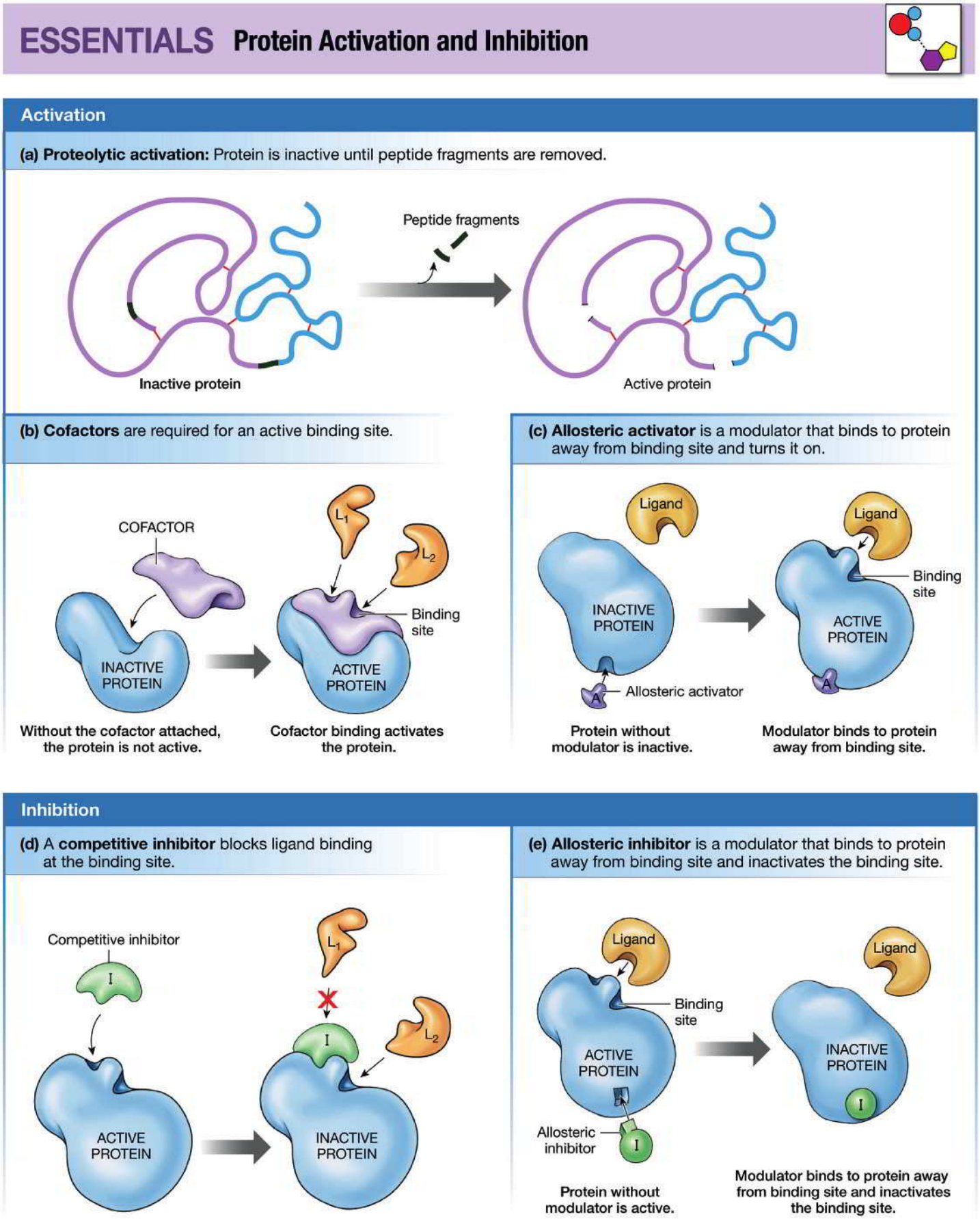
Inhibitors are chemical modulators that bind to a protein and decrease or stop its activity. The action of inhibitors may be reversible (competitive inhibitors) or irreversible (irreversible antagonists). **Competitive inhibitors** are reversible antagonists that compete with the typical ligand for the binding site (Fig. 2.12d). The degree of inhibition depends on the relative concentrations of the competitive inhibitor and the customary ligand, as well as on the protein's affinities for the ligand and inhibitor. The binding of competitive inhibitors is reversible: increasing the concentration of the customary ligand can displace the competitive inhibitor and decrease the inhibition.

Irreversible antagonists, on the other hand, bind tightly to the protein and cannot be displaced by competition. Antagonist drugs have proven useful for treating many conditions. For example, tamoxifen, an estrogen receptor antagonist, is used in the treatment of hormone-dependent cancers of the breast.

Allosteric modulators {*allos*, other + *stereos*, solid (as a shape)} bind to a protein at a regulatory site away from the binding site, and by doing so change the shape of the binding site. The effects of allosteric modulators may be reversible or irreversible. *Allosteric inhibitors* are antagonists that decrease the affinity of the binding site for the ligand and inhibit protein activity (Fig. 2.12e). *Allosteric activators* increase the probability of protein-ligand binding and enhance protein activity (Fig. 2.12c). For example, the oxygen-binding ability of hemoglobin changes with allosteric modulation by carbon dioxide, H^+ and several other factors [Fig. 19.9].

Covalent modulators are atoms or functional groups that bind covalently to proteins and alter the proteins' properties. Like allosteric modulators, covalent modulators may either increase or decrease a protein's binding ability or its activity. One of the most common covalent modulators is the phosphate group. Many proteins in the cell are activated or inactivated when a phosphate group forms a covalent bond with them, a process known as

Fig. 2.12 ESSENTIALS Protein Activation and Inhibition



phosphorylation. Phosphorylation can be reversed by enzymes that break the covalent bond.

One of the best known covalent inhibitor drugs is the antibiotic penicillin. Alexander Fleming discovered this compound in 1928, when he noticed that *Penicillium* mold inhibited bacterial growth in a petri dish. By 1938, researchers had extracted the active ingredient penicillin from the mold and used it to treat infections in humans. But it was not until 1965 that researchers figured out exactly how the antibiotic works. Penicillin is an irreversible antagonist that binds covalently to a key bacterial protein by mimicking the normal ligand. Because penicillin forms unbreakable bonds with the protein, the protein is irreversibly inhibited. Without the protein, the bacterium is unable to make a rigid cell wall. Without a rigid cell wall, the bacterium swells, ruptures, and dies.

Physical Factors

Physical conditions such as temperature and pH (acidity) can have dramatic effects on protein structure and function. Small changes in pH or temperature act as modulators to increase or decrease the activity of proteins such as enzymes (**FIG. 2.13a**). However, once these physical factors exceed some critical value, they disrupt the noncovalent bonds holding the protein in its tertiary conformation. The protein loses its shape and, along with that, its activity. When the protein loses its conformation, it is said to be *denatured*.

If you have ever fried an egg, you have watched this transformation happen to the egg white proteins as they change from a slithery clear state to a firm white state. Hydrogen ions in high enough concentration to be called acids have a similar effect on protein structure. During preparation of ceviche, a popular dish in several Latin American countries, raw fish is marinated in lime juice. The acidic lime juice contains hydrogen ions that disrupt hydrogen bonds in the muscle proteins of the fish, causing the proteins to become denatured. As a result, the meat becomes firmer and opaque, just as it would if it were cooked with heat.

In a few cases, protein activity can be restored if the original temperature or pH returns. The protein then resumes its original shape as if nothing had happened. Usually, however, denaturation produces a permanent loss of activity. There is certainly no way to unfry an egg or uncook a piece of fish. The potentially disastrous influence of temperature and pH on proteins is one reason these variables are so closely regulated by the body.

Concept Check

15. Match each chemical to its action(s).

(a) Allosteric modulator	**1.** Bind away from the binding site
(b) Competitive inhibitor	**2.** Bind to the binding site
(c) Covalent modulator	**3.** Inhibit activity only
	4. Inhibit or enhance activity

The Body Regulates the Amount of Protein in Cells

The final characteristic of proteins in the human body is that the amount of a given protein varies over time, often in a regulated fashion. The body has mechanisms that enable it to monitor whether it needs more or less of certain proteins. Complex signaling pathways, many of which themselves involve proteins, direct particular cells to make new proteins or to break down (*degrade*) existing proteins. This programmed production of new proteins (receptors, enzymes, and membrane transporters, in particular) is called **up-regulation.** Conversely, the programmed removal of proteins is called **down-regulation.** In both instances, the cell is directed to make or remove proteins to alter its response.

The amount of protein present in a cell has a direct influence on the magnitude of the cell's response. For example, the graph in Figure 2.13b shows the results of an experiment in which the amount of ligand is held constant while the amount of protein is varied. As the graph shows, an increase in the amount of protein present causes an increase in the response.

As an analogy, think of the checkout lines in a supermarket. Imagine that each cashier is an enzyme, the waiting customers are ligand molecules, and people leaving the store with their purchases are products. One hundred customers can be checked out faster when there are 25 lines open than when there are only 10 lines. Likewise, in an enzymatic reaction, the presence of more protein molecules (enzyme) means that more binding sites are available to interact with the ligand molecules. As a result, the ligands are converted to products more rapidly.

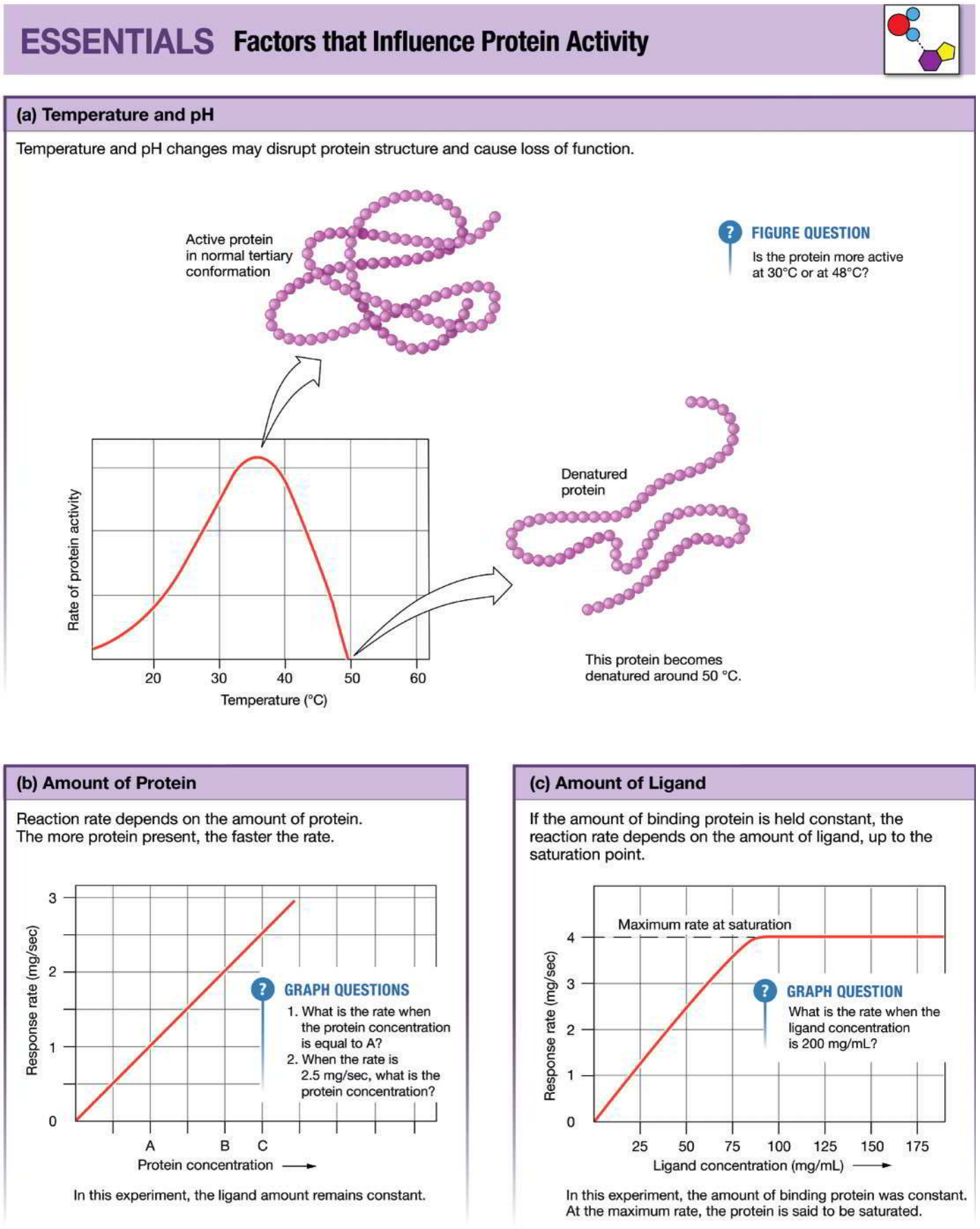
Regulating protein concentration is an important strategy that cells use to control their physiological processes. Cells alter the amount of a protein by influencing both its synthesis and its breakdown. If protein synthesis exceeds breakdown, protein accumulates and the reaction rate increases. If protein breakdown exceeds synthesis, the amount of protein decreases, as does the reaction rate. Even when the amount of protein is constant, there is still a steady turnover of protein molecules.

Reaction Rate Can Reach a Maximum

If the concentration of a protein in a cell is constant, then the concentration of the ligand determines the magnitude of the response. Fewer ligands activate fewer proteins, and the response is low. As ligand concentrations increase, so does the magnitude of the response, up to a maximum where all protein binding sites are occupied.

Figure 2.13c shows the results of a typical experiment in which the protein concentration is constant but the concentration of ligand varies. At low ligand concentrations, the response rate is directly proportional to the ligand concentration. Once the concentration of ligand molecules exceeds a certain level, the protein molecules have no more free binding sites. The proteins are fully occupied, and the rate reaches a maximum value. This condition is known as **saturation.** Saturation applies to enzymes, membrane transporters, receptors, binding proteins, and immunoglobulins.

Fig. 2.13 ESSENTIALS Factors That Influence Protein Activity



An analogy to saturation appeared in the early days of television on the *I Love Lucy* show and can be viewed today by searching YouTube (https://www.youtube.com/watch?v=AnHiAWlrYQc). Lucille Ball's character was working at the conveyor belt of a candy factory, wrapping chocolates to go into a candy box. Initially, the belt moved slowly, and she had no difficulty wrapping the candy. Gradually, the belt brought candy to her more rapidly, and she had to increase her wrapping speed to keep up. Finally, the belt brought candy to her so fast that she could not wrap it all because she was working at her maximum rate. That was Lucy's saturation point.

In conclusion, you have now learned about the important and nearly universal properties of proteins: shape-function relationships, ligand binding, specificity, competition, activation/inhibition, and saturation. You will revisit these concepts many times as you work through the organ systems of the body.

Concept Check

16. What happens to the rate of an enzymatic reaction as the amount of enzyme present decreases?
17. What happens to the rate of an enzymatic reaction when the enzyme has reached saturation?

Running Problem 2.7 Conclusion: Chromium Supplements

In this running problem, you learned that claims of chromium picolinate's ability to enhance muscle mass have not been supported by evidence from controlled scientific experiments. You also learned that studies suggest that the biological trivalent form of chromium may damage cells. In 2022 the NIH *Chromium Fact Sheet for Health Professionals*[5] says evidence indicates chromium may not be an essential nutrient as previously believed and there is insufficient research at this time to support its use as a nutritional supplement. Now compare your answers with those in the summary table.

Question	Facts	Integration and Analysis
Q1: *What is chromium's atomic number? Atomic mass? How many electrons does one atom of chromium have?*	Reading from the table, chromium (Cr) has an atomic number of 24 and an average atomic mass of 52. Atomic number is the number of protons in one atom. An atom has equal numbers of protons and electrons.	The atomic number of chromium is 24; therefore, one atom of chromium has 24 protons and 24 electrons.
Q2: *Which elements close to chromium are also essential elements?*	Molybdenum, manganese, and iron.	N/A
Q3: *If people have chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*	Chromium helps move glucose from blood into cells.	If chromium is absent or lacking, less glucose would leave the blood and blood glucose would be higher than normal.
Q4: *From the result of the Chinese study, can you conclude that all people with diabetes suffer from chromium deficiency?*	Higher doses of chromium supplements lowered elevated blood glucose levels, but lower doses have no effect. This is only one study, and no information is given about similar studies elsewhere.	We have insufficient evidence from the information presented to draw a conclusion about the role of chromium deficiency in diabetes.
Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*	For each electron lost from an ion, a positively charged proton is left behind in the nucleus of the ion.	The hexavalent ion of chromium, Cr^{6+}, has six unmatched protons and therefore has lost six electrons. The trivalent ion, Cr^{3+}, has lost three electrons.
Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*	The hexavalent form is used in industry and, when inhaled, has been linked to an increased risk of lung cancer. Enough studies have shown an association that California's Hazard Evaluation System and Information Service has issued warnings to chromium workers. Evidence to date for toxicity of trivalent chromium in chromium picolinate comes from studies done on isolated cells in tissue culture.	Although the toxicity of Cr^{6+} is well established, the toxicity of Cr^{3+} has not been conclusively determined. Studies performed on cells in vitro may not be applicable to humans. Additional studies need to be performed in which animals are given reasonable doses of chromium picolinate for an extended period of time.
Q7: *Based on the study that did not support enhanced muscle development from chromium supplements and the studies that suggest that chromium picolinate might cause cancer, do you think Malik should continue taking picolinate?*	No research evidence supports a role for chromium picolinate in increasing muscle mass or strength in humans. Other research suggests that chromium picolinate may cause cancerous changes in isolated cells.	The evidence presented suggests that for Malik, there is no benefit from taking chromium picolinate, and there may be risks. Using risk–benefit analysis, the evidence supports stopping the supplements. However, the decision is Malik's personal responsibility. He should keep himself informed of new developments that would change the risk–benefit analysis.

Chemistry Review Quiz

Use this quiz to see what areas of chemistry and basic biochemistry you might need to review. The title above each set of questions refers to a review figure on this topic. Answers are in Appendix A.

Atoms and Molecules (Fig. 2.5)

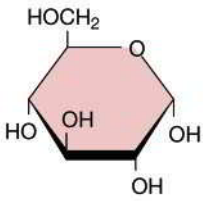
Match each subatomic particle in the left column with all the phrases in the right column that describe it. A phrase may be used more than once.

1. electron	(a) one has atomic mass of 1 amu
2. neutron	(b) found in the nucleus
3. proton	(c) negatively charged
	(d) changing the number of these in an atom creates a new element
	(e) adding or losing these makes an atom into an ion
	(f) gain or loss of these makes an isotope of the same element
	(g) determine(s) an element's atomic number
	(h) contribute(s) to an element's atomic mass

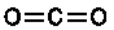
4. Isotopes of an element have the same number of _____ and _____, but differ in their number of _____. Unstable isotopes emit energy called _____.
5. Name the element associated with each of these symbols: C, O, N, and H.
6. Write the one- or two-letter symbol for each of these elements: phosphorus, potassium, sodium, sulfur, calcium, and chlorine.
7. Use the periodic table of the elements to answer the following questions:
   (a) Which element has 30 protons?
   (b) How many electrons are in one atom of calcium?
   (c) Find the atomic number and average atomic mass of iodine.
   (d) What is the letter symbol for iodine?
8. A magnesium ion, Mg^{2+}, has (*gained/lost*) two (*protons/ neutrons/ electrons*).
9. H^+ is also called a proton. Why is it given that name?
10. Use the periodic table of the elements to answer the following questions about an atom of sodium.
    (a) How many electrons does the atom have?
    (b) What is the electrical charge of the atom?
    (c) How many neutrons does the average atom have?
    (d) If this atom loses one electron, it would be called a(n) *anion/cation*.
    (e) What would be the electrical charge of the substance formed in (d)?
    (f) Write the chemical symbol for the ion referred to in (d).
    (g) What does the sodium atom become if it loses a proton from its nucleus?
    (h) Write the chemical symbol for the atom referred to in (g).

11. Write the chemical formulas for each molecule depicted. Calculate the molecular weight of each molecule.

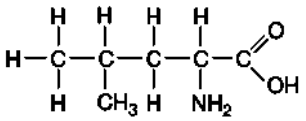
(a)



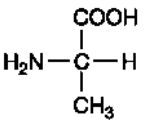
(b)



(c)



(d)



Lipids (Fig. 2.1)

12. Match each lipid with its best description.

(a) triglyceride	**1. most common form of lipid in the body**
(b) eicosanoid	**2. liquid at room temperature, usually from plants**
(c) steroid	**3. important component of cell membrane**
(d) oil	**4. structure composed of carbon rings**
(e) phospholipids	**5. modified 20-carbon fatty acid**

13. Use the chemical formulas given to decide which of the following fatty acids is most **unsaturated**:
    (a) $C_{18}H_{36}O_2C_{18}H_{36}O_2$
    (b) $C_{18}H_{34}O_2$
    (c) $C_{18}H_{30}O_2$

Carbohydrates (Fig. 2.2)

14. Match each carbohydrate with its description.

(a) starch	1. monosaccharide
(b) chitin	2. disaccharide, found in milk
(c) glucose	3. storage form of glucose for animals
(d) lactose	4. storage form of glucose for plants
(e) glycogen	5. structural polysaccharide of invertebrates

Proteins (Fig. 2.3)

15. Match these terms pertaining to proteins and amino acids:

(a) the building blocks of proteins	1. essential amino acids
(b) must be included in our diet	2. primary structure
(c) protein catalysts that speed the rate of chemical reactions	3. amino acids
	4. globular proteins
(d) sequence of amino acids in a protein	5. enzymes
(e) protein chains folded into a ball-shaped structure	6. tertiary structure
	7. fibrous proteins

16. What aspect of protein structure allows proteins to have more versatility than lipids or carbohydrates?
17. Peptide bonds form when the _____ group of one amino acid joins the _____ of another amino acid.

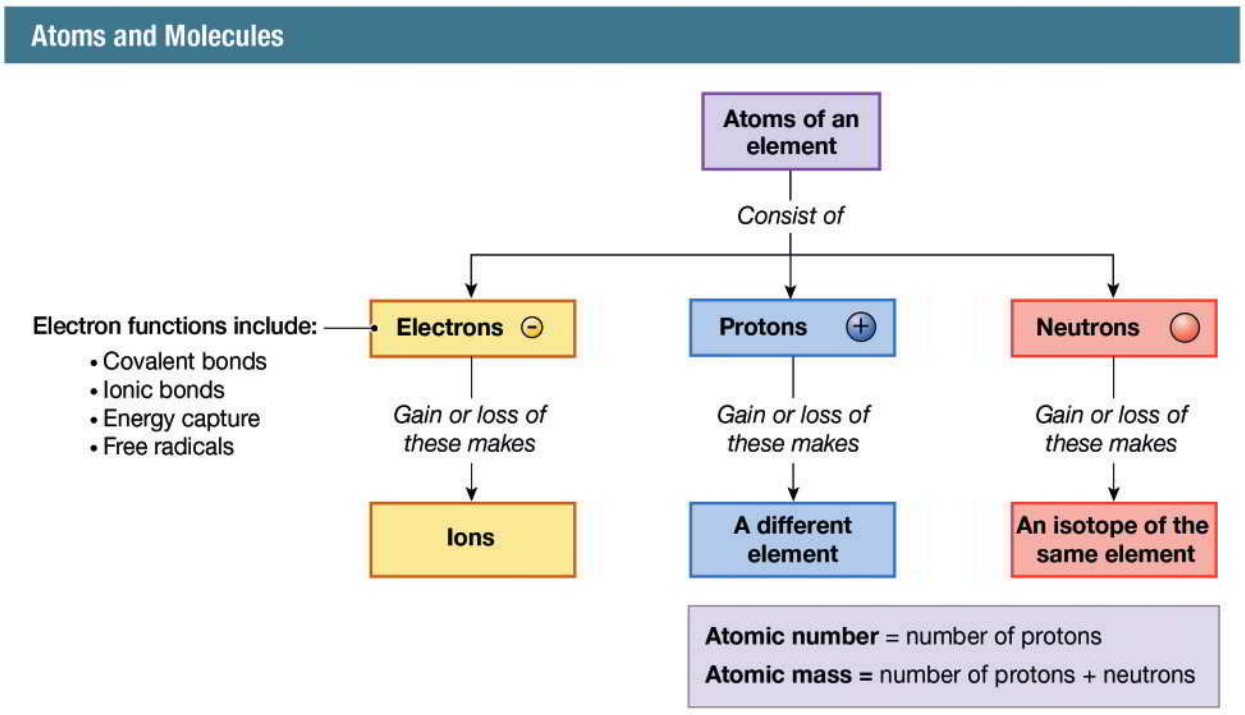
Nucleotides (Fig. 2.4)

18. List the three components of a nucleotide.
19. Compare the structure of DNA with that of RNA.
20. Distinguish between purines and pyrimidines.

Chapter Summary

This chapter has focused on the core concept of molecular interactions. Key ideas that will occur repeatediy in your study of physiology include:

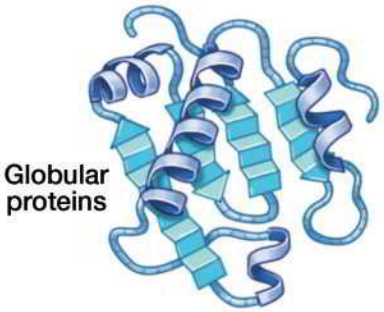
- The four main classes of **biomolecules**, their building blocks and variations. Fig. 2.1-2.4
- Key elements, **functional groups**, and **ions**. Tbl. 2.1, 2.2, Fig. 2.5
- The importance of **noncovalent interactions** in molecular shape and **solubility**. Fig. 2.6, 2.8
- **Solutions** and how to express concentration. Fig. 2.7
- Acids, bases, and **pH** Fig. 2.9
- The importance of **protein binding interactions** that play a role in nearly every physiological process. Fig. 2.8, 2.10



Functional Categories of Proteins

- Enzymes
- Membrane transporters
- Signal molecules
- Receptors
- Binding proteins
- Immunoglobulins
- Molecular motors
- Structural proteins
- Regulatory proteins

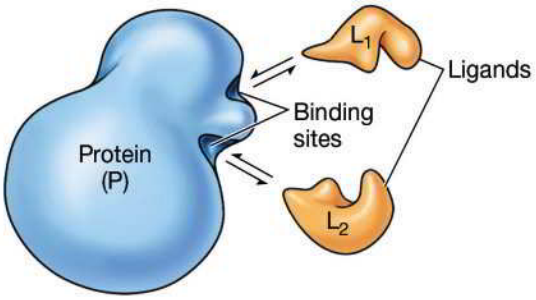
Fibrous proteins

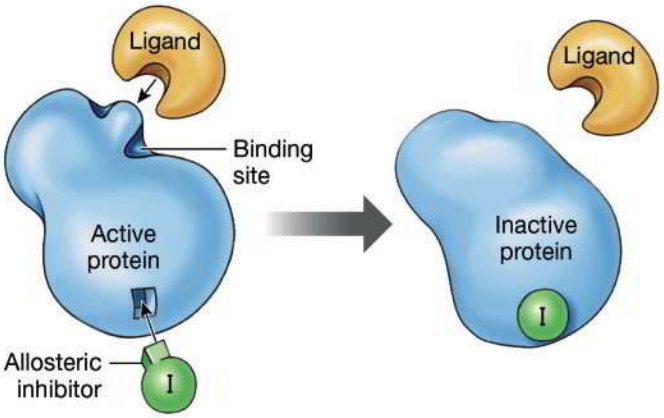


Protein Binding Interactions

Proteins (P) bind to Ligands (L)

$P + L \rightleftharpoons PL$

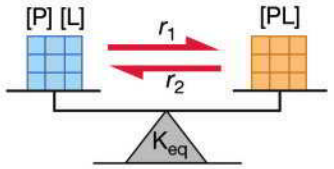




Protein binding demonstrates:

- **Specificity** and **affinity** for ligands
  - **Isoforms** of proteins
- **Competition** for the binding site
  - From **agonists**
  - From **antagonists** (competitive inhibitors)
- **Modulation** Fig. 2.12, 2.13
  - Activate, enhance, or inhibit
  - Reversible or irreversible
  - Noncovalent interaction or covalent bonding
  - At binding site or allosteric
  - Molecular or temperature, pH

Law of Mass Action Fig. 2.11



Rate of reaction in forward direction (r_1) = Rate of reaction in reverse direction (r_2)

At equilibrium

Equilibrium Constant K_{eq}

$$K_{eq} = \frac{[PL]}{[P]\,[L]}$$

Larger K_{eq} means higher affinity of the protein for the ligand.

Links to Resources

[1]DM Stearns *et al*. Chromium(III) picolinate produces chromosome damage in Chinese hamster ovary cells. *FASEB J* 9: 1643–1648, 1995. *https://doi.org/10.1096/fasebj.9.15.8529845*

[2]DM Stearns *et al*. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. *Mutat Res Genet Toxicol Environ Mutagen* 513: 135–142, 2002.*https://doi.org/10.1016/S1383-5718(01)00301-1*

[3]The reciprocal of the equilibrium constant is called the **dissociation constant** (K_d).

$$K_d = \frac{[P][L]}{[PL]}$$

A large K_d indicates low binding affinity of the protein for the ligand, with more P and L remaining in the unbound state. Conversely, a small K_d indicates higher protein affinity for the ligand.

[4]MA Hallmark *et al*. Effects of chromium and resistive training on muscle strength and body composition. *Med Sci Sports Exerc* 28(1):139–144,1996.*https://doi.org/10.1097/00005768-199601000-00025*

[5]National Institutes of Health (NIH) Office of Dietary Supplements (ODS). *Chromium: Fact sheet for health professionals*. 2022. *https://ods.od.nih.gov/factsheets/Chromium-HealthProfessional/*

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. List the four kinds of biomolecules. Give an example of each kind that is relevant to physiology.
2. True or false? All organic molecules are biomolecules.
3. When atoms bind tightly to one another, such as H_2O or O_2, one unit is called a(n) _____.
4. An atom of carbon has four unpaired electrons in an outer shell with space for eight electrons. How many covalent bonds will one carbon atom form with other atoms?
5. Fill in the blanks with the correct bond type.

   In a(n) _____ bond, electrons are shared between atoms. If the electrons are attracted more strongly to one atom than to the other, the molecule is said to be a(n) _____ molecule. If the electrons are evenly shared, the molecule is said to be a(n) _____ molecule.
6. Name two elements whose presence contributes to a molecule becoming a polar molecule.
7. Based on what you know from experience about the tendency of the following substances to dissolve in water, predict whether they are polar or nonpolar molecules: table sugar, vegetable oil.
8. A negatively charged ion is called a(n) _____, and a positively charged ion is called a(n) _____.
9. Define the pH of a solution. If pH is less than 7, the solution is _____; if pH is greater than 7, the solution is _____.
10. A molecule that moderates changes in pH is called a _____.
11. Proteins combined with fats are called _____, and proteins combined with carbohydrates are called _____.
12. A molecule that binds to another molecule is called a(n) _____.
13. Match these definitions with their terms (not all terms are used):

(a) the ability of a protein to bind one molecule but not another	1. irreversible inhibition
(b) the part of a protein molecule that binds the ligand	2. induced fit
(c) the ability of a protein to alter shape as it binds a ligand	3. binding site
	4. specificity
	5. saturation

14. An ion, such as Ca^{2+} or Mg^{2+}, that must be present in order for an enzyme to work is called a(n) _____.
15. A protein whose structure is altered to the point that its activity is destroyed is said to be _____.

Level Two Reviewing Concepts

16. Mapping exercise: Make the list of terms into a map describing solutions.

• concentration	• nonpolar molecule
• equivalent	• polar molecule
• hydrogen bond	• solubility
• hydrophilic	• solute
• hydrophobic	• solvent
• molarity	• water
• mole	

17. A solution in which $[H^+] = 10^{-3}$ M is (acidic/basic), whereas a solution in which $[H^+] = 10^{-10}$ M is (acidic/basic). Give the pH for each of these solutions.
18. Name three nucleotides or nucleic acids, and tell why each one is important.
19. You know that two soluble proteins are isoforms of each other. What can you predict about their structures, functions, and affinities for ligands?

20. You have been asked to design some drugs for the purposes described next. Choose the desirable characteristic(s) for each drug from the numbered list.

(a) Drug A must bind to an enzyme and enhance its activity.	1. antagonist
(b) Drug B should mimic the activity of a normal nervous system signal molecule.	2. competitive inhibitor
(c) Drug C should block the activity of a membrane receptor protein.	3. agonist
	4. allosteric activator
	5. covalent modulator

Level Three Problem Solving

21. You have been summoned to assist with the autopsy of an alien being whose remains have been brought to your lab. The chemical analysis returns with 33% C, 40% O, 4% H, 14% N, and 9% P. From this information, you conclude that the cells contain nucleotides, possibly even DNA or RNA. Your assistant is demanding that you tell him how you knew this. What do you tell him?

22. The harder a cell works, the more CO_2 it produces. CO_2 is carried in the blood according to the following equation:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

What effect does hard work by your muscle cells have on the pH of the blood?

Level Four Quantitative Problems

23. Calculate the amount of NaCl you would weigh out to make one liter of 0.9% NaCl. Explain how you would make a liter of this solution.

24. A 1.0 M NaCl solution contains 58.5 g of salt per liter.

a. How many molecules of NaCl are present in 1 L of this solution?

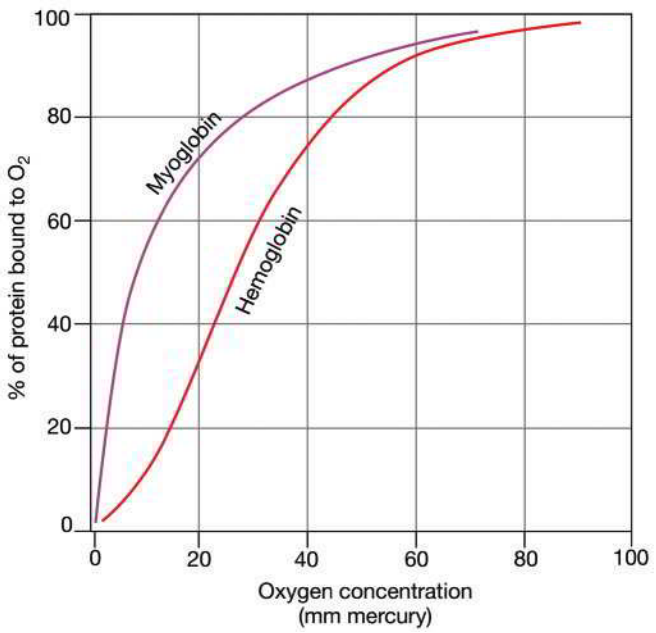
b. How many millimoles of NaCl are present?

c. How many **equivalents** of Na^+ are present?

d. Express 58.5 g of NaCl per liter as a **percent solution**.

25. How would you make 200 mL of a 10% glucose solution? Calculate the molarity of this solution. How many millimoles of glucose are present in 500 mL of this solution? (*Hint:* What is the molecular mass of glucose?)

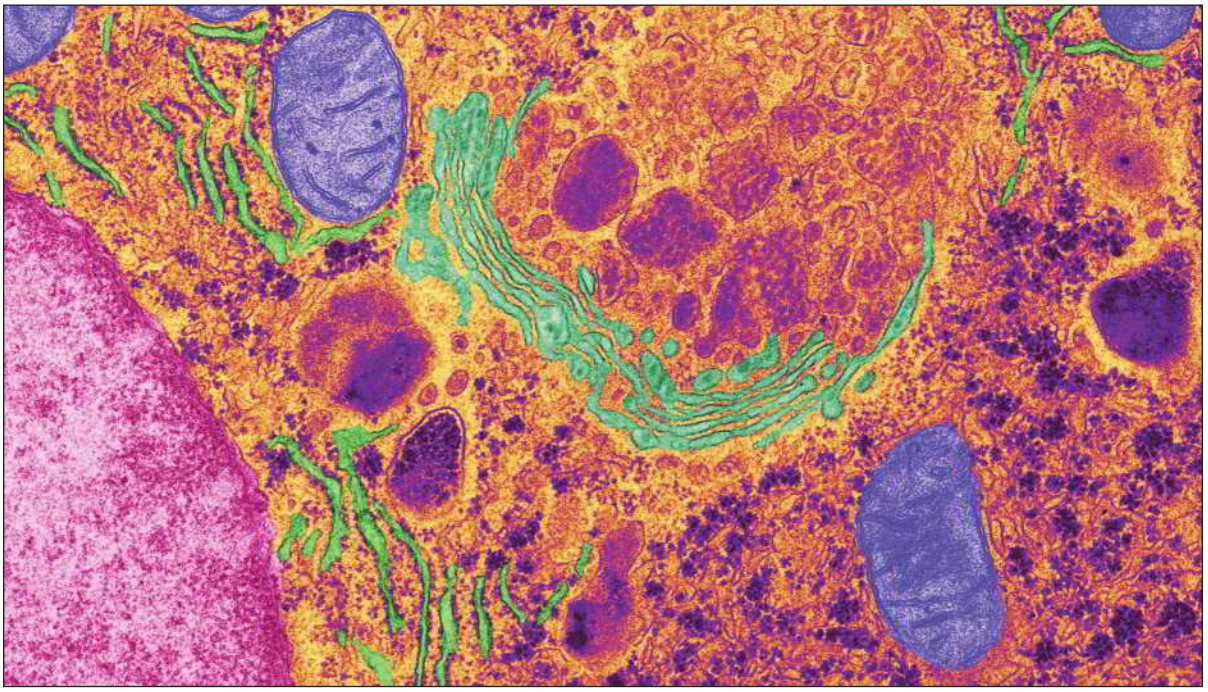
26. The graph shown below represents the binding of oxygen molecules (O_2) to two different proteins, myoglobin and hemoglobin, over a range of oxygen concentrations. Based on the graph, which protein has the higher affinity for oxygen? Explain your reasoning.



Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

3

Compartmentation: Cells and Tissues



Colored electron micrograph of liver organelles

Cells are organisms, and entire animals and plants are aggregates of these organisms.

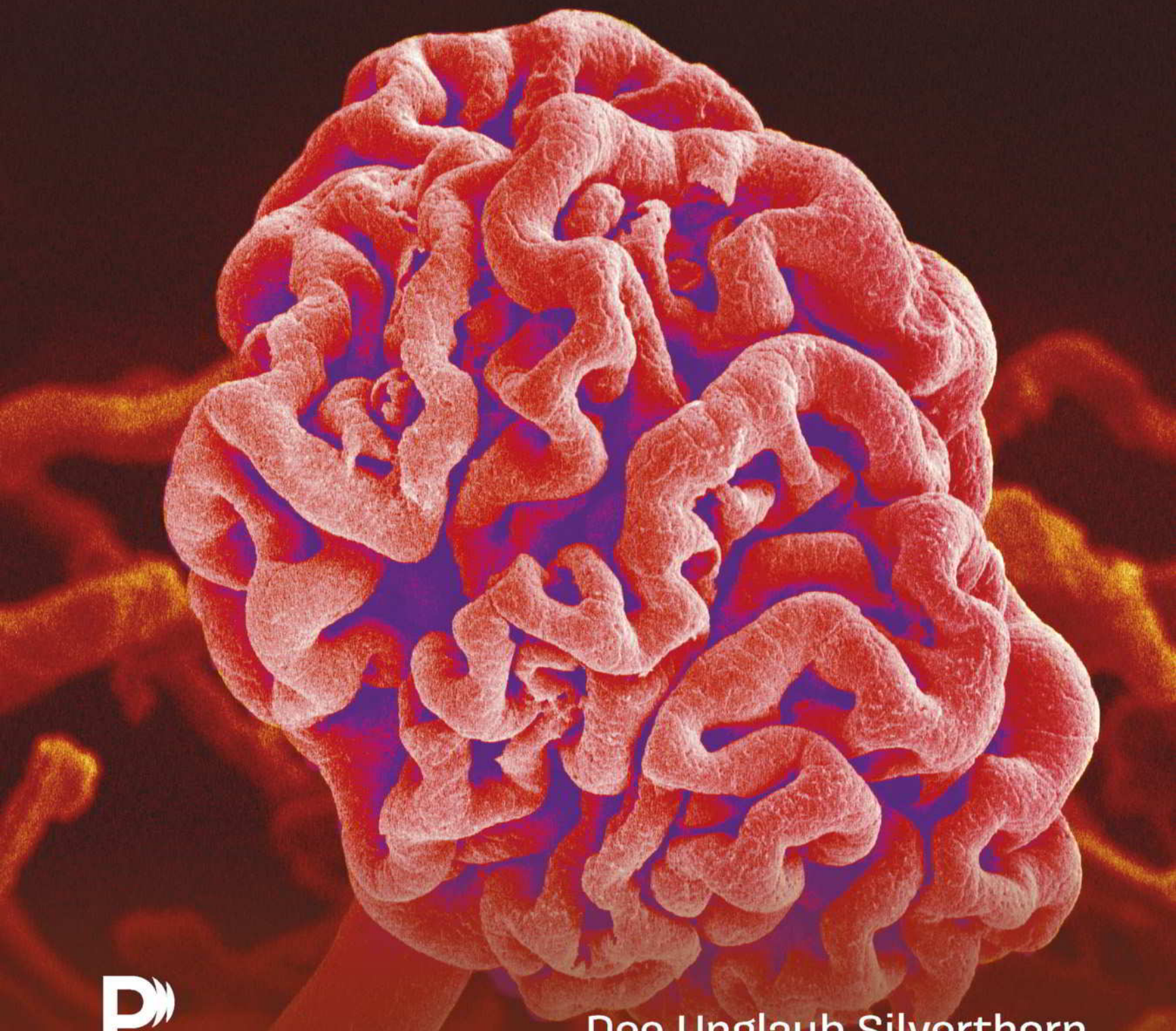
Theodor Schwann, 1839

This chapter focuses on the core concept of compartmentation. The human body has functional compartments at all levels of organization, from the large body cavities like the abdomen to nearly invisible compartments within cells. Compartments serve a vital function by allowing physiological and biochemical processes to be separated in space.

Compartmentation

HUMAN PHYSIOLOGY

AN INTEGRATED APPROACH NINTH EDITION



Dee Unglaub Silverthorn

This page intentionally left blank

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- **Bioflix:** Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- **Bioflix:** Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- **Bioflix:** Electron Transport System
- **Bioflix:** Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- **Physiology in Action:** Osmolarity and Tonicity

Module 5.2

- **A&P Flix:** Membrane Transport

Module 5.7

- **Physiology in Action:** Membrane Potential
- **A&P Flix:** Resting Membrane Potential

Chapter 5 Links to Resources

- **Interactive Physiology Animation:** Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- **Microbiology Animation:** Host Defenses

Module 7.3

- **Microbiology Animation:** Antigen Processing and Presentation: Overview

Module 7.7

- **Microbiology Animation:** Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- **Bioflix:** Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- **BioFlix:** How Synapses Work

Module 9.3

- **Interactive Physiology Animation:** Generation of an Action Potential
- **BioFlix:** Action Potential Conduction

Chapter 9 Links to Resources

- **Interactive Physiology 2.0 Animation:** Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- **Biointeractives:** Circadian Rhythms and the SCN

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

Module 12.2

- **A&P Flix:** The Cross Bridge Cycle

Chapter 13 Muscles

Module 13.1

- **A&P Flix:** The Cross Bridge Cycle
- **Interactive Physiology Animation:** Neuromuscular Junction
- **Interactive Physiology 2.0 Animation:** Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- **Interactive Physiology Animation:** Pathway of Blood through the Heart
- **Interactive Physiology Animation:** Action Potentials in Autorhythmic Cells

Module 15.4

- **Physiology in Action:** Electrocardiogram
- **Interactive Physiology Animation:** Intrinsic Conduction System of the Heart
- **Interactive Physiology Animation:** Cardiac Output

Chapter 15 Links to Resources

- **Interactive Physiology 2.0 Animation:** Electrical Activity of the Heart
- **Interactive Physiology 2.0 Animation:** Cardiac Cycle
- **Interactive Physiology 2.0 Animation:** Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- **Physiology in Action:** Orthostatic Hypotension
- **Interactive Physiology Animation:** Arterial Baroreceptor Reflex

Chapter 16 Links to Resources

- **Interactive Physiology Animation:** Factors Affecting Blood Pressure
- **Interactive Physiology 2.0 Animations:** Factors Affecting Blood Pressure

Chapter 18 Mechanics of Breathing

Module 18.3

- **Physiology in Action:** The Spirometer
- **Physiology in Action:** Subatmospheric Pleural Cavity
- **Physiology in Action:** Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- **BioFlix:** Gas Exchange
- **Physiology in Action:** Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- **Interactive Physiology 2.0 Animation:** Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- **Interactive Physiology Animation:** Glomerular Filtration

Module 20.6

- **Interactive Physiology 2.0 Animation:** Prox tubule Reabsorption & Secretion

Module 20.7

- **Physiology in Action:** Renal Clearance

Chapter 20 Links to Resources

- **Interactive Physiology 2.0 Animation:** Glomerular Filtration
- **Interactive Physiology Animation:** Anatomy Review: Urinary System
- **Interactive Physiology 2.0 Animation:** Tubular Reabsorption & Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- **Interactive Physiology Animation:** Aldosterone and ADH in Salt & Water Processing
- **Interactive Physiology Animation:** Mechanisms for Acid-Base Homeostasis
- **Interactive Physiology Animation:** Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- **Interactive Physiology Animation:** Anatomy Review
- **Interactive Physiology Animation:** Control of Digestion
- **Interactive Physiology Animation:** Digestive System Secretion
- **Interactive Physiology Animation:** Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- **Physiology in Action:** Blood Pressure and Exercise

Strategies for Success

Top Ten Ways to Succeed in Classes that Use Active Learning

By Marilla Svinicki, Ph.D., former Director of the University of Texas Center for Teaching Effectiveness

1. Make the switch from an authority-based conception of learning to a self-regulated conception of learning. Recognize and accept your own responsibility for learning.
2. Be willing to take risks and go beyond what is presented in class or the text.
3. Be able to tolerate ambiguity and frustration in the interest of understanding.
4. See errors as opportunities to learn rather than failures. Be willing to make mistakes in class or in study groups so that you can learn from them.
5. Engage in active listening to what's happening in class.
6. Trust the instructor's experience in designing class activities and participate willingly if not enthusiastically.
7. Be willing to express an opinion or hazard a guess.
8. Accept feedback in the spirit of learning rather than as a reflection of you as a person.
9. Prepare for class physically, mentally, and materially (do the reading, work the problems, etc.).
10. Provide support for your classmate's attempts to learn. The best way to learn something well is to teach it to someone who doesn't understand.

Dr. Dee's Eleventh Rule:
DON'T PANIC! Pushing yourself beyond the comfort zone is scary, but you have to do it in order to improve.

Word Roots for Physiology

Simplify physiology and medicine by learning Latin and Greek word roots. The list below has some of the most common ones.

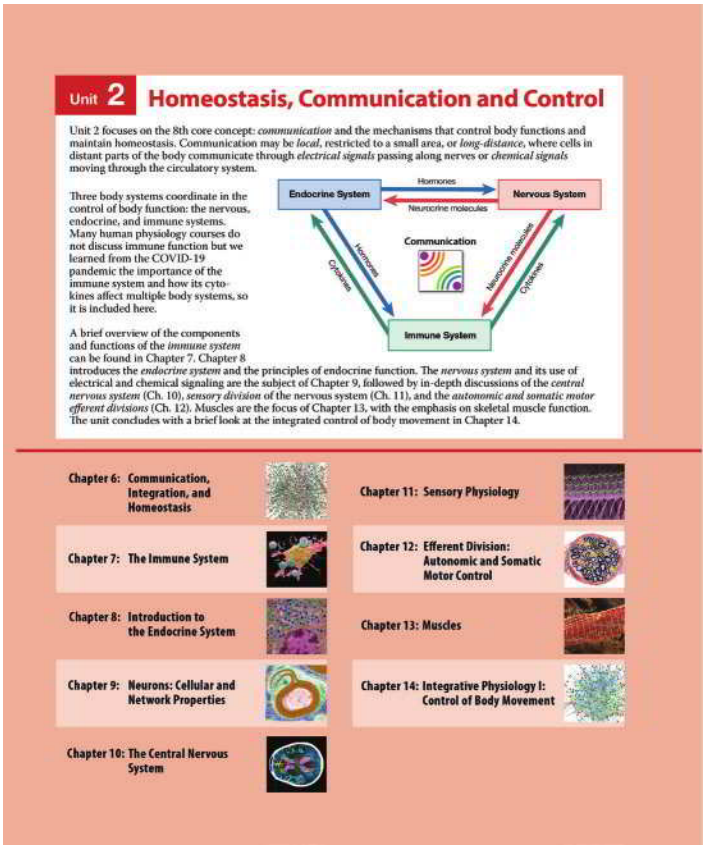
Using the list, can you figure out what *hyperkalemia* means?*

a- or **an-** without, absence
anti- against
-ase signifies an enzyme
auto self
bi- two
brady- slow
cardio- heart
cephalo- head
cerebro- brain
contra- against
-crine a secretion
crypt- hidden
cutan- skin
-cyte or **cyto-** cell
de- without, lacking
di- two
dys- difficult, faulty
-elle small
-emia in the blood
endo- inside or within
epi- over
erythro- red
exo- outside
extra- outside
gastro- stomach
-gen, -genie produce
gluco-, glyco- sugar or sweet
hemi- half
hemo- blood
hepato- liver
homo- same
hydro- water
hyper- above or excess
hypo- beneath or deficient
inter- between
intra- within
-itis inflammation of
kali- potassium
leuko- white
lipo- fat
lumen inside of a hollow tube
-lysis split apart or rupture
macro- large
micro- small
mono- one
multi- many
myo- muscle
oligo- little, few
para- near, close
patho-, -pathy related to disease
peri- around
poly- many
post- after
pre- before
pro- before
pseudo- false
re- again
retro- backward or behind
semi- half
sub- below
super- above, beyond
supra- above, on top of
tachy- rapid
trans- across, through

*Hyper = excess, kali = potassium, -emia = in the blood, or elevated blood potassium

Owner's Manual

Welcome to Human Physiology! As you begin your study of the human body, one of your main tasks will be to construct for yourself a global view of the body, its systems, and the many processes that keep the systems working. This "big picture" is what physiologists call the integration of systems, and it is a key theme in this book. To integrate information, however, you must do more than simply memorize it. You need to truly understand it and be able to use it to solve problems that you have never encountered before. If you are headed for a career in the health professions, you will do this in the clinics. If you plan a career in biology, you will solve problems in the laboratory, field, or classroom. Analyzing, synthesizing, and evaluating information are skills you need to develop while you are in school, and I hope that the features of this book will help you with this goal.



Pattern recognition is important for all healthcare professionals, so you can begin to develop this skill by learning the **core concepts of physiology** that repeat over and over as you study different organ systems. The core concepts are introduced in Unit 1, and each chapter begins with a brief summary of the core concepts in that chapter.

We have also retained the four approaches to learning physiology that proved so popular since this book was first published.

1. **Cellular and Molecular Physiology**
   Most physiological research today is being done at the cellular and molecular level, and there are constantly exciting developments in molecular medicine and physiology. For example, scientists have discovered a new method of cell-to-cell communication: exosomes and ectosomes. We are still learning how these extracellular vesicles play a role in health and disease. Look for similar links between molecular and cellular biology, physiology, and medicine throughout the book.

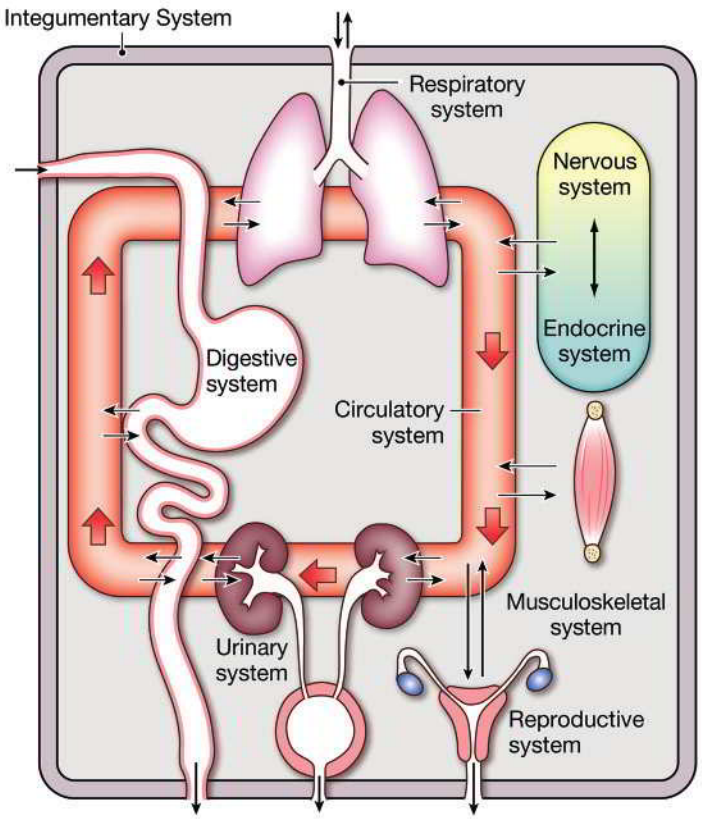
2. **Physiology is a Dynamic Field**
   Physiology is a dynamic discipline, with numerous unanswered questions that merit further investigation and research. Many of the "facts" presented in this text are really only our current theories, so you should be prepared to update your mental models as new information emerges from scientific research.

3. **Physiology is Integrative**
   The organ systems of the body do not work in isolation, although we study them one at a time. To emphasize the integrative nature of physiology, three chapters (Chapters 14, 21, and 25) focus on how the physiological processes of multiple organ systems coordinate with each other, especially when homeostasis is challenged.

4. **A Focus on Problem Solving**
   One of the most valuable life skills all students should acquire is the ability to think critically and use information to solve problems. As you study physiology, you should be prepared to practice these skills. You will find a number of "test yourself" questions designed to challenge your critical thinking and analysis skills.

One of my aims is to provide you not only with information about how the human body functions but also with tips for studying and problem solving. Many of these study aids have been developed with the input of my students, so I think you may find them particularly helpful. The list below is a brief tour of the special features of the book, especially those that you may not have encountered previously in textbooks. Please take a few minutes to read about them so that you can make optimum use of the book as you study.

- **Learning Outcomes** on the chapter opening page list the key questions you should be able to answer by the end of the chapter.
- **Background Basics**, also on the chapter opening page, lists topics you will need to master for understanding the material that follows. The terms include links for review.
- **Anatomy Summaries** provide succinct visual overviews of a physiological system from a macro to micro perspective. Whether you are learning the anatomy for the first time or refreshing your memory, these summaries show you the essential features of each system in a single figure
- **Essentials and Review figures** occur throughout the book. These figures distill the basics about a topic onto one or two pages, much as the Anatomy Summaries do. My students tell me they find them particularly useful for review when there isn't time to go back and read all the text.
- **Reflex Pathways & Concept Maps** organize physiological processes and details into a logical, visual format. These figures use consistent colors and shapes to represent different steps, making it easier to understand complex physiological processes. Chapter 1 includes a special Focus On feature showing you how to do your own concept mapping.
- **Running Problems** in each chapter are clinical scenarios related to the chapter topic. Read the segments as you work through the text and see if you can answer the questions that ask you to apply what you're learning to the problem. Answers are in the summary table at the conclusion of the problem.



- **Figure Questions and Graph Questions** challenge you to apply visual literacy or data interpretation skills as you read an illustration, photo, or graph.
- **Concept Checks** are placed at intervals throughout the chapters, helping to test your understanding before continuing to the next topic. Click the interactive buttons to show the answer or get a hint.
- **Quick Reference to Integrated Media by Chapter** provides an easy reference to key animations and videos.
- The **Appendices** have answers to the end-of-chapter questions, as well as reviews of physics, logarithms, and basic genetics.
- The **Useful Resources** section of the eTextbook includes a periodic table of the elements, diagrams of anatomical positions of the body, tables with unit conversions. and normal values of blood components.

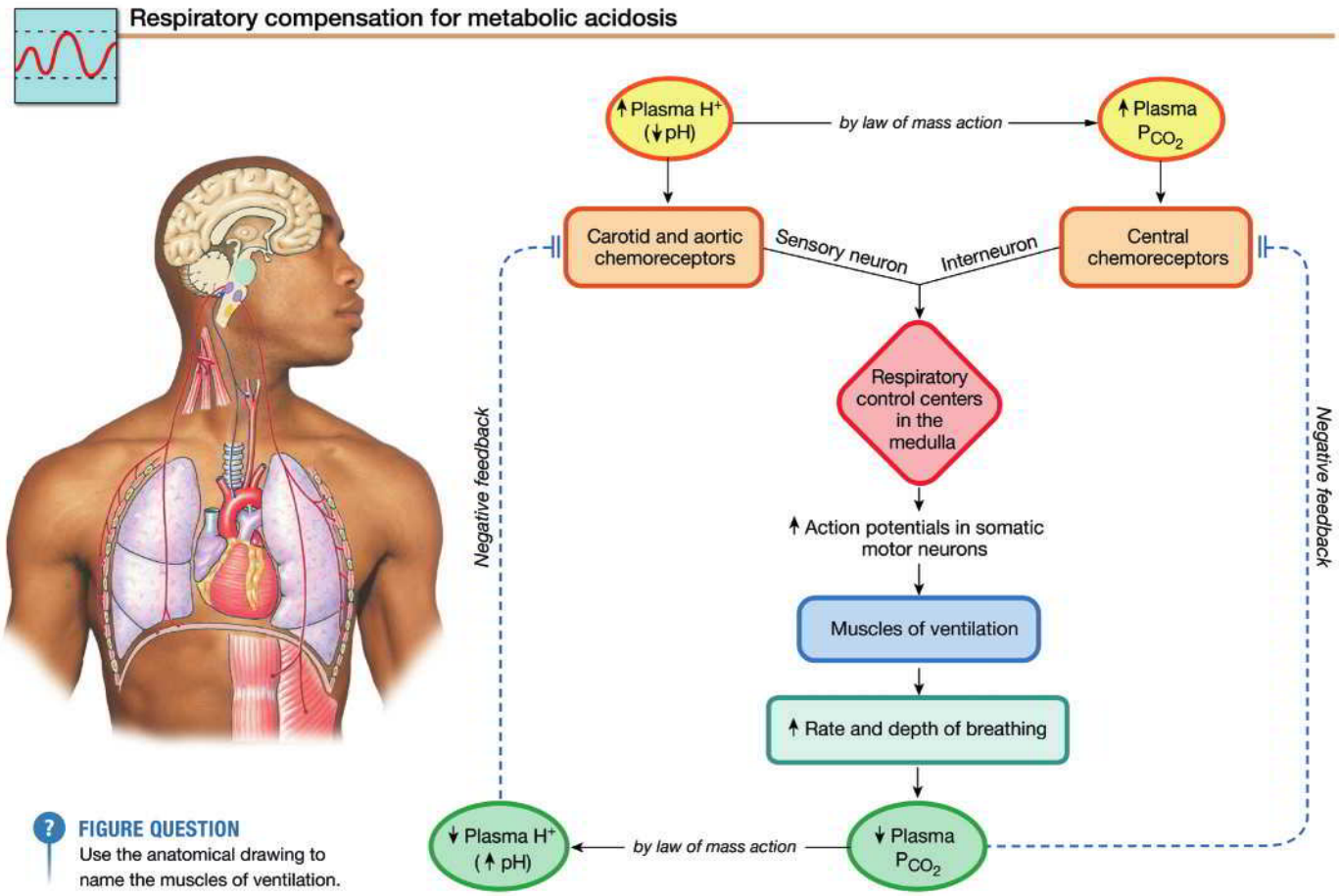
Take a few minutes to look at all these features so that you can make optimum use of them.

It is my hope that by using this book, you will develop an integrated view of physiology that allows you to enter your chosen profession with respect for the complexity of the human body and a clear vision of the potential of physiological and biomedical research. May you find physiology as fun and exciting I do. Good luck with your studies!

Warmest regards,

Dr. Dee (as my students call me)

silverthorn@utexas.edu



Human Physiology

An Integrated Approach

Ninth Edition

Dee Unglaub Silverthorn, Ph.D.
UNIVERSITY OF TEXAS, AUSTIN

with contributions by

Bruce R. Johnson, Ph.D.
CORNELL UNIVERSITY

Michael Chirillo, M.D., Ph.D.
UNIVERSITY OF RHODE ISLAND

and

William C. Ober, M.D.
ILLUSTRATION COORDINATOR

Claire E. Ober, R.N.
ILLUSTRATOR

Anita Impagliazzo
ILLUSTRATOR

Andrew C. Silverthorn, M.D.
CLINICAL CONSULTANT

Pearson

Content and Product Management: Michael Gillespie; Serina Beauparlant; Alexa Frank; Caroline Ayres; Ayushi Khandelwal
Content Production: Katie Foley; Titas Basu; Win Clark; Sharon Cahill; Francesca Monaco; Annamarie Boley, *Straive*; Kerri Tomasso, *Straive*; Rajesh Kumar Rajan, *Straive*; Carrie Keller, *Straive*; Krishnamurthy Muralidharan, *Straive*; Rebecca Marshall, *Lachina*; Molly Montanaro, *Lachina*; Cathryn Gear, *Lachina*; Lalitha Srinivasan, *Continual Engine*; Kani Kapoor, *Integra*
Product Marketing: Courtney Davis, Tim Galligan, Yez Alayan
Rights and Permissions: Ben Ferrini; Matthew Perry, *Straive*; Chenley Calites, *Straive*

Please contact www.AskPearsonSupport.com with any queries on this content.

Pearson puts care into the creation of our products. Our learning materials undergo content reviews to minimize bias and ensure the content is inclusive, accurate, and relevant. Please use this link to report instances of bias and inaccuracies: https://www.pearson.com/report-bias.html

You can learn more about Pearson's commitment to accessibility at https://www.pearson.com/us/accessibility.html

Cover Image by Susumu Nishinaga/Science Source.

Library of Congress Cataloging-in-Publication Data
Library of Congress Control Number: 2025938090

$PrintCode

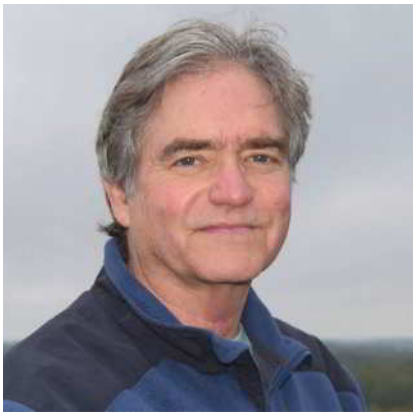
Pearson

ISBN 10: 0-135-31445-3
ISBN 13: 978-0-135-31445-6

About the Author

DEE UNGLAUB SILVERTHORN studied biology as an undergraduate at Newcomb College of Tulane University, where she did research on cockroaches. For graduate school, she switched to studying crabs and received a PhD in marine science from the Belle W. Baruch Institute for Marine and Coastal Sciences at the University of South Carolina. Her research interest is epithelial transport in systems ranging from the crab gill to the chick allantoic membrane. Dr. Dee has taught in a variety of settings, from medical schools (Medical University of South Carolina, Dell Medical School, UT-Austin) to high school. For most of her career, at the University of Texas–Austin, she has taught undergraduate and graduate physiology lectures and labs, and she trains graduate students to develop teaching skills in the life sciences. Dr. Dee has received numerous teaching awards and honors, including a UT System Regents' Outstanding Teaching Award, the American Physiological Society (APS) Arthur C. Guyton Physiology Educator of the Year, and multiple UT–Austin awards, including the Burnt Orange Apple Award. Dr. Dee is past-president of the APS (2022–23) and the Human Anatomy and Physiology Society (2012–2013). She has served as editor-in-chief of *Advances in Physiology Education*, and she is currently an associate editor. Dr. Dee works with members of the International Union of Physiological Sciences to improve physiology education globally, and this book has been translated into seven languages. Her free time is spent creating multimedia fiber art, gardening, and enjoying the Texas hill country with her husband, Andrew, and their dogs.

About the Contributors



Bruce Johnson, PhD is a Senior Lecturer in the Department of Neurobiology and Behavior at Cornell University. He earned biology degrees at Florida State University (BA), Florida Atlantic University (MS), and at the Marine Biological Laboratory in Woods Hole (PhD) through the Boston University Marine Program. He directs Cornell's Principles of Neurophysiology course that he joined in 1988, in which undergraduate and graduate students receive hands-on instruction in principles and methods of neurophysiology. He is a coauthor of *Crawdad: a CD-ROM Lab Manual for Neurophysiology* and the *Laboratory Manual for Physiology*. Bruce has directed and taught in faculty workshops for neuroscience laboratory teaching sponsored by NSF (Crawdad), ADInstruments (CrawFly), the Grass Foundation and the Faculty for Undergraduate Neuroscience (FUN). He has taught in international workshops and neuroscience courses at the Universities of Copenhagen (Denmark), Cologne (Germany), Ibadan (Nigeria), and the Marine Biological Laboratory. Bruce was named a Most Influential Faculty Member by the graduating senior class at Cornell and awarded the John M. and Emily B. Clark Award for Distinguished Teaching at Cornell. His other teaching awards include the FUN Educator of the Year Award, FUN Career Service Award, and he is a co-recipient of the 2016 Award for Education in Neuroscience, sponsored by the Society for Neuroscience. He is currently Senior Editor of the *Journal of Undergraduate Neuroscience Education*. Bruce's research addressed the cellular and synaptic mechanisms of motor network plasticity. His work now focuses on development of open-source neurophysiology and imaging equipment for laboratory teaching and research.

Michael Chirillo, MD, PhD is an assistant teaching professor at the University of Rhode Island in the College of the Environment and Life Sciences. He earned degrees in music performance (BM) at the College-Conservatory of Music at the University of Cincinnati and at the Butler School of Music at UT Austin (MM). He completed concurrent degrees in medicine (MD) at the McGovern Medical School in the Texas Medical Center in Houston and in neuroscience (PhD) at UT Austin. During his time as a doctoral student in Austin, Michael met and worked with Dr. Silverthorn on best teaching practices in the undergraduate physiology classroom. Following his internship in internal medicine-pediatrics at the University of Utah, he was awarded a Fulbright U.S. Scholar Grant to work with colleagues at the University of Belgrade in Serbia, investigating how to best incorporate core concepts of physiology into introductory courses. He frequently travels to southeastern Europe to continue this work.

About the Illustrators

William C. Ober, MD (*art coordinator and illustrator*) received his undergraduate degree from Washington and Lee University and his M.D. from the University of Virginia. He also studied in the Department of Art as Applied to Medicine at Johns Hopkins University. After graduation, Dr. Ober completed a residency in Family Practice and later was on the faculty at the University of Virginia in the Department of Family Medicine and in the Department of Sports Medicine. He also served as Chief of Medicine of Martha Jefferson Hospital in Charlottesville, VA. He most recently taught at Washington & Lee University, where he also led student trips to the Galapagos Islands. He was part of the Core Faculty at Shoals Marine Laboratory, where he taught Biological Illustration for 22 years. The textbooks illustrated by Medical & Scientific Illustration have won numerous design and illustration awards.

Claire E. Ober, RN (*illustrator*) practiced pediatric and obstetric nursing before turning to medical illustration as a full-time career. She returned to school at Mary Baldwin College where she received her degree with distinction in studio art. Following a five-year apprenticeship, she has worked as Dr. Ober's partner in Medical and Scientific Illustration since 1986. She was also on the Core Faculty at Shoals Marine Laboratory and co-taught Biological Illustration at both Shoals Marine Lab and at Washington and Lee University.

Anita Impagliazzo, MA is a medical and scientific illustrator in Howardsville, VA. She studied art and biology at the University of Virginia and obtained her graduate degree in biomedical illustration from University of Texas Southwestern Medical Center at Dallas in 1987. She has contributed to many textbooks, creates exhibits for medical malpractice cases, and illustrates current discoveries for research labs across the US.

About the Clinical Consultant

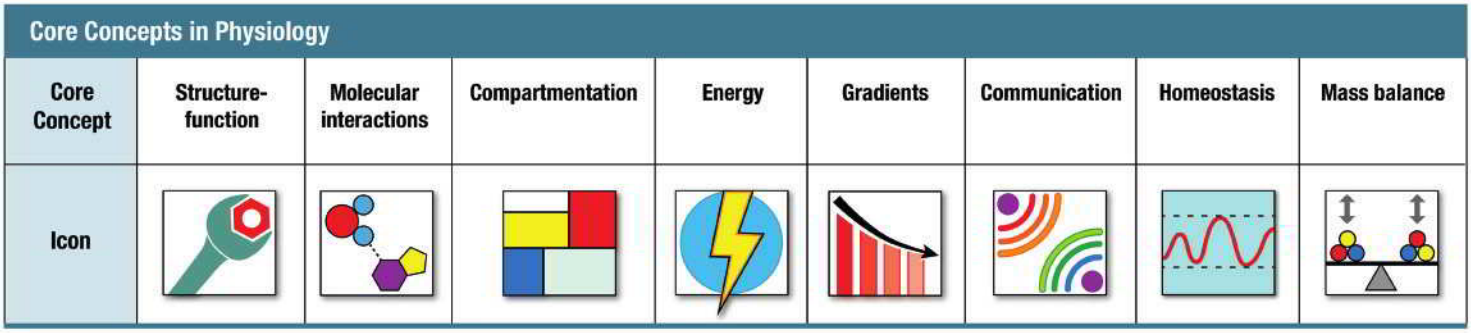
Andrew C. Silverthorn, MD is a graduate of the United States Military Academy (West Point). He served in the infantry in Vietnam, and upon his return entered medical school at the Medical University of South Carolina in Charleston. He was chief resident in family medicine at the University of Texas Medical Branch, Galveston, and is a family physician in solo practice in Austin, Texas. When Andrew is not busy with patients, he may be found on the golf course or playing with his two rescue dogs, Molly and Callie.

Dedication

I would like to dedicate this 9th edition to all the people who have worked out of the spotlight on different aspects of this book as it evolved through the years: physiologists, educators, and publishing professionals alike. A special thanks goes to two of my editors—DKB and AAR—for their vision and support.

New to this Edition

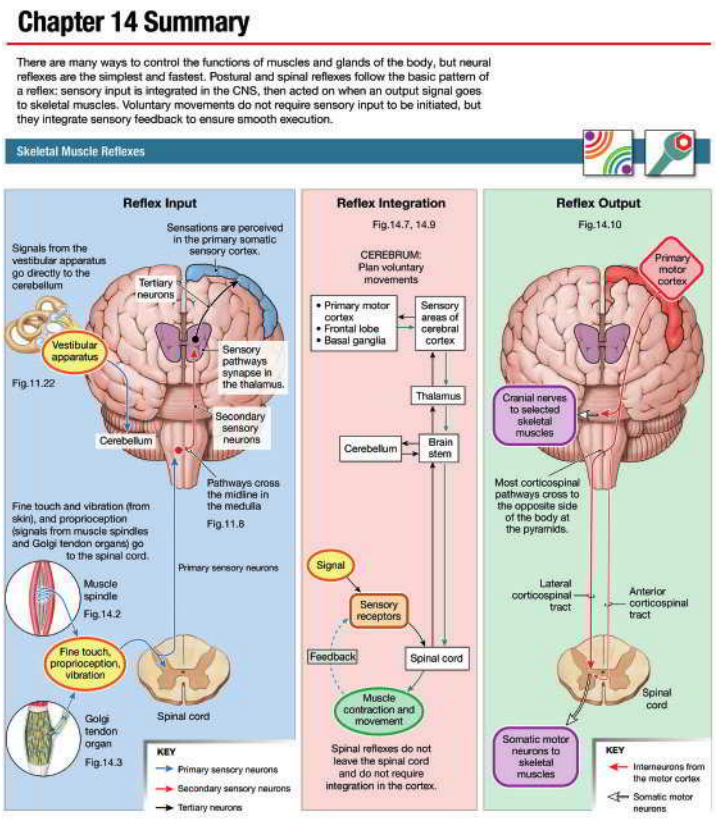
The Ninth Edition of *Human Physiology: An Integrated Approach* builds upon the thorough coverage of integrative and molecular physiology topics that have always been the foundation of this book. It has been nearly eight years since the last revision, and a lot has changed in the world of physiology and medicine, including the global SARS-CoV-2 pandemic. Studying the pathophysiology of COVID-19 made biomedical scientists aware of how the immune system influences body functions in ways we had not previously realized. In recognition of that fact, we have **promoted the immune system from Chapter 24 in the last edition to Chapter 7**, giving it new status as the third control system, coordinating with the nervous and endocrine systems through chemical signals.



The other major change in this edition is a focus throughout the book on the **core concepts of physiology**. The eight selected core concepts are introduced and discussed, along with their icons, in Unit 1, then become a unifying theme throughout the text. The four units in the book—Core Concepts in Physiology; Homeostasis, Communication, and Control; Integration of Function; and Metabolism, Growth, and Reproduction—are now introduced with a visual overview page that previews the unit's chapters. Each chapter begins with a brief introduction to the core concepts featured in that chapter. Core concept icons can be found on many pieces of art, challenging students to see if they can find the core concept represented in the art. Finally, the **text chapter summaries have been replaced with visual summaries**, many featuring new art, that review the key ideas covered in the chapter.

This edition was written to take advantage of the interactive features available only in the eTextbook. Answers to the Concept Checks and Figure and Graph questions are now visible with a click on the SHOW ANSWER button, as are HINTS. Key words have popup definitions, and the links for quick review of topics covered earlier in the book take you to that content. Short animations and the Physiology in Action videos featuring two of my early-career colleagues are embedded right in the eTextbook. Learn more about the other features of Pearson eTextbooks after the Owner's Manual.

Finally, when revising this book, we kept in mind the new **HAPS Physiology Learning Outcomes (PLOs) for Human Physiology**. *https://www.hapsweb.org/haps-learning-outcomes/haps-physiology-learning-outcomes/*. There can be tremendous variability in how introductory physiology is taught, so a **correlation guide** between this ninth edition's learning outcomes and the HAPS PLOs has been provided within the Instructor Resources. In addition, we reviewed the entire text and updated language to be more inclusive, following suggested guidelines from the U.S. National Institutes of Health and various biomedical and clinical societies. All art has been updated to reflect the latest WCAG guidelines to ensure our figures are fully accessible to all learners.



As always, the major focus of the book is to incorporate the latest findings from biomedical research and relate them to the physiology that is the basis for human health and disease. The list that follows highlights the new content in this ninth edition.

Chapter-by-Chapter Changes in the Ninth Edition

Chapter 1 Introduction to Physiology

- Revised themes into eight core concepts. Added gradients as a core concept
- New core concepts figure with icons
- Updated discussion of reflex loops
  - Adds open-loop and closed-loop control systems to address misconception that all reflexes are for homeostasis
  - Difference between regulated and controlled variables
- New table of 10 key regulated physiological variables
- New figure of homeostatic control system model with a regulated variable
- New Running Problem on searching for information about health benefits of probiotics; added artificial intelligence as a search method
- Updated
  - "Omics" box and added *multiomics*
  - Use of the word *normal*

Chapter 2 Molecular Interaction

- Updated research on chromium picolinate (Running Problem)
- Revised Section 2.3 on protein binding interactions
- Added *motor proteins* to protein function list

Chapter 3 Compartmentation: Cells and Tissues

- Added *transcellular compartments* to body compartmentation
- Section 3.3 on Cells updated and revised. New art and table in Fig. 3.4
  - Updated discussion on mitochondrial dynamics
  - Primary cilia moved from Emerging Topics box into the text
  - New topics: biomolecular condensates, proteasomes and ubiquitin
  - Clearly distinguished inclusions from nonmembranous organelles
- Section 3.4 Tissues
  - Clarification of difference between basal lamina and basement membrane
  - Added specialized epithelia as a sixth category
  - Added the ependyma to ciliated epithelia
- Section 3.5: Updated discussion on stem cells includes organoids and regenerative medicine

Chapter 4 Energy and Cellular Metabolism

- New figure on the electron transport system

Chapter 5 Membrane Dynamics

- Updated Section 5.5 on vesicular transport
  - Revised mechanisms: micropinocytosis, clathrin-dependent and -independent endocytosis
  - Extracellular vesicles: exosomes and ectosomes
  - New map of vesicular transport
- Added discussion of ectoenzymes
- Updated information on cystic fibrosis

Chapter 6 Communication, Integration, and Homeostasis

- Added immune system as the third control system
- Updated information on cytokines
- New figure showing neuro-endo-immune interactions
- Added extracellular vesicles to discussion and art

Chapter 7 The Immune System

This chapter was rewritten to focus on the immune system's role as a control system.

- Multiple figures were significantly revised. Added two new figures
- Updated ethnic distributions of blood types table
- Added information on:
  - Lifestyle-associated molecular patterns or LAMPs
  - Toll-like receptors (TLRs)
  - Pro-inflammatory cytokines
  - SARS-CoV-2, COVID-19, coronavirus

Chapter 8 Introduction to the Endocrine System

- Updated information on calcitonin gene-related peptide (CGRP) and migraine
- Updated information on oxytocin and autism

Chapter 9 Neurons: Cellular and Network Properties

- New introduction on undergraduate researchers and cone snail toxins
- Updated discussions and revised figures:
  - Neuron structure and function

- Channel activation and inactivation
- Axonal transport
- mRNA transport and neuronal protein synthesis
- Glial cell functions
- Types of neurotransmitter receptors (Tbl. 9.4)
- Signaling by gaseous signal molecules
- Mechanisms for LTP and LTD, including local protein synthesis in dendrites
- Plasticity

- Updated Try It! box on Venus flytrap action potential mechanism

Chapter 10 The Central Nervous System

- Moved glymphatics from Emerging Concepts box into the text
  - New art for blood-brain barrier
  - Paravascular CSF flow
- Note on changing terminology for CNS directions
- New section on mind-body interactions and psychoneuroimmunology
- Updated information on:
  - Alzheimer's
  - BRAIN initiative progress
  - Emergent properties
  - Evolution of electrical signaling
- Added:
  - Nonmotor functions of the cerebellum
  - Role of pericytes in control of cerebral blood flow
  - Associative learning doesn't require a brain

Chapter 11 Sensory Physiology

- New introduction to Meniere's Running Problem (astronaut Alan Shepard)
- New box on COVID-19 and loss of taste and smell
- Updated model of pain and nociception
  - Gate control theory of pain is no longer the current model
- Updated:
  - Sound transduction
  - Melanopsin and mRCG cells
  - Models for taste cell transduction
- Added:
  - Piezo cation channels and TRPV1 ion channels for somatic senses
  - 2021 Nobel Prize in Physiology or Medicine for sensory receptors
  - Intrinsically photosensitive retinal ganglion cell (ipRGC)
  - Blood-retinal barrier

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

- Expanded somatic motor disorders
  - Myasthenia gravis
  - Poliomyelitis
  - Lambert-Eaton myasthenic syndrome
- Transcutaneous vagal nerve stimulation in medicine
- Updated information on nicotine addiction to include vaping and recent statistics

Chapter 13 Muscles

- Changed sliding filament theory to sliding filament mechanism
- Updated information about myosin family of proteins
- Updated figure of muscle fiber mitochondrial anatomy
- Introduced new theories:
  - Role of titin in muscle contraction
  - Branching of sarcomeres
  - Myosin activation in sliding filament mechanism

Chapter 14 Integrative Physiology I: Control of Body Movement

- Revised discussion of proprioception
  - Updated functions of spindles, joint receptors, Golgi tendon organs
  - Add Piezo2 ion channels
- Updated information on deep brain stimulation for Parkinson's
- New examples of innate reflexes
- Clinical applications of reflex testing

Chapter 15 Cardiovascular Physiology

- New title for Section 15.2 Core Concept: Gradients and Flow
  - Review gradients from earlier chapters and relate to pressure gradients
- Expanded discussion of cyanosis to reflect signs in people with dark skin
- Introduced sinoatrial and atrioventricular nodes and Purkinje fiber cells as the three autorhythmic tissues of the heart
- New terminology: His-Purkinje system
  - Clarify that all ventricular conducting cells are Purkinje fiber cells

Chapter 16 Blood Flow and the Control of Blood Pressure

- Added focus on core concepts of mass balance and homeostasis

- Corrected model for anatomy of the microcirculation, with new text and new art
- Reorganized discussion on blood pressure, resistance, and flow to tissues
- Added intraosseous infusion into bone marrow sinusoids
- Updated:
  - Vasovagal (neurocardiogenic) syncope
  - Lymphatics, with new art
  - Myogenic autoregulation
  - Cardiovascular disease

Chapter 17 Blood

- Consolidated discussion of iron homeostasis with 2 new figures
  - Ferroportin (FPN)
  - Hepcidin
- Updated:
  - Thrombopoietin and thrombopoietin receptor agonists (TPO-RAs)
  - Gene therapy for sickle cell disease
  - Platelet-rich plasma
  - Schematic of hematopoietic stem cells and hematopoietic cytokines
  - Gene therapy for hemophilia

Chapter 18 Mechanics of Breathing

- New introduction about COVID-19 and the respiratory system
- New discussion, figure, and table of airway epithelial cells
  - Club cells, ionocytes, tuft cells, pulmonary neuroendocrine cells, and basal cells
  - Periciliary mucus layer
- New section on respiratory system defense mechanisms
- Revised:
  - Discussion of gas laws
  - Effect of altitude on gas partial pressures
- Updated type II alveolar cell functions

Chapter 19 Gas Exchange and Transport

- Revised model and new figure on central control of breathing
  - Respiratory central pattern generator (rCPG)
  - Pontine-medullary network
- Updated:
  - Factors that affect pulse oximeter accuracy
  - Blood substitutes
  - Protective reflexes

Chapter 20 The Kidneys

- Added alternate terminology for anatomical structures
- Updated:
  - Mesangial cell functions
  - Gout and uric acid excretion
  - SGLT2 inhibitors and urate excretion
- Moved Glucosuria and Diabetes Try It! activity to Chapter 23

Chapter 21 Integrative Physiology II: Fluid and Electrolyte Balance

- New Clinical Focus box and figure on SARS-CoV-2 and ACE2
- New Try It! box on Osmotic Diuresis with calculations
- Updated:
  - Cell volume regulation
  - Vasopressin pathologies

Chapter 22 The Digestive System

- Reorganized to put function before anatomy
  - Moved hepatic portal system to anatomy section
  - New discussion and figure of gut mucosal cells, including immune cells of the mucosa
    - Lymphoid follicles
    - Paneth cells
    - Enteroendocrine cells (EEC)
- New Section 22.3 on overview of digestive processes
- New Section 22.9 on microbiome and gut-brain communication
- Expanded discussion and new figure on bile salt recycling and enterohepatic circulation
- Updated:
  - Table 22.1 on signal peptides
  - Guanylin and uroguanylin in natriuretic peptide family
  - Role of immune system in digestive diseases
  - Section 22.8 on defense mechanisms
  - Information on colorectal cancer

Chapter 23 Metabolism and Energy Balance

- Reorganized introduction to put energy balance before food intake
- Revised model for control of food intake
  - Set point theory
  - Role of POMC and agouti-related peptide (AgRP)
- Updated discussion of body mass index (BMI)
- Updated:
  - Statistics on obesity and diabetes

  - Table 23.4 on drugs for diabetes
    - Semaglutide
- New information on diagnosis and treatment of diabetes
  - Hemoglobin A1C (HbA1c)
  - New section on how physiology is related to drug development for diabetes
  - Try It! box on glucosuria and insulin

Chapter 24 Endocrine Control of Growth and Metabolism

- Updated information on growth hormone therapy
- Updated information on control of bone remodeling
  - Coupling of bone remodeling
  - Clastokines
- Updated information on calcitonin
  - Calcitonin gene-related peptide (CGRP)

Chapter 25 Integrative Physiology III: Exercise

- Updated model of autonomic control of heart rate increase during exercise
- Discussion of difficulty of doing research on exercise
- Updated chemical signals affecting exercise metabolism
  - Myokines and exerkines

Chapter 26 Reproduction and Development

- Updated discussions on:
  - Biological sex and gender
  - Sex as a biological variable and the importance of sex in health and disease
- Revised discussion of sex determination and differentiation
  - X chromosome inactivation
  - Testis-determining genes: SRY and SOX9 genes
- Revised figure and explanation of gametogenesis
- Introduction of differences of sex development (DSD) and ambiguous genitalia
  - Non-invasive prenatal testing (NIPT)
- Role of exosomes in sperm maturation
- Updated table on contractive methods
- Revised model for endocrine control of initiation of labor

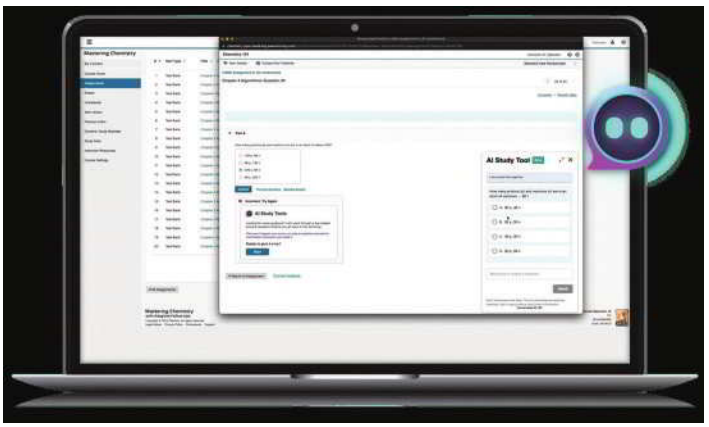
Pearson eTextbook

The Pearson eTextbook is a simple-to-use, mobile-optimized, personalized reading experience. It allows students to easily highlight, take notes, listen to the textbook, and review vocabulary all in one—even when offline. Students using the Pearson eTextbook will reap all the benefits of the new text features, while also benefitting from the following new and existing interactive features, which are integrated directly into the online text:

EXPANDED! Over 50 animations and videos embedded in the Pearson eTextbook bring A&P concepts to life featuring A&P Flix, Interactive Physiology, BioFlix, and more.

NEW! Hot Topics in Physiology bring regularly updated author-written articles to the eTextbook to inform readers of new research and developments in human physiology today. Located in each unit opener, these articles help students relate core content to the world around them.

NEW! AI Study Tool pulls from vetted Pearson content to help students achieve proficiency and master key course concepts. Our generative AI chat tool goes beyond a one-size-fits-all approach to provide individualized support, practice and feedback that meet the unique needs of every learner.

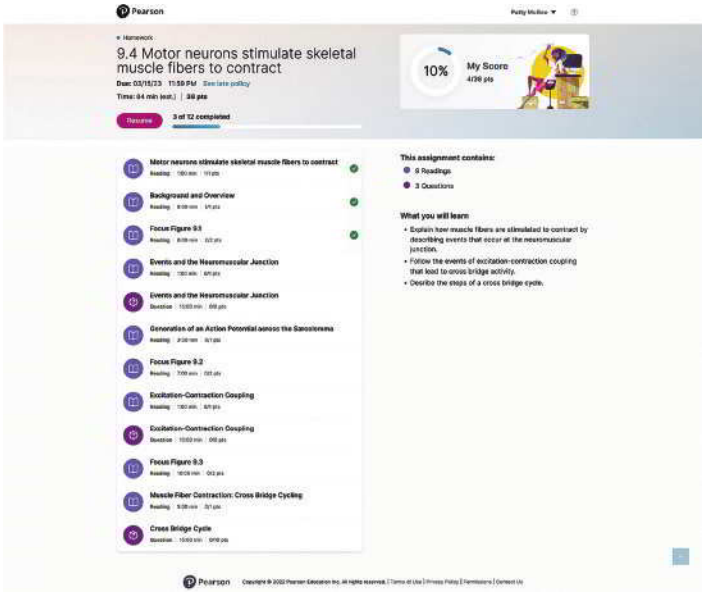


NEW! Quick Reference—Pearson eTextbook Integrated Media by Chapter provides easy reference to key animations and videos available for each chapter in the eTextbook and in Mastering. Media call-outs are also highlighted in the relevant chapter pages.

What's New in Mastering A&P

Mastering A&P is the most widely used online assessment and tutorial program for A&P, providing an extensive library of hundreds of animations, tutorials, and questions that are graded automatically.

NEW: Interactive Reading Assignments let students read, watch and practice in one seamless experience. Instructors can now assign specific sections of the eTextbook plus coaching and drag and drop assignments, and more for auto-grading.



NEW! Interactive Labs for Anatomy and Physiology are a fully customizable and auto-graded wet lab experience for your specific course objectives. Students engage with thought-provoking readings, videos, and realistic simulations aimed at critical thinking and data interpretation. These virtual labs can be assigned as a wet lab replacement, pre-lab preparation, post-lab review, or as a make-up lab. We recommend previewing the pre-built learning path by navigating to the Assignment Manager>Create>Import Pre-Built Assignment. See section below on Assignment Settings, Scoring, and LMS Integration.

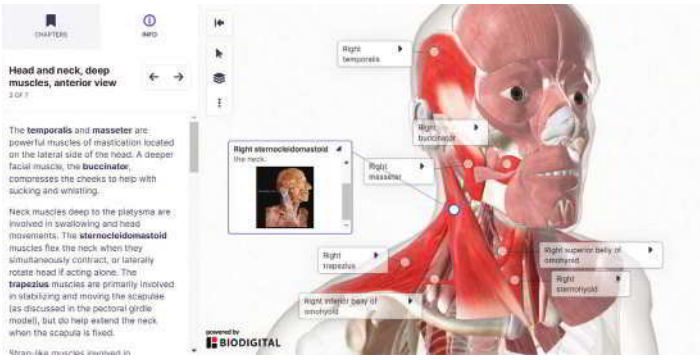
EXPANDED! Interactive Physiology 2.0 helps students advance beyond memorization to a genuine understanding of the toughest topics in A&P. Fully accessible on all mobile devices. I.P. 2.0 tutorials are assignable as coaching activities in Mastering A&P. New topics include Carbon Dioxide Transport and Exchange and Propagation of an Action Potential.

PhysioEx™10.0 Laboratory Simulations in Physiology provide newly formatted exercises in HTML for increased stability, web browser flexibility, and improved accessibility. The 12 Exercises contain 63 easy-to-use laboratory simulation activities that complement or replace wet labs, including those that are expensive or time-consuming to perform in class. PhysioEx allows students to repeat labs as often as they like, perform experiments without harming live animals, and conduct experiments that are difficult to perform in a wet lab environment because of time, cost, or safety concerns.

NEW! Gap Finder: A&P Diagnostic Assessment identifies any student knowledge gaps for material they should know for success in the course. This Diagnostic module contains approximately 130 questions based on these topics: Study Skills, Math Essentials, Chemistry Basics, Cell Biology Basics, and Biology Basics. Instructors can deselect as many questions as they want. There's no minimum number they have to adhere to in order for the program to work.

NEW and UPDATED! Dynamic Study Modules have been updated to reflect new content in the ninth edition. In addition, shadow questions, that change the root of the question, have been created for select questions to help keep students from memorizing questions.

NEW! Practice Anatomy Lab (PAL 4.0) featuring fully interactive 3-D models and custom assignability of your structure list is available in Mastering Assignment Manager and student Study Area.



NEW! Histology Videos include 10 new videos of histology tissues that provide short, focused walk-throughs of commonly covered tissue types in A&P.

NEW! TEAS and HESI exam practice questions help students prep for nursing school entrance exams with 150 TEAS and 300 HESI multiple-choice questions with wrong answer feedback for all questions.

UPDATED! Instructor Resources. This area of Mastering provides one-stop shopping for PowerPoint Lecture Presentations; all figures in JPEG and PPT format; Instructor Guide with Running Problems; Test Bank; animations; videos; Interactive Physiology (including the worksheets); Clinical Case Studies with Teaching Strategies and case study worksheets; PAL 4.0 Resources; PhysioEx

Resources; Interactive Lab Resources; and the new HAPS Learning Outcomes Correlation Guide.

NEW! Teaching Strategies for Active Learning is an invaluable resource for instructors looking for strategies for actively engaging students in the classroom. Edited by Cathy Whiting, this manual includes over 40 hands-on activities on key topics in A&P submitted by thought leaders across the country. Each activity is tied to HAPS Learning Outcomes and includes estimated time for the activity.

Learning Catalytics allows students to use their smartphone, tablet, or laptop to respond to questions in class. For more information, visit learningcatalytics.com.

Study Area features Resources by chapter; Practice Quizzes; TEAS & HESI Exam Practice, Animations and Videos including "Physiology in Action"; Interactive Physiology 2.0; Practice Anatomy Lab 4.0; Physio Ex; Clinical Case Studies, and more.

Acknowledgements

Writing, editing, and publishing a textbook is a group project that requires the talent and expertise of many people. No one scientist has the detailed background needed in all areas to write a book of this scope, and I am indebted to all my colleagues who so generously share their expertise in each edition. I particularly want to acknowledge Bruce Johnson, Cornell University, Department of Neurobiology and Behavior, a superb neurobiologist and educator, who once again ensured that the chapters on neurobiology are accurate and reflect the latest developments in that rapidly changing field. Bruce was joined in this edition by Michael Chirillo, UT-Austin Center for Learning and Memory, a former graduate teaching assistant of mine who has worked with me for over ten years. You can meet Michael if you watch the Physiology in Action videos.

The art team of Bill Ober, MD, and Claire Ober, RN, has worked with me since the first edition, and I am always grateful for their scientifically astute suggestions and revisions. They have been joined by Anita Impagliazzo, who brings a fresh eye and new figure ideas to our illustration program.

As we were developing the new core concepts chapter introductions and visual summaries for this edition, I relied on feedback from several colleagues to tell me if what I was creating would be helpful for their teaching. Thanks go to Jennifer Stokes, Jan M. Machart, Jennifer L. Thompson, and Meg Flemming for their prompt and honest input.

Special thanks go to some of my former students who over the years suggested topics and created storyboards for running problems: Matt Pahnke, Susan E. Johnson, Claire Conroy, and Douglas Shannon.

Instructors and students often contact me directly about the book, and for this edition I would particularly like to thank Collin Ellis, Heidi Engelhardt, and David Poole for comments and suggestions. Thanks also to my students who keep me informed of the typos that creep in no matter how many people look at the manuscript in production.

Many other people devoted their time and energy to making this book a reality, and I would like to thank them all, collectively and individually. I apologize in advance to anyone whose name I have omitted.

Ninth Edition Reviewers

I am particularly grateful to the instructors who reviewed one or more chapters of the last edition. There were many suggestions in their thoughtful reviews that I was unable to include in the text, but and others that I did. I appreciate the time and thought that went into their comments. The reviewers for this edition include:

- Sulekha Anand, *San Jose State University*
- Erwin Bautista, *University of California, Davis*
- Shawn Bearden, *Idaho State University*
- Simone Brito, *Fresno City College*
- George Brusch, *Oklahoma State University*
- Edward Eivers, *California State University, Los Angeles*
- Collin Ellis, *Santa Monica College*
- Heidi Engelhardt, *University of Waterloo*
- Luke Hoekstra, *Oklahoma State University*
- Erin Jacobs, *Mount Saint Mary's University*
- Mary Kinkel, *Appalachian State University*
- Catalina Reyes Gonzalez, *University of California, San Diego*
- Otto Sanchez, *University of Minnesota*

Many other instructors and students took time to write or e-mail queries or suggestions for clarification, for which I thank them. I am always delighted to have input, and I apologize that I do not have room to acknowledge them all individually.

Specialty Reviews

No one can be an expert in every area of physiology, and I am deeply grateful for my friends and colleagues who have reviewed entire chapters or answered specific questions over many editions. Even with their help, there may be errors, for which I take full responsibility.

In this edition, I am indebted to David Poole (Kansas State University) for his input on exercise physiology and for guidance to correct the erroneous figure of pre-capillary sphincters in the microcirculation (Chapter 16) that can be found in most physiology textbooks. Every instructor should read the article by Tatsuo Sakai and Yasue Hosoyamada (*https://link.springer.com/article/10.1007/s12576-013-0274-7*) to learn how we perpetuate errors in our teaching.

Photographs

I would like to thank Kristen Harris, University of Texas, who generously provided micrographs of dendritic spines from her research.

Supplements

Thank you to Meg Flemming, *Austin Community College* and Pat Clark, *Indiana University, Bloomington*, for updating the Test Bank, and to Eric Walsh, *University of Wisconsin-Madison*, for revising the PowerPoints for the ninth edition. Mastering assets for this edition were possible thanks to Catalina Reyes Gonzalez, *University of California, San Diego*, and to Max Adolphs, *University of Florida*, for their contributions to Mastering reading quizzes and chapter tests; as well as to Janet Casagrand, *University of Colorado Boulder*, and Simone Brito, *Fresno City College*, for their collective work on the improved Dynamic Study Modules. Additional thanks to *Pat Clark, Indiana University, Bloomington*, for

creating the prebuilt Interactive Reading Assignments for the ninth edition. Finally, thank you to Dr. Ryan Downey, *American University of the Caribbean School of Medicine; Georgetown University* and Genevieve Wager, *Cornell University* for their contributions to the Instructor Guide.

The Development and Production Team

Writing a manuscript is only a first step in the long and complicated process that results in a published book with all its ancillaries. The team that works with me on book development deserves a lot of credit for the finished product. Carie Keller at Straive designed the ninth edition's striking cover that continues our tradition of images that show science as art.

The team at Pearson Education worked tirelessly to see this edition move from manuscript to eText and bound book. My Editor and Commercial Product Manager, Alexa Frank, has been supportive, encouraging, and fun to work with as we scrambled to catch up on eight years of scientific advances and add the new emphasis on core concepts while staying on schedule. I also want to recognize Serina Beauparlant, Senior Manager of Product Management, who has been the one constant in the ebb and flow of publishing over many years. Serina's approach to the care and feeding of authors, especially during assorted crises, has kept writing and publishing fun.

Behind the scenes, thanks go to Ayushi Khandelwal, Editorial Assistant, who kept track of reviewers and feedback for this revision. Thank you also to our Product Marketer, Courtney Davis, who used her talents to shine a spotlight on this important revision and to Caroline Ayres, Senior Digital Program Director, for her support in the new revision workflow.

Special recognition goes to my team of Content Producers. The revision workflow for this edition completely changed to put creation of the eText before the print text, and it was a major adjustment for the authors and illustrators. The team of Francesca Monaco, Sharon Cahill, and Win Clark guided us through the new process with cheerfulness and infinite patience. Thanks also go to Katie Foley, Managing Producer, and Titas Basu, Assistant Managing Producer. The old production sequence of reviewing page proofs is gone, and I am grateful for the help of Kerri Tomasso, Project Management, in figuring out where we were in the review process. Thanks to Molly Montanaro, Rebecca Marshall, and Cathryn Gear from Lachina Creative who prepared the art for production. I would also like to thank Ben Ferrini, Matthew Perry and Chenley Calites for their many roles contributing to the Rights and Permissions as well as Kani Kapoor, Krishnamurthy Muralidharan, and Rajesh Kumar for sharing their skills and talents to make this edition possible.

Special Thanks

As always, I would like to thank my students and colleagues who looked for errors and areas that needed improvement. I've learned that awarding one point of extra credit for being the first student to report a typo works really well. My graduate teaching assistants over the years have all played a huge role in my teaching, and their input has helped shape how I teach. Many of them are now faculty members themselves. They include:

Ari Berman, PhD; Lawrence Brewer, PhD; Kevin Christmas, PhD; Michael Chirillo, MD, PhD; Lynn Cialdella Kam, MS, MBA, PhD; Sarah Davies Kanke, PhD; Peter English, PhD; Carol C. Linder, PhD; Karina Loyo-Garcia, PhD; Jan M. Machart, PhD; Tonya Thompson, MD; Patti Thorn, PhD; Justin Trombold, PhD; Kurt Venator, PhD; and Kira Wenstrom, PhD.

Finally, special thanks to my colleagues in the American Physiological Society, the Human Anatomy and Physiology Society, and the International Union of Physiological Sciences whose experiences in the classroom have enriched my own understanding of how to teach physiology. I would also like to recognize a special group of friends for their continuing support: Penelope Hansen (Memorial University, St. John's), Mary Anne Rokitka (SUNY Buffalo), Rob Carroll (East Carolina University School of Medicine), Joel Michael (Rush Medical College), Jennifer Stokes (Southwestern University), and Ryan Downey (American University of the Caribbean), as well as Peter English, Jan M. Machart, Ruth Buskirk, and Marilla Svinicki (University of Texas).

As always, I thank my family and friends for their patience, understanding, and support during the chaos that seems inevitable with book revisions. The biggest thank you goes to my husband Andrew, whose love, support, and willingness to forgo home-cooked meals on occasion have helped me meet my deadlines for nine editions.

A Work in Progress

One of the most rewarding aspects of writing a textbook is the opportunity it has given me to meet or communicate with other instructors and students. In the many years since the first edition was published, I have heard from people around the world and have had the pleasure of hearing how the book has been incorporated into their teaching and learning.

Because science textbooks are revised periodically, they are always works in progress. I invite you to contact me or my publisher with any suggestions, corrections, or comments about this edition. I am most reachable through e-mail at silverthorn@utexas.edu.

Dee U. Silverthorn *silverthorn@utexas.edu* University of Texas Austin, Texas.

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- Bioflix: Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- Bioflix: Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- Bioflix: Electron Transport System
- Bioflix: Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- Physiology in Action: Osmolarity and Tonicity

Module 5.7

- Physiology in Action: Membrane Potential
- A&P Flix: Resting Membrane Potential

Chapter 5 Links to Resources

- Interactive Physiology Animation: Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- Microbiology Animation: Host Defenses

Module 7.3

- Microbiology Animation: Antigen Processing and Presentation: Overview

Module 7.7

- Microbiology Animation: Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- Bioflix: Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- BioFlix: How Synapses Work

Module 9.3

- Interactive Physiology Animation: Generation of an Action Potential
- BioFlix: Action Potential Conduction

Chapter 9 Links to Resources

- Interactive Physiology 2.0 Animation: Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- Biointeractives: Circadian Rhythms and the SCN

Chapter 13 Muscles

Module 13.1

- A&P Flix: The Cross Bridge Cycle
- Interactive Physiology Animation: Neuromuscular Junction
- Interactive Physiology 2.0 Animation: Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- Interactive Physiology Animation: Pathway of Blood through the Heart
- Interactive Physiology Animation: Action Potentials in Autorhythmic Cells

Module 15.4

- Physiology in Action: Electrocardiogram
- Interactive Physiology Animation: Intrinsic Conduction System of the Heart
- Interactive Physiology Animation: Cardiac Output

Chapter 15 Links to Resources

- Interactive Physiology 2.0 Animation: Electrical Activity of the Heart
- Interactive Physiology 2.0 Animation: Cardiac Cycle
- Interactive Physiology 2.0 Animation: Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- Physiology in Action: Orthostatic Hypotension
- Interactive Physiology Animation: Arterial Baroreceptor Reflex

Chapter 18 Mechanics of Breathing

Module 18.3

- Physiology in Action: The Spirometer
- Physiology in Action: Subatmospheric Pleural Cavity
- Physiology in Action: Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- BioFlix: Gas Exchange
- Physiology in Action: Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- Interactive Physiology 2.0 Animation: Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- Interactive Physiology Animation: Glomerular Filtration

Module 20.6

- Interactive Physiology 2.0 Animation: Proximal Tubule Reabsorption and Secretion

Module 20.7

- Physiology in Action: Renal Clearance

Chapter 20 Links to Resources

- Interactive Physiology 2.0 Animation: Glomerular Filtration
- Interactive Physiology Animation: Anatomy Review: Urinary System
- Interactive Physiology 2.0 Animation: Tubular Reabsorption and Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- Interactive Physiology Animation: Aldosterone and ADH in Salt and Water Processing
- Interactive Physiology Animation: Mechanisms for Acid-Base Homeostasis
- Interactive Physiology Animation: Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- Interactive Physiology Animation: Anatomy Review
- Interactive Physiology Animation: Control of Digestion
- Interactive Physiology Animation: Digestive System Secretion
- Interactive Physiology Animation: Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- Physiology in Action: Blood Pressure and Exercise

Brief Contents

Contents

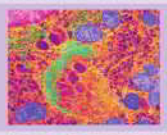
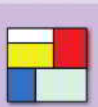
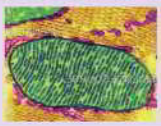
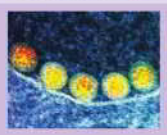
UNIT 1

Basic Cell Processes: Integration and Coordination

Unit 1 Core Concepts in Physiology

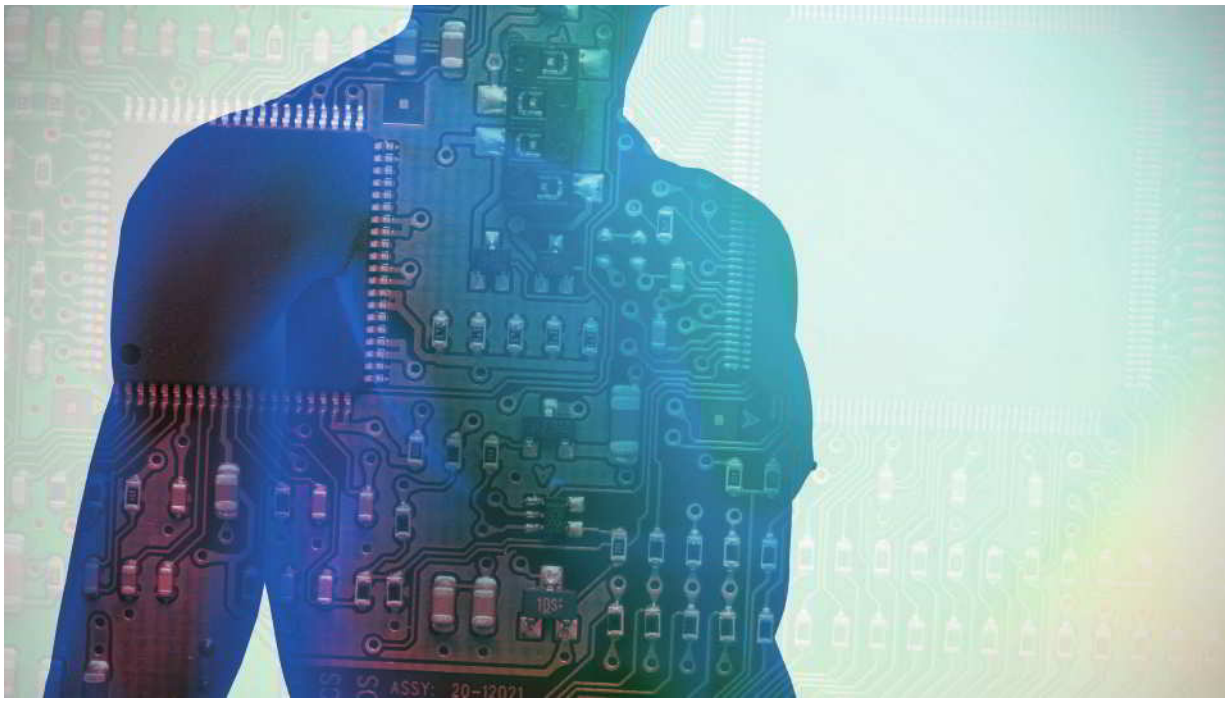
Welcome to the study of human physiology! In the first six chapters of this book you will learn about the core concepts of physiology – the general models or patterns that repeat over and over throughout the different body systems. Being able to recognize these patterns each time you encounter them will simplify learning physiology because you are seeing something familiar in a different context rather than learning a new concept. Pattern recognition is an important skill to acquire in your studies because it is a critical element in developing expertise. Studies have shown that when clinicians make a diagnosis, they are using rapid subconscious pattern recognition to help decide what might be going on.

To simplify learning the eight core concepts in this book, we have created icons that will appear at the start of each chapter to show the important core concepts discussed in that chapter. The icons and their descriptions appear next to the unit chapter titles where they are first discussed. Chapter 6 is the first chapter in Unit 2.

Chapter		Core Concepts	Icon
Chapter 1: Introduction to Physiology		Homeostasis	
		Mass Balance	
		Structure-Function Relationships	
		Communication	
Chapter 2: Molecular Interactions		Molecular Interactions	
Chapter 3: Compartmentation: Cells and Tissues		Compartmentation	
Chapter 4: Energy and Cellular Metabolism		Energy	
Chapter 5: Membrane Dynamics		Gradients	

1

Introduction to Physiology



The current tendency of physiological thought is clearly toward an increasing emphasis upon the unity of operation of the Human Body.

Ernest G. Martin, preface to The Human Body *10th edition, 1917*

Welcome to the study of human physiology! In this chapter you will be introduced to the core concepts of physiology—the general models or patterns that repeat over and over throughout the body systems of living organisms. Here are the core concepts featured in Chapter 1.

Homeostasis

A healthy body stays in homeostasis. Loss of homeostasis can result in illness.

Communication

The organ systems of the body must communicate with each other.

Mass Balance

Body stability requires that what comes in and what goes out remain balanced.

Structure-Function

The structure and function of body parts are closely related, from the tiniest subcellular fibers to the most complex organs.

Compartmentation

Compartments at all levels of organization separate functions.

Learning Outcomes

1.1 Physiology Is an Integrative Science
- **LO 1.1.1** Define physiology.
- **LO 1.1.2** List the levels of organization from atoms to the biosphere.
- **LO 1.1.3** Name the 10 physiological organ systems of the body and give their functions.

1.2 Function and Mechanism
- **LO 1.2.1** Distinguish between mechanistic explanations and teleological explanations.

1.3 Core Concepts in Physiology
- **LO 1.3.1** List and give examples of eight core concepts in physiology.

1.4 Homeostasis
- **LO 1.4.1** Define homeostasis. What happens when homeostasis fails?
- **LO 1.4.2** Name and describe the two major compartments of the human body.
- **LO 1.4.3** Explain the law of mass balance and how it applies to the body's load of a substance.
- **LO 1.4.4** Define mass flow using mathematical units and explain how it relates to mass balance.
- **LO 1.4.5** Define clearance and give an example.
- **LO 1.4.6** Distinguish between equilibrium and steady state.

1.5 Control Systems and Homeostasis
- **LO 1.5.1** List the three components of a control system and give an example.
- **LO 1.5.2** Explain the relationship between a regulated variable and its setpoint.
- **LO 1.5.3** Compare local control, long-distance control, and reflex control.
- **LO 1.5.4** Explain the relationship between a response loop and a feedback loop.
- **LO 1.5.5** Compare negative feedback, positive feedback, and feedforward control. Give an example of each.
- **LO 1.5.6** Explain what happens to setpoints in biological rhythms and give some examples.

1.6 The Science of Physiology
- **LO 1.6.1** Explain and give examples of the following components of scientific research: independent and dependent variables, experimental control, data, replication, variability.
- **LO 1.6.2** Compare and contrast the following types of experimental study designs: blind study, double-blind study, crossover study, prospective and retrospective studies, cross-sectional study, longitudinal study, meta-analysis.
- **LO 1.6.3** Define placebo and nocebo effects and explain how they may influence the outcome of experimental studies.

Welcome to the fascinating study of the human body! For most of recorded history, humans have been interested in how their bodies work. Early Egyptian, Indian, and Chinese writings describe attempts by physicians to treat various diseases and to restore health. Although some ancient remedies, such as camel dung and powdered sheep horn, may seem bizarre, we are still using others, such as blood-sucking leeches and chemicals derived from medicinal plants. The way we use these treatments has changed through the centuries as we have learned more about the human body.

There has never been a more exciting time in human physiology. **Physiology** is the study of the typical functioning of a living organism and its component parts, including all its chemical and physical processes. The term *physiology* literally means "knowledge of nature." Aristotle (384–322 BCE) used the word in this broad sense to describe the functioning of all living organisms, not just of the human body. However, Hippocrates (ca. 460–377 BCE), considered the father of medicine, used the word *physiology* to mean "the healing power of nature," and thereafter the field became closely associated with medicine. By the sixteenth century in Europe, physiology had been formalized as the study of the vital functions of the human body. Currently the term is again used to refer to the study of all living organisms.

Today, we benefit from centuries of work by physiologists who constructed a foundation of knowledge about how the human body functions. Since the 1970s, rapid advances in the fields of cellular and molecular biology have supplemented this work. A few decades ago, we thought that we would find the key to the secret of life by sequencing the human *genome*, which is the collective term for all the genetic information contained in the DNA of a species. However, this deconstructionist view of biology has proved to have its limitations, because living organisms are much more than the simple sum of their parts.

1.1 Physiology Is an Integrative Science

Many complex systems—including those of the human body—possess **emergent properties,** which are properties that cannot be predicted to exist based only on knowledge of the system's individual components. An emergent property is not a property of any single component of the system, and it is greater than the simple sum of the system's individual parts. Emergent properties result from complex, nonlinear interactions of the different components.

For example, suppose someone broke down a car into its nuts and bolts and pieces and laid them out on a floor. Could you predict that, properly assembled, these bits of metal and plastic would become a vehicle capable of converting the energy in gasoline into movement? Who could predict that the right combination of elements into molecules and assemblages of molecules would result in a living organism? Among the most complex emergent properties in humans are emotion, intelligence, and other aspects of brain function. None of these properties can be predicted from knowing the individual properties of nerve cells.

When the Human Genome Project began in 1990, scientists thought that by identifying and sequencing all the genes in human DNA, they would understand how the body worked. However, as research advanced, scientists had to revise their original idea that a given segment of DNA contained one gene that coded for one protein. It became clear that one DNA sequence could code for many proteins. The Human Genome Project ended in 2003, but before then researchers had moved beyond genomics to *proteomics*, the study of proteins in living organisms.

Now scientists have realized that knowing that a protein is made by a particular cell does not always tell us the significance of that protein to the cell, the tissue, or the functioning organism. The exciting new areas in biological research are using a *multiomics approach* that applies data from many fields of study to explain the integrated function of the human body.

Emerging Concepts

The Changing World of Omes

Contemporary research is now in an era of "omes" and "omics." What is an "ome"? The term apparently derives from the Latin word for a mass or tumor and refers to a collection of items that make up a whole, such as a genome. One of the earliest uses of the "ome" suffix in biology is the term *biome*, meaning all organisms living in a major ecological region, such as the marine biome. A *genome* is all the genetic material of an organism. Its *physiome* describes the organism's coordinated molecular, cellular, and physiological functioning. The related adjective "omics" describes the research related to studying an "ome."

New "omes" emerge every year. The human connectome project sponsored by the U.S. National Institutes of Health is a collaborative effort to map all the neural connections of the human brain. The human microbiome project is studying the influence of microbes that normally live on or in the human body. Long ignored for many years, these microbes have now been shown to have an influence on both health and disease.

1.2 Function and Mechanism

We define physiology as the typical functioning of the body, but physiologists are careful to distinguish between *function* and *mechanism*. The **function** of a physiological system or event is the "why" of the system or event: Why does a certain response help an animal survive in a particular situation? In other words, what is the *adaptive significance* of this event for this animal?

For example, humans are large, mobile, terrestrial animals, and our bodies maintain relatively constant water content despite living in a dry, highly variable external environment. Dehydration is a constant threat to our well-being. What processes have evolved in our anatomy and physiology that allow us to survive in this hostile environment? One is the production of highly concentrated urine by the kidney, which allows the body to conserve water. This statement tells us *why* we produce concentrated urine but does not tell us *how* the kidney accomplishes that task.

Thinking about a physiological event in terms of its adaptive significance is the **teleological approach** to science. For example, the teleological answer to the question of why red blood cells transport oxygen is "because cells need oxygen and red blood cells bring it to them." This answer explains *why* red blood cells transport oxygen—their function—but says nothing about *how* the cells transport oxygen.

In contrast, most physiologists study physiological processes, or **mechanisms**—the "how" of a system. The **mechanistic approach** to physiology examines process. The mechanistic answer to the question "How do red blood cells transport oxygen?" is "Oxygen binds to hemoglobin molecules in the red blood cells." This very concrete answer explains exactly how oxygen transport occurs but says nothing about the significance of oxygen transport to the animal.

Students often confuse these two approaches to thinking about physiology. Studies have shown that even medical students tend to answer questions with teleological explanations when the more appropriate response would be a mechanistic explanation.[1] Often they do so because instructors ask why a physiological event occurs when they really want to know how it occurs. Staying aware of the two approaches will help prevent confusion.

Although function and mechanism seem to be two sides of the same coin, it is possible to study mechanisms, particularly at the cellular and subcellular level, without understanding their function in the life of the organism. As biological knowledge becomes more complex, scientists sometimes become so involved in studying complex processes that they fail to step back and look at the adaptive significance of those processes to cells, organ systems, or the animal. Conversely, it is possible to use teleological thinking incorrectly by saying, "Oh, in this situation the body needs to do this." *This* may be a good solution, but if a mechanism for doing *this* doesn't exist, the situation cannot be corrected.

Applying the concept of integrated functions and mechanisms is the underlying principle in **translational research,** an approach sometimes described as "bench to bedside." Translational research uses the insights and results gained from basic biomedical research on mechanisms to develop treatments and strategies for preventing human diseases. For example, researchers working on rats found that a chemical from the pancreas named *amylin* reduced the rats' food intake. These findings led directly to a translational research study in which human volunteers injected a synthetic form of amylin and recorded their subsequent food intake, but without intentionally modifying their lifestyle.[2] The drug suppressed food intake in humans, and was later approved by the Food and Drug Administration for treatment of diabetes mellitus.

At the systems level, we know about most of the mechanics of body function from centuries of research. The unanswered questions today mostly involve integration and control of these mechanisms, particularly at the cellular and molecular levels. Nevertheless, explaining what happens in test tubes or isolated cells can only partially answer questions about function. For this reason, animal and human trials are essential steps in the process of applying basic research to treating or curing diseases.

Running Problem 1.1: What to Believe?

Hiro had just left his first physiology class when he saw a friend's social media link to a video claiming that everyone should take probiotics for gut health. He watched some of the video but he wasn't sure exactly what probiotics were and whether the information in the video was accurate. "I wonder if there is any scientific evidence supporting this claim," Hiro thought. "Let's see what I can find out."

1.3 Core Concepts in Physiology

"Physiology is not a science or a profession but a point of view."[3] Physiologists pride themselves on relating the mechanisms they study to the functioning of the organism as a whole. For students, being able to think about how multiple body systems integrate their function is one of the more difficult aspects of learning physiology. To develop expertise in physiology, you must do more than simply memorize facts and learn new terminology. Researchers have found that the ability to solve problems requires a conceptual framework, or "big picture," of the field.

This book will help you build a conceptual framework for physiology by explicitly emphasizing the basic biological themes, or **core concepts** that are common to all living organisms. These concepts form patterns that repeat over and over, and you will begin to recognize them when you encounter them in specific contexts. Pattern recognition is an important skill in healthcare professions, and it will also simplify learning physiology.

In the recent years, multiple organizations issued reports to encourage the teaching of biology using these fundamental concepts.[4] Although the descriptions vary from report to report, five major ideas emerge:

1. structure and function across all levels of organization
2. energy transfer, storage, and use
3. information flow, storage, and use within single organisms and within a species of organism
4. homeostasis and the control systems that maintain it
5. evolution

In addition, these reports emphasize the importance of understanding how science is done and of the quantitative nature of biology.

FIGURE 1.1 lists the eight core concepts we will focus on in this book. The major core concepts most related to physiology are structure-function relationships (anatomy and levels of organization, molecular interactions, compartmentation), biological energy use, gradients and flow, communication, and homeostasis, which includes mass balance. The first six chapters introduce the fundamentals of these core concepts, which you may already be familiar with from earlier biology or chemistry classes. The core concepts, with variations, then re-appear over and over in subsequent chapters of this book. Look for their icons throughout the chapters and in the summary material at the end of each chapter.

Core Concept 1: Structure and Function Are Closely Related

This overarching core concept subdivides into three major ideas: anatomy and levels of organization, molecular interactions, and compartmentation.

Anatomy and Levels of Organization

Anatomy is the study of body structures, and in all living organisms, structure and function are closely linked. The **integration of function** across many **levels of organization,** from the molecular level to the intact body, is a special focus of physiology. (To *integrate* means to bring varied elements together to create a unified whole.)

FIGURE 1.2 illustrates levels of organization ranging from the molecular level all the way up to populations of different species living together in *ecosystems* and in the *biosphere*. The levels of organization are shown along with the various subdisciplines of chemistry and biology related to the study of each organizational level. There is considerable overlap between the different fields of study, and these artificial divisions vary according to who is defining them. Notice, however, that physiology includes multiple levels, from molecular and cellular biology to the ecological physiology of populations.

Fig. 1.1 Core concepts and their icons

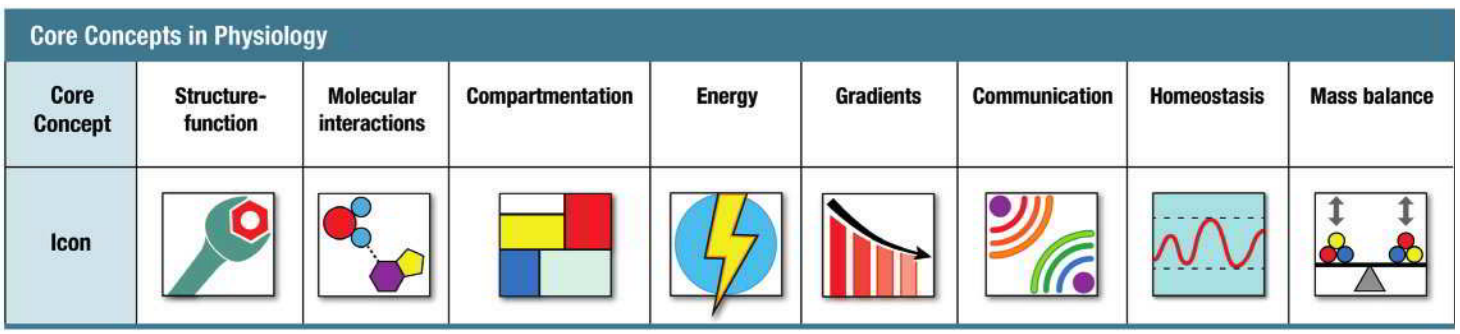
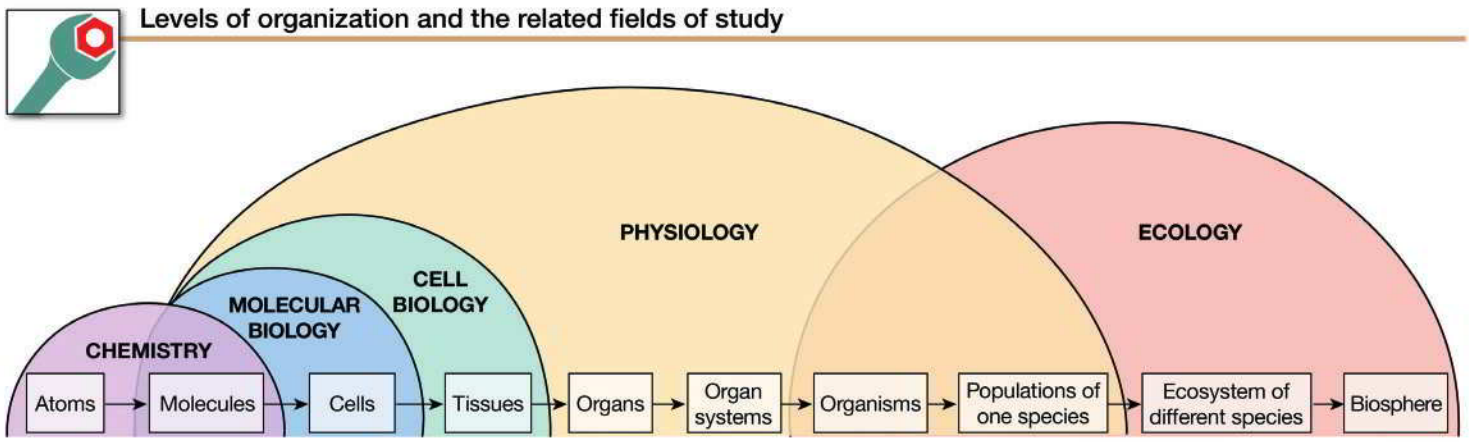


Fig. 1.2 Levels of organization



At the most basic level of organization shown in Figure 1.2, atoms of elements link together to form molecules. Collections of molecules in living organisms form **cells,** the smallest unit of structure capable of carrying out all life processes. A lipid and protein barrier called the **cell membrane** (also called the *plasma membrane*) separates cells from their external environment. Simple organisms are composed of only one cell, but complex organisms have many cells with different structural and functional specializations.

Collections of cells that carry out related functions are called **tissues** {*texere*, to weave}. Tissues form structural and functional units known as **organs** {*organon*, tool}, and groups of organs integrate their functions to create **organ systems**. Chapter 3 reviews the anatomy of cells, tissues, and organs.

The structure of a cell, tissue, or organ must provide an efficient physical base for its function. For this reason, it is nearly impossible to study the physiology of the body without understanding the underlying anatomy. Because of the interrelationship of anatomy and physiology, you will find Anatomy Summaries throughout the book. These special review features illustrate the basic anatomy of the physiological systems at different levels of organization.

Running Problem 1.2

When Hiro got back to his room, he sat down at his computer and googled *probiotics*. Almost instantly, he got back more than 244 million results. The first results were sponsored links from *seed.com*, *amazon.com*, and *ritual.com*. These were followed by pages from *mayoclinic.org*, *www.nccih.nih.gov*, *webmd.com*, *healthline.com*, *health.harvard.edu*, *en.wikipedia.org*, and *www.ods.od.nih.gov*. Hiro thought to himself, "Wow, there is a lot of information out there. What should I look at first?"

Q1: *Rank these 10 results from most to least likely to have good information and explain how you chose your rankings.*

The 10 physiological organ systems in the human body are illustrated in **FIGURE 1.3**. Several of the systems have alternate names, given in parentheses, that are based on the organs of the system rather than the function of the system. The **integumentary system** {*integumentum*, covering}, composed of the skin, forms a protective boundary that separates the body's internal environment from the external environment (the outside world). The **musculoskeletal system** provides support and body movement.

Four systems move material into and out of the body. The **respiratory system (pulmonary)** exchanges gases; the **digestive system (gastrointestinal)** takes up nutrients and water and eliminates wastes; the **urinary system (renal)** removes excess water and waste material; and the **reproductive system** produces eggs or sperm.

The remaining four systems extend throughout the body. The **circulatory system (cardiovascular)** distributes materials by pumping blood through vessels. The **nervous system** and **endocrine system** coordinate body functions. Note that the figure shows them as a continuum rather than as two distinct systems. Why? Because the lines between these two systems have blurred as we have learned more about the integrative nature of physiological function.

The one system not illustrated in Figure 1.3 is the diffuse **immune system,** which includes but is not limited to the anatomical structures known as the **lymphatic system**. The specialized cells of the immune system are scattered throughout the body. They protect the internal environment from foreign substances by intercepting material that enters through the intestines and lungs or through a break in the skin. In addition, immune tissues are closely associated with the circulatory system. Cells of the immune system secrete chemical messengers that communicate and coordinate with the nervous and endocrine systems.

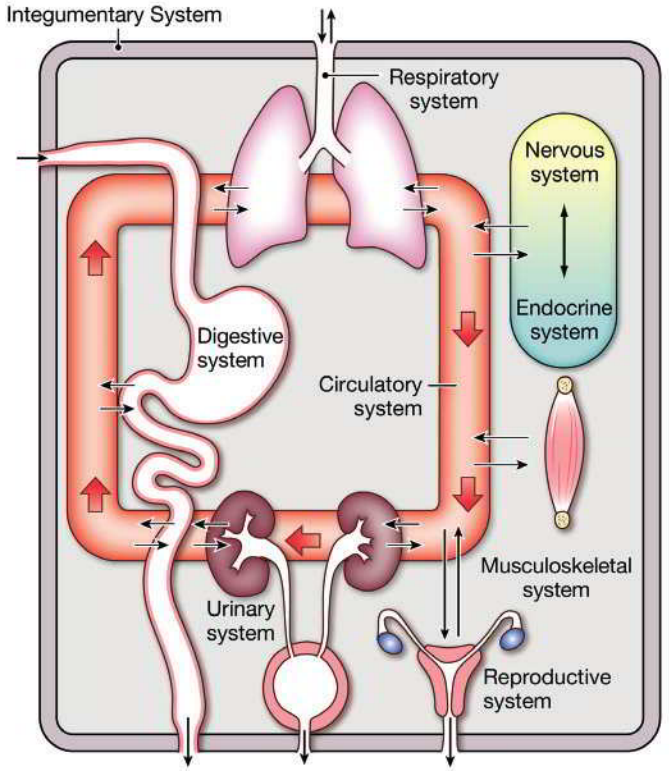
Traditionally, physiology courses and books are organized by organ system. Students study cardiovascular physiology and regulation of blood pressure in one chapter, and then study the kidneys and control of body fluid volume in a different chapter. In the functioning human, however, the cardiovascular and renal systems communicate with each other, so that a change in one is

Fig. 1.3 Organ systems of the human body and their integration

ESSENTIALS Organ Systems of the Human Body

System Name	Includes	Representative Functions
Circulatory	Heart, blood vessels, blood	Transport of materials between all cells of the body
Digestive	Stomach, intestine, liver, pancreas	Conversion of food into particles that can be transported into the body; elimination of some wastes
Endocrine	Thyroid gland, adrenal gland	Coordination of body function through synthesis and release of regulatory molecules
Immune	Thymus, spleen, lymph nodes	Defense against foreign invaders
Integumentary	Skin	Protection from external environment
Musculoskeletal	Skeletal muscles, bone	Support and movement
Nervous	Brain, spinal cord	Coordination of body function through electrical signals and release of regulatory molecules
Reproductive	Ovaries and uterus, testes	Perpetuation of the species
Respiratory	Lungs, airways	Exchange of oxygen and carbon dioxide between the internal and external environments
Urinary	Kidneys, bladder	Maintenance of water and solutes in the internal environment; waste removal

The Integration between Systems of the Body



This schematic figure indicates relationships between systems of the human body. The interiors of some hollow organs (shown in white) are part of the external environment.

likely to cause a reaction in the other. For example, body fluid volume influences blood pressure, while changes in blood pressure alter kidney function because the kidneys regulate fluid volume. In this book, each of the four units ends with an integrative physiology chapter that highlights the coordination of function across multiple organ systems.

Understanding how different organ systems work together is just as important as memorizing facts, but the complexity of interactions can be challenging. One way physiologists simplify and integrate information is by using visual representations of physiological processes called maps. The Focus on Mapping feature in this chapter will help you learn how to make maps. The first type of map, shown in **FIGURE 1.4**, is a schematic representation of structure or function. The second type of map diagrams a physiological process as it proceeds through time. These process maps are also called *flow charts*, and they are frequently used in health care. You will be able to practice creating maps with special end-of-chapter questions throughout the book. You will also find maps in the visual summary at the end of each chapter.

Molecular Interactions

The ability of individual molecules to bind to or react with other molecules is essential for biological function. A molecule's function depends on its structure and shape, and even a small change to the structure or shape may have significant effects on the function. The classic example of this phenomenon is the change in one amino acid of the hemoglobin protein. (Hemoglobin is the oxygen-carrying pigment of the blood.) This one small change in the protein converts normal hemoglobin to the form associated with sickle cell disease.

Many physiologically significant molecular interactions that you will learn about in this book involve the class of biological molecules called *proteins*. Functional groups of proteins include *enzymes* that speed up chemical reactions, *signal molecules* and the *receptor proteins* that bind signal molecules, and specialized proteins that function as biological pumps, filters, motors, or transporters. Chapter 2 describes molecular interactions involving proteins in more detail.

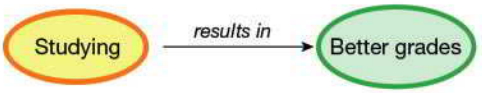
Fig. 1.4 Focus on . . . Mapping

Focus on . . . Mapping

Why use maps to study physiology? The answer is simple: maps will help you organize information you are learning in a way that makes sense to you and they will make that information easier to recall on a test. Creating a map requires higher-level thinking about the relationships among items on the map.

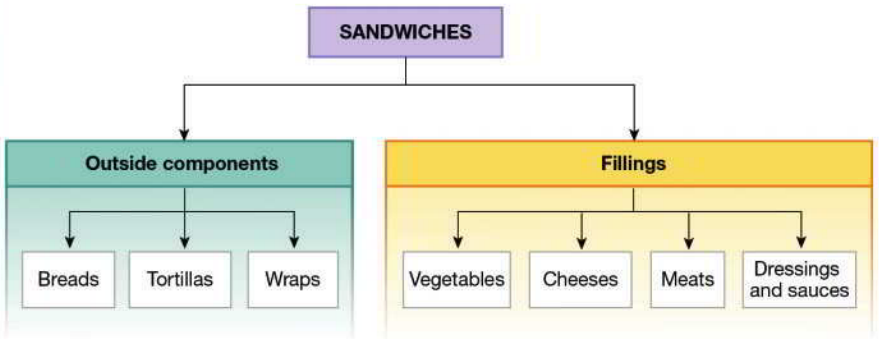
Mapping is not just a study technique. Scientists map out the steps in their experiments. Healthcare professionals create maps to guide them while diagnosing and treating patients. You can use mapping for almost every subject you study.

What is a map? Mapping is a nonlinear way of organizing material. A map can take a variety of forms but usually consists of terms (words or short phrases) linked by arrows to indicate associations. You can label the connecting arrows to describe the type of linkage between the terms (structure/function, cause/effect) or with explanatory phrases.

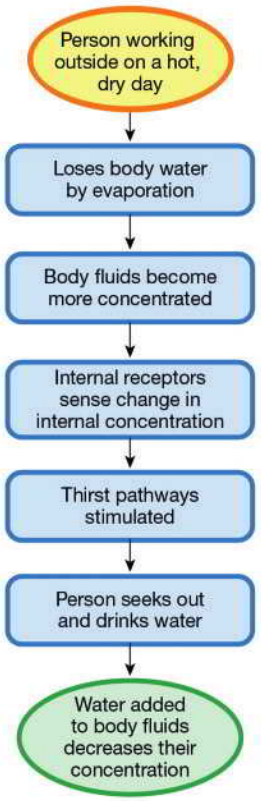


Here are two typical maps used in physiology.

Structure/function maps focus on the relationships between anatomical structures and their functions.



Process maps or **flow charts** follow normal homeostatic control pathways or the body's responses to abnormal (pathophysiological) events as they unfold over time.



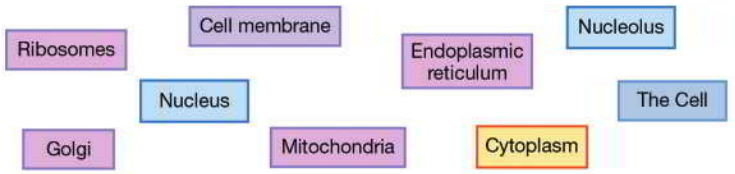
Practice making maps. Many maps appear in this textbook, and they can serve as the starting point for your own maps. However, the real benefit of mapping comes from preparing maps yourself rather than memorizing someone else's maps. Your instructor can help you get started.

HINTS

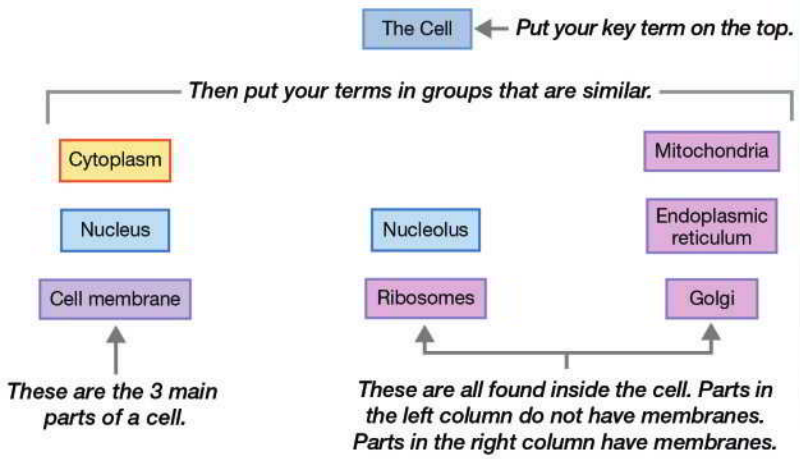
- To help you get started, the end-of-chapter questions in this book include at least one list of terms to map for each chapter.
- Write your terms on individual slips of paper or small sticky notes so that you can rearrange the map more easily.
- Some terms may seem to belong to more than one group. Do not duplicate the item but make a note of it, as this term will probably have several arrows pointing to it or leading away from it.
- If arrows crisscross, try rearranging the terms on the map.
- Use color to indicate similar items.
- Add pictures and graphs that are associated with specific terms in your map.

Electronic mapping. Some people do not like the messiness of hand-drawn maps. There are several electronic ways of making maps, including PowerPoint or free and commercial software programs. Free concept mapping software is available from IHMC CmapTools at https://cmap.ihmc.us.

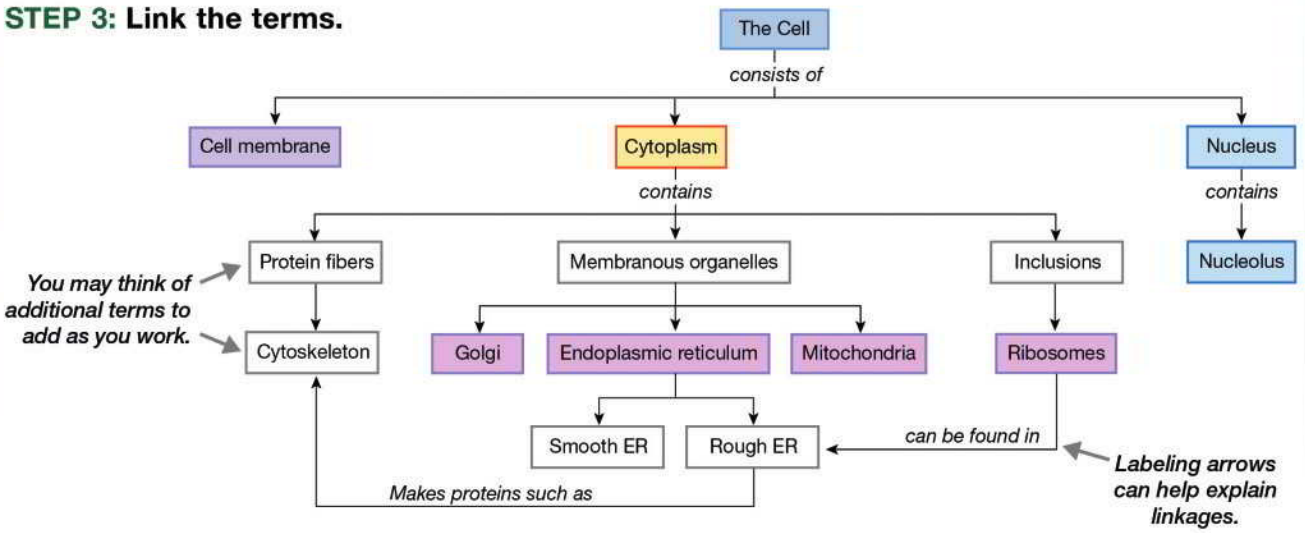
STEP 1: Write out the terms to map.
If you need help generating ideas for topics to map, the end-of-chapter mapping questions in each chapter have lists of terms to help you get started.



STEP 2: Organize the terms.



STEP 3: Link the terms.



Once you have created your map, sit back and think about it. Are all the items in the right place? You may want to move them around once you see the big picture. Add new concepts or correct wrong links. Review by recalling the main concept and then moving to the more specific details. Ask yourself questions like, What is the cause and what is the effect? What parts are involved? What are the main characteristics?

Science is a collaborative field. A useful way to study with a map is to **trade maps with a classmate** and try to understand each other's maps. Your maps will almost certainly not look the same! It's OK if they are different. Remember that your map reflects the way you think about the subject, which may be different from the way someone else thinks about it. Did one of you put in something the other forgot? Did one of you have an incorrect link between two items?

Interactions between proteins, water, and other molecules influence cell structure and the mechanical properties of cells and tissues. Mechanical properties you will encounter in your study of physiology include *compliance* (ability to stretch), *elastance* (stiffness or the ability to return to the unstretched state), strength, flexibility, and fluidity (*viscosity*).

Compartmentation

Compartmentation is the division of space into separate compartments, with or without obvious dividing walls. Compartments allow a cell, a tissue, or an organ to specialize and isolate functions. Each level of organization is associated with different types of compartments. At the macroscopic level, the tissues and organs of the body form discrete functional compartments, such as body cavities or the insides of hollow organs. At the microscopic level, cell membranes separate cells from the fluid surrounding them and also create tiny compartments within the cell called organelles. Compartmentation is the theme of Chapter 3.

Running Problem 1.3

Hiro looked at the results on the first page. He had heard of the NIH, and knew it was the U.S. National Institutes of Health, run by the federal government, so he clicked on *www.nccih.nih.gov*. This link went to a page for the NIH-Sponsored National Center for Complementary and Integrative Health (NCCIH). Hiro decided to learn more about NCCIH by using the ABOUT link. He used the SEARCH box to see what NCCIH said about probiotics.

Q2: *Go to www.nccih.nih.gov. What is the mission of NCCIH?*

Q3: *What does NCCIH say about whether probiotics are helpful and whether they are safe?*

Core Concept 2: Living Organisms Need Energy

Growth, reproduction, movement, homeostasis—these and all other processes that take place in an organism require the continuous input of energy. Where does this energy come from, and how is it stored? We will answer those questions and describe some of the ways that energy in the body is used for building and breaking down molecules in Chapter 4. In subsequent chapters, you will learn how energy is used to transport molecules across cell membranes and to create movement.

Core Concept 3: Gradients and Flow

A **gradient** {*gradiens*, to walk} is a gradual change in the value or magnitude of a function over distance or over time. In physiology, most of the gradients you will encounter represent a change in magnitude from one location to another, such as from the beginning to the end of a tube or between the inside and outside of a cell. The gradients icon (Fig. 1.1) shows two gradients moving from left to right: a decrease in size and a decrease in color intensity. Three types of gradients are particularly important in physiology: concentration (chemical) gradients, pressure gradients, and electrical gradients. You may also encounter other gradients, such as temperature gradients. Gradients are a form of stored (*potential*) energy, and substances will move or flow down a gradient unless there is a barrier blocking their movement.

Core Concept 4: Communication Coordinates Body Functions

Communication is the transmission of information within or between organisms. Information flow in living systems ranges from the transfer of information stored in DNA from generation to generation (genetics) to the flow of information within the body of a single organism. At the organismal level, information flow includes translation of DNA's genetic code into proteins responsible for cell structure and function as well as the communication signals between cells that coordinate function.

Cell-to-cell communication uses chemical signals, electrical signals, or a combination of both. Information may go from one cell to its neighbors (local communication) or from one part of the body to another (long-distance communication). Chapter 5 looks at the electrical gradients responsible for electrical signaling, while Chapter 6 discusses chemical communication in the body.

When chemical signals reach their target cells, they must get their information into the cell. Some molecules are able to pass through the barrier of the cell membrane, but signal molecules that cannot enter the cell must transfer their message across the cell membrane. How molecules cross biological membranes is the topic of Chapter 5, Chapter 6 looks at how chemical signals pass their information across the cell membrane.

Core Concept 5: Homeostasis Maintains Internal Stability

Organisms that survive in challenging habitats cope with external variability by keeping their internal environment relatively stable, an ability known as **homeostasis** {*homeo-*, similar + *-stasis*, condition}. Homeostasis and regulation of the internal environment are key principles of physiology and form an underlying core concept in each chapter of this book. The next section looks in detail at the key elements of this important core concept.

1.4 Homeostasis

The concept of a relatively stable internal environment is attributed to the French physician Claude Bernard in the mid-1800s. During his studies of experimental medicine, Bernard noted the stability of various physiological functions, such as body temperature, heart rate, and blood pressure. As the chair of physiology at the University of Paris, he wrote "La fixité du milieu intérieur est la condition de la vie libre, indépendante." (The constancy of the

internal environment is the condition for a free and independent life.)[5] This idea was applied to many of the experimental observations of his day, and it became the subject of discussion among physiologists and physicians.

In 1929, an American physiologist named **Walter B. Cannon** wrote a review for the American Physiological Society.[6] Using observations made by numerous physiologists and physicians during the nineteenth and early twentieth centuries, Cannon proposed a list of variables that are under homeostatic control. We now know that his list was both accurate and complete. Cannon divided his variables into what he described as environmental factors that affect cells (osmolarity, temperature, and pH) and "materials for cell needs" (nutrients, water, sodium, calcium, other inorganic ions, oxygen, as well as "internal secretions having general and continuous effects"). Cannon's "internal secretions" are the hormones and other chemicals that our cells use to communicate with one another.

In his essay, Cannon created the word *homeostasis* to describe the regulation of the body's internal environment. He explained that he selected the prefix *homeo-* (meaning *like* or *similar*) rather than the prefix *homo-* (meaning *same*) because the internal environment is maintained within a range of values rather than at an exact fixed value. He also pointed out that the suffix *-stasis* in this instance means a *condition*, not a state that is static and unchanging. Cannon's homeostasis, therefore, is a state of maintaining "a similar condition," similar to Claude Bernard's relatively constant internal environment.

Some physiologists contend that a literal interpretation of *stasis* {a state of standing} in the word *homeostasis* implies a static, unchanging state. They argue that we should use the word *homeodynamics* instead, to reflect the small changes constantly taking place in our internal environment {*dynamikos*, force or power}. Whether the process is called homeostasis or homeodynamics, the important concept to remember is that the body monitors its internal state and takes action to correct disruptions that threaten its normal function. Physiologists today generally recognize 10 variables (**TABLE 1.1**) that the body monitors and regulates to maintain homeostasis.

If the body fails to maintain homeostasis of the critical variables listed by Walter Cannon, then healthy function is disrupted and a disease state, or **pathological** condition {*pathos*, suffering}, may result. Diseases fall into two general groups according to their origin: those in which the problem arises from internal failure of some normal physiological process, and those that originate from some outside source. Internal causes of disease include the abnormal growth of cells, which may cause cancer or benign tumors; the production of antibodies by the body against its own tissues (autoimmune diseases); and the premature death of cells or the failure of cell processes. Inherited disorders are also considered to have internal causes. External causes of disease include toxic chemicals, physical trauma, and foreign invaders such as viruses and bacteria.

In both internally and externally caused diseases, when homeostasis is disturbed, the body attempts to compensate (**FIG. 1.5**). If the compensation is successful, homeostasis is restored. If compensation fails, illness or disease may result. The study of body functions in a disease state is known as **pathophysiology.** You will encounter many examples of pathophysiology as we study the various systems of the body.

One very common pathological condition in the United States is **diabetes mellitus,** a metabolic disorder characterized by abnormally high blood glucose concentrations. Although we speak of diabetes as if it were a single disease, it is actually a whole family of diseases with various causes and manifestations. You will learn more about diabetes in the focus boxes scattered throughout the chapters of this book. The influence of this one disorder on many systems of the body makes it an excellent example of the integrative nature of physiology.

What Is the Body's Internal Environment?

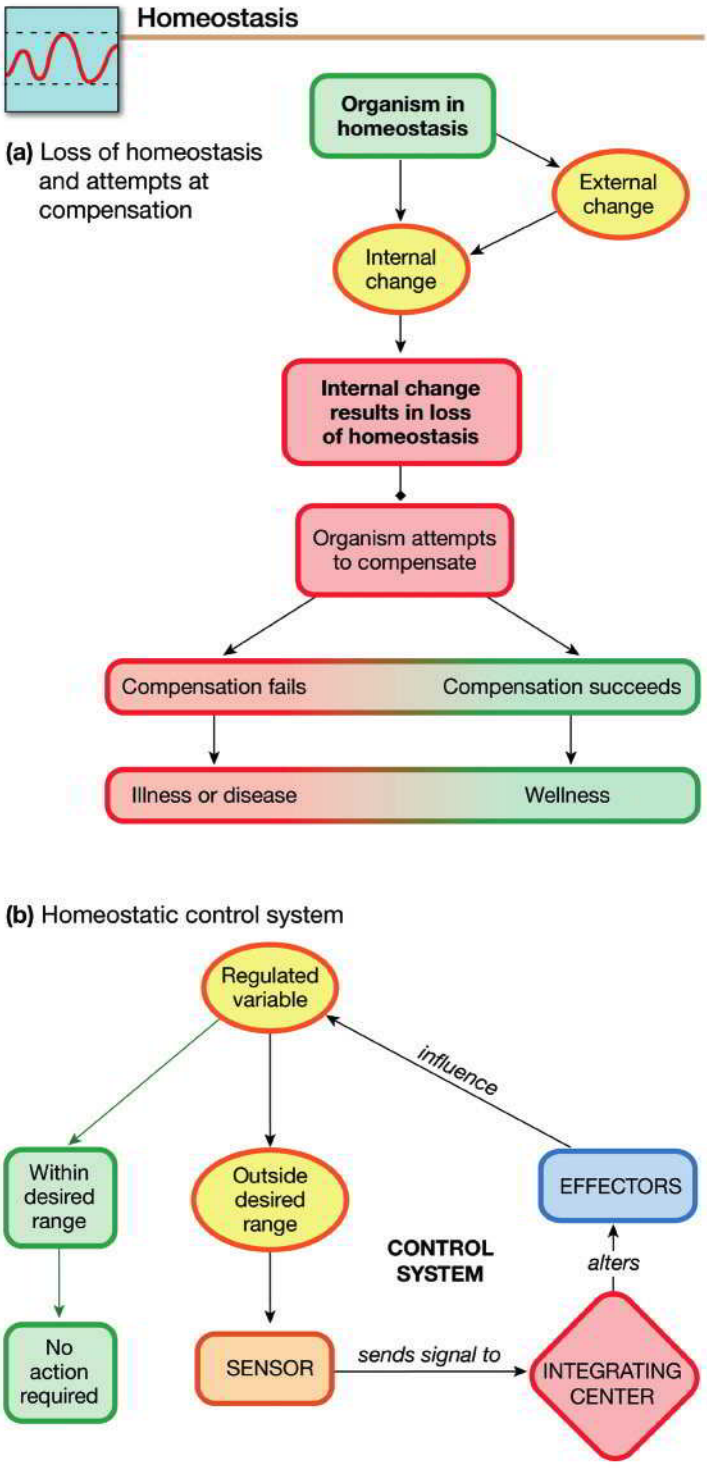
Claude Bernard wrote of the "constancy of the internal environment," but why is constancy so essential? As it turns out, most cells in our bodies are not very tolerant of changes in their surroundings. In this way they are similar to early organisms that lived in tropical seas, a stable environment where salinity, oxygen content, and pH vary little and where light and temperature cycle in predictable ways. The internal composition of these ancient creatures was almost identical to that of seawater. If environmental conditions changed, conditions inside the primitive organisms changed as well. Even today, marine invertebrates cannot tolerate significant changes in salinity and pH, as you know if you have ever maintained a saltwater aquarium.

In both ancient and modern times, many marine organisms relied on the constancy of their external environment to keep their internal environment in balance. In contrast, as organisms evolved and migrated from the ancient seas into estuaries, then into freshwater environments and onto the land, they encountered highly variable external environments. Rains dilute the salty water of estuaries, and organisms that live there must cope with the influx of water into their body fluids. Terrestrial organisms, including humans, face the challenge of dehydration—constantly losing internal water to the dry air around them. Keeping the internal environment stable means balancing water loss with appropriate water intake.

Table 1.1 Regulated Physiological Variables

Blood gases	Blood solutes	
• Oxygen • Carbon dioxide	• Potassium K^+ • Calcium Ca^{2+} • Hydrogen H^+ (pH) • Glucose	• Arterial blood pressure • Blood volume • Blood osmolarity • Body temperature (core)

Fig. 1.5 Homeostasis



But what exactly is the internal environment of the body? For multicellular animals, it is the watery internal environment that surrounds the cells, a "sea within" the body called the **extracellular fluid (ECF)** {*extra-*, outside of} (**FIG. 1.6**). Extracellular fluid serves as the transition between an organism's external environment and the **intracellular fluid (ICF)** inside cells {*intra-*, within}. Because extracellular fluid is a buffer zone between cells and the outside world, elaborate physiological processes have evolved to keep its composition relatively stable.

When the extracellular fluid composition varies outside its acceptable range of values, compensatory mechanisms are activated in an attempt to return the fluid to its usual state. For example, when you drink a large volume of water, the dilution of your extracellular fluid triggers a mechanism that causes your kidneys to remove excess water and protect your cells from swelling. Most cells of multicellular animals do not tolerate much change. They depend on the constancy of extracellular fluid to maintain their function.

Homeostasis Depends on Mass Balance

In the 1960s, a group of conspiracy theorists obtained a lock of Napoleon Bonaparte's hair and sent it for chemical analysis in an attempt to show that he died from arsenic poisoning. Today, a group of students sharing a pizza joke about the garlic odor on their breath. At first glance these two scenarios appear to have little in common, but in fact Napoleon's hair and "garlic breath" both demonstrate how the human body works to maintain the balance that we call *homeostasis*.

The human body is an open system that exchanges heat and materials with the outside environment. To maintain homeostasis, the body must maintain mass balance. We will consider mass balance to be another of our core concepts in physiology (Fig. 1.1).

The **law of mass balance** says that if the amount of a substance in the body is to remain constant, any gain must be offset by an equal loss (**FIG. 1.7a**). The amount of a substance in the body is also called the body's **load,** as in "sodium load."

For example, water loss to the external environment (output) in sweat and urine must be balanced by water intake from the external environment plus metabolic water production (input). The concentrations of other substances, such as oxygen and carbon dioxide, salts, and hydrogen ions (pH), are also maintained through mass balance. The following equation summarizes the law of mass balance:

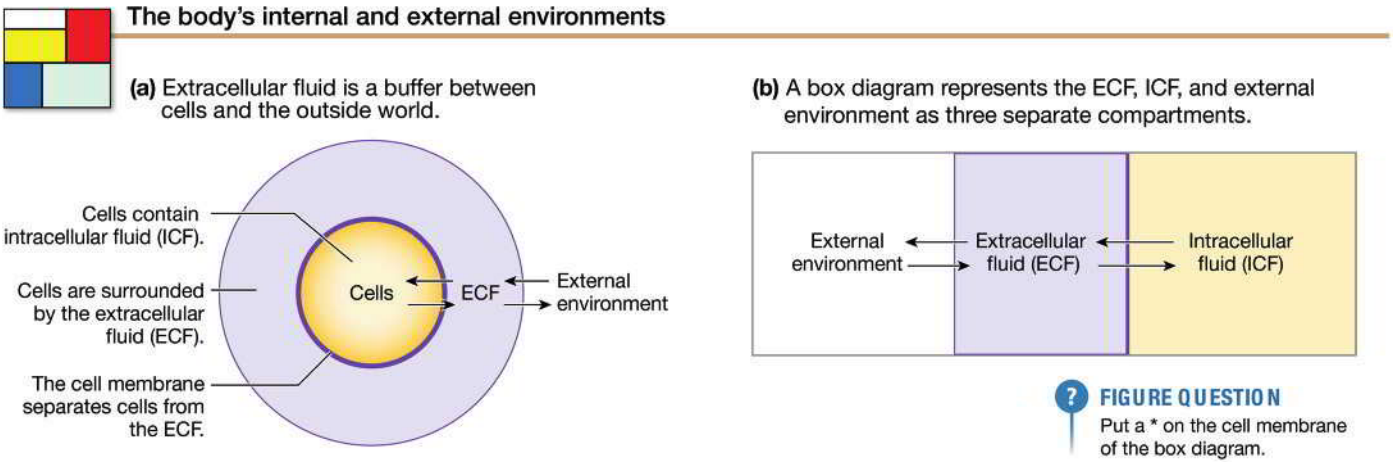
$$\text{Total amount of substance } x \text{ in the body} = \text{intake} + \text{production} - \text{excretion} - \text{metabolism}$$

Most substances enter the body from the outside environment, but some (such as carbon dioxide) are produced internally through metabolism (Fig. 1.7b). In general, water and nutrients enter the body as food and drink absorbed through the intestine. Oxygen and other gases and volatile molecules enter through the lungs. A few lipid-soluble chemicals make their way to the internal environment by penetrating the barrier of the skin.

To maintain mass balance, the body has two options for output. The simplest option is simply to excrete the material. **Excretion** is defined as the elimination of material from the body, usually through the urine, feces, lungs, or skin. For example, carbon dioxide (CO_2) produced during metabolism is excreted by the lungs. Many foreign substances that enter the body, such as drugs or artificial food additives, are excreted by the liver and kidneys. (Any foreign substance in the body is called a *xenobiotic*, from the Greek word *xenos*, a stranger.)

A second output option for maintaining mass balance is to convert the substance to a different substance through metabolism. Nutrients that enter the body become the starting point for

Fig. 1.6 Internal and external environments



metabolic pathways that convert the original nutrient to a different molecule. However, converting the original nutrient to something different then creates a new mass balance disturbance by adding more of the new substance, or *metabolite*, to the body. (*Metabolite* is the general term for any product created in a metabolic pathway.)

Mass Flow

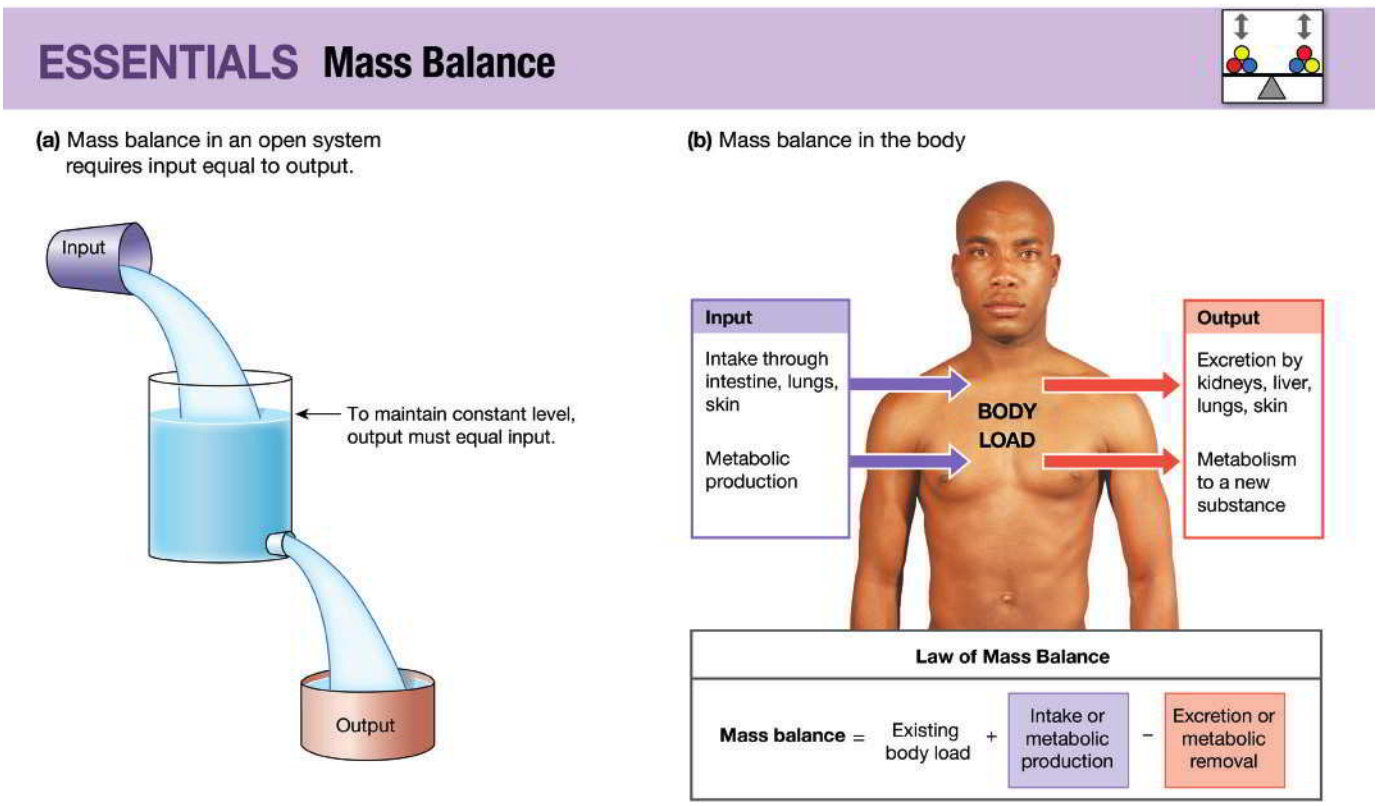
Scientists use **mass flow** to follow material throughout the body. Mass flow describes the rate of transport of a substance x as it moves through body fluids or into and out of the body. The equation for mass flow is

$$\text{Mass flow (amount } x/\text{min)} = \text{concentration of } x \text{ (amount } x/\text{vol)} \times \text{volume flow (vol/min)}$$

where volume flow describes the flow rate of a volume of blood, air, urine, and the like.

For example, suppose a person is given an intravenous (IV) infusion of glucose solution that has a concentration of 50 grams of glucose per liter of solution. If the infusion is given

Fig. 1.7 Mass balance



at a rate of 2 milliliters per minute, the mass flow of glucose into the body is:

$$\frac{50 \text{ g glucose}}{1000 \text{ mL solution}} \times 2 \text{ mL solution/min} = 0.1 \text{ g glucose/min}$$

The rate of glucose input into the body is 0.1 g glucose/min.

Mass flow applies not only to the entry, production, and removal of substances but also to the movement of substances from one compartment in the body to another. When materials enter the body, they first become part of the extracellular fluid. Where a substance goes after that depends on whether or not it can cross the barrier of the cell membrane and enter the cells.

Running Problem 1.4

Hiro wondered if there was another option for finding more information about probiotics, so he asked Jennifer, a friend who had just started graduate school in Public Health, how she would search. "I usually start with Google Scholar (scholar.google.com) rather than just googling. Google Scholar only shows you scholarly literature, so you won't get all the websites that are trying to sell you something. Or if you want to search the way scientists and healthcare professionals do, then try PubMed (www.pubmed.gov), the free database published by the U.S. National Library of Medicine." Hiro entered *probiotics* into Google Scholar and then repeated the same search in PubMed. "This is still way too much information," Hiro thought. "Surely there are ways to narrow this down."

Q4: *Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from the simple Google search.*

Q5: *One way to get fewer results is to limit the results to only recent papers. Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*

Excretion and Metabolism Clear Substances from the Body

It is relatively easy to monitor how much of a substance enters the body from the outside world, but it is more difficult to track molecules inside the body to monitor their excretion or metabolism. Instead of directly measuring the substance, we can follow the rate at which the substance disappears from the blood, a concept called **clearance.** Clearance is usually expressed as a volume of blood *cleared* of substance x per unit of time. For this reason, clearance is only an indirect measure of how substance x is handled by the body.

Clearance cannot tell you if the substance is disappearing by excretion or metabolism or by both. For example, urea is a normal metabolite produced from protein metabolism. A typical value for urea clearance is 70 mL plasma cleared of urea per minute, written as $urea\ clearance = 70\ mL\ plasma/min$. Knowing the rate at which urea disappears does not tell us anything about where urea is going. (It is being excreted by the kidneys.)

The kidney and the liver are the two primary organs that clear solutes from the body. *Hepatocytes* {*hepaticus*, pertaining to the liver + *cyte*, cell}, or liver cells, metabolize many different types of molecules, especially xenobiotics such as drugs. The resulting metabolites may be secreted into the intestine for excretion in the feces or released into the blood for removal by the kidneys. Pharmaceutical companies testing chemicals for their potential use as therapeutic drugs must know the clearance of the chemical before they can develop the proper dosing schedule.

Clearance also takes place in tissues other than the liver and kidneys. Saliva, sweat, breast milk, and hair all contain substances that have been cleared from the body. Salivary secretion of the hormone *cortisol* provides a simple noninvasive source of hormone for monitoring chronic stress.

An everyday example of clearance is "garlic breath," which occurs when volatile lipid-soluble garlic compounds in the blood pass into the airways and are exhaled. The lungs also clear ethanol in the blood: exhaled alcohol is the basis of the "breathalyzer" test used by law enforcement agencies. Drugs and alcohol secreted into breast milk are potentially dangerous because a breastfeeding infant will ingest these substances.

The 1960s analysis of Napoleon Bonaparte's hair tested it for arsenic because hair follicles help clear some compounds from the body. The test results showed significant concentrations of the poison in his hair, but the question remains whether Napoleon was murdered, poisoned accidentally, or died from stomach cancer.

Concept Check

1. If a person eats 12 milligrams (mg) of salt in a day and excretes 11 mg of it in the urine, what happened to the remaining 1 mg?
2. Glucose is metabolized to CO_2 and water. Explain the effect of glucose metabolism on mass balance in the body.

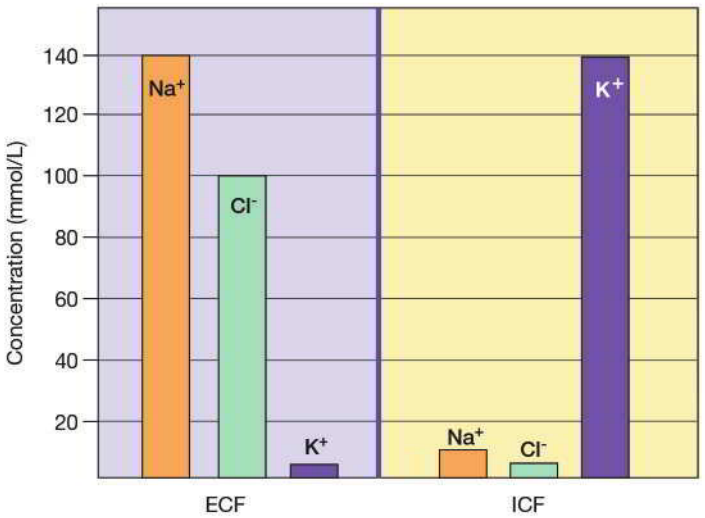
Homeostasis Does Not Mean Equilibrium

When physiologists talk about homeostasis, they are speaking of the stability of the body's **internal environment**—in other words, the stability of the extracellular fluid compartment (ECF). One reason for focusing on extracellular fluid homeostasis is that it is relatively easy to monitor by taking a blood sample. When you centrifuge blood, it separates into two parts: **plasma,** the fluid component, plus the heavier blood cells. Plasma is part of the extracellular fluid compartment, and its composition can be easily analyzed. It is much more difficult to follow what is taking place in the intracellular fluid compartment (ICF), although cells do maintain *cellular homeostasis*.

Fig. 1.8 Steady-state disequilibrium

Steady-state disequilibrium

The body compartments are in a dynamic steady state but are not at equilibrium. Ion concentrations are very different in the extracellular fluid compartment (ECF) and the intracellular fluid compartment (ICF).



In a state of homeostasis, the composition of both body compartments is relatively stable. This condition is a dynamic **steady state.** The modifier *dynamic* indicates that materials are constantly moving back and forth between the two compartments. In a steady state, there is no *net* movement of materials between the compartments.

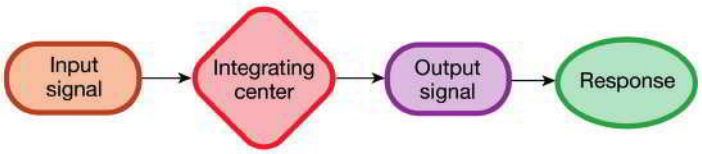
Steady state is not the same as **equilibrium** {*aequus*, equal + *libra*, balance}, however. Equilibrium implies that the composition of the body compartments is identical. If we examine the composition of the ECF and ICF, we find that the concentrations of many substances are different in the two compartments (**FIG. 1.8**). For example, sodium (Na^+) and chloride (Cl^-) are far more concentrated in the ECF than in the ICF, while potassium (K^+) is most concentrated in the ICF. Because of these concentration differences, the two fluid compartments are not at equilibrium. Instead the ECF and ICF exist in a state of relatively stable **disequilibrium** {*dis-* is a negative prefix indicating the opposite of the base noun}. For living organisms, the goal of homeostasis is to maintain the dynamic steady states of the body's compartments, not to make the compartments the same.

1.5 Control Systems and Homeostasis

In their simplest form, all **control systems** have three components (**FIG. 1.9**): (1) an input signal; (2) a controller, or **integrating center** {*integrare*, to restore}, that integrates incoming information and initiates an appropriate response; and (3) an output signal that creates a response. Long-distance reflex control systems are more complex than this simple model, however, as they may include input from multiple sources and have output that acts on multiple targets.

Fig. 1.9 A simple control system

A simple control system



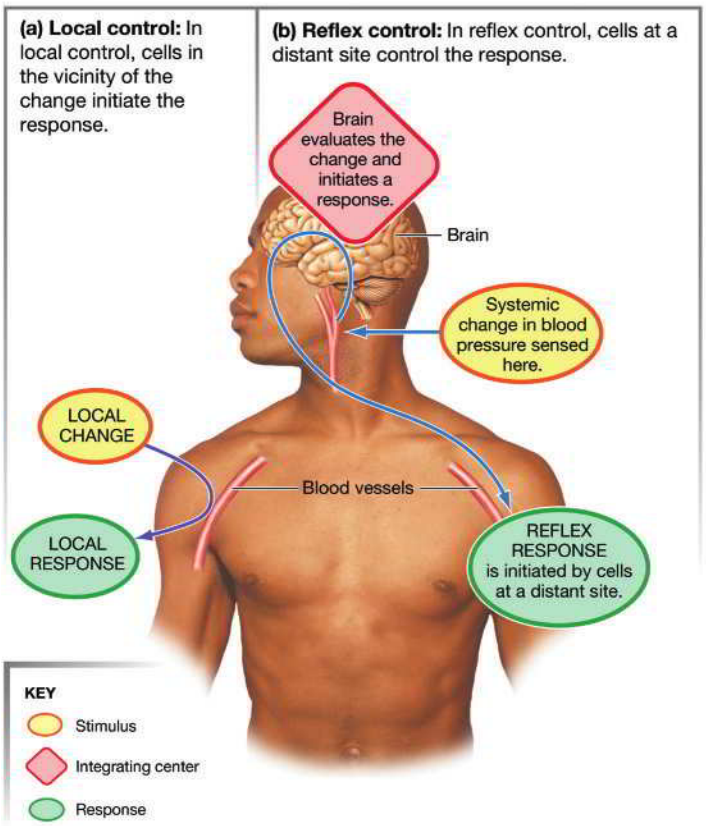
Local Control Is Restricted to a Tissue

The simplest form of control is **local control,** which is restricted to the tissue or cell involved (**FIG. 1.10**). In local control, a relatively isolated change occurs in a tissue. A nearby cell or group of cells senses the change in their immediate vicinity and responds, usually by releasing a chemical. The response is restricted to the region where the change took place—hence the term *local control*.

One example of local control can be observed when oxygen concentration in a tissue decreases. Cells lining the small blood vessels that bring blood to the area sense the lower oxygen concentration and respond by secreting a chemical signal. The signal molecule diffuses to nearby muscles in the blood vessel

Fig. 1.10 Local control and reflex control

A comparison of local control and reflex control



wall, bringing them a message to relax. Relaxation of the muscles widens (*dilates*) the blood vessel, which increases blood flow into the tissue and brings more oxygen to the area.

Reflex Control Uses Long-Distance Signaling

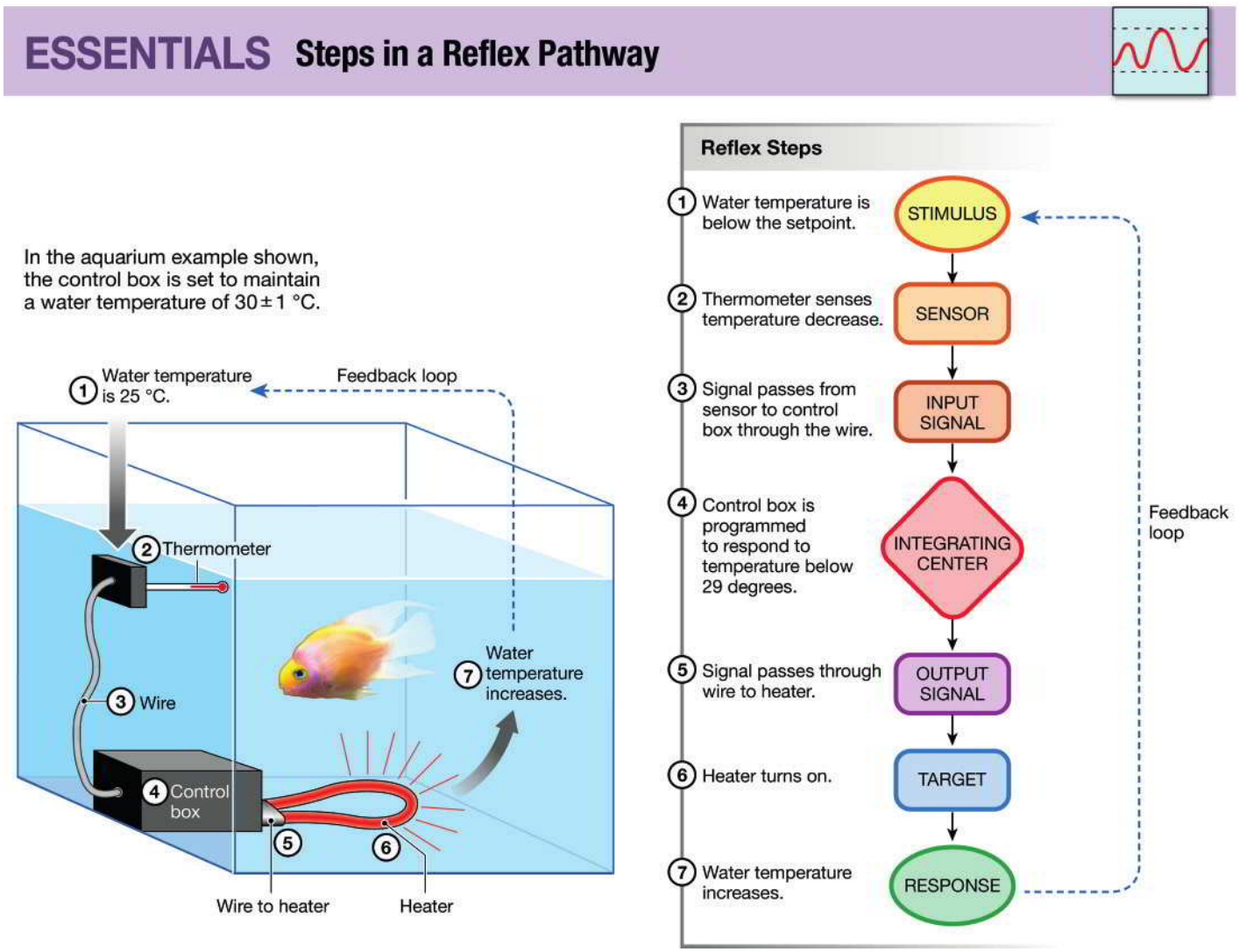
Changes that are widespread throughout the body, or *systemic* in nature, require more complex control systems. For example, maintaining blood pressure to drive blood flow throughout the body is a systemic issue rather than a local one. Because blood pressure is body-wide, maintaining it requires long-distance communication and coordination. We will use the term **reflex control** to mean any long-distance pathway that uses the nervous system, endocrine system, or both. Chapter 6 discusses different reflex pathways in more detail. It is important to note that not all reflexes are homeostatic! For example, the knee jerk reflex (patellar tendon reflex), where your lower leg kicks out after a tap just below the kneecap, is a reflex but it has nothing to do with homeostasis.

Physiological reflexes can be represented by response loops (**FIG. 1.11**). As with the simple control system just described, a **response loop** has three primary components: an *input signal*, an *integrating center* to integrate the signal, and an *output signal*. These three components can be expanded into the following sequence of seven steps to form a pattern that is found with slight variations in all reflex pathways:

Stimulus → sensor → input signal → integrating center → output signal → target → response

The input side of the response loop starts with a *stimulus*—the change that occurs when the regulated variable moves out of its desirable range. A specialized **sensor** monitors the variable. If the sensor is activated by the stimulus, it sends an input signal to the integrating center. The integrating center evaluates the information coming from the sensor and initiates an output signal. The output signal directs a target to carry out a response.

Fig. 1.11 The steps in a reflex pathway



In mammals, integrating centers are usually part of the nervous system or endocrine system. Output signals may be chemical signals, electrical signals, or a combination of both. The targets activated by output signals can be any cell of the body. If the reflex ends with the response, such as the knee-jerk reflex, the reflex is considered an **open-loop control system**. Open response loops are not homeostatic. A *closed-loop control system* has **feedback**, where the pathway's response "feeds back" to inform the sensor that a change has occurred. You will encounter both open and closed response loops as you study physiology, but homeostasis requires closed response loops with negative feedback.

Homeostasis Requires Monitored Variables

To maintain homeostasis, the human body monitors certain key functions, such as blood pressure and blood glucose concentration, that must stay within a particular operating range if the body is to remain healthy (Tbl. 1.1). These important **regulated variables** (monitored variables) are kept within their acceptable (normal) range by long-distance reflex control mechanisms that kick in if the variable ever strays too far from its **setpoint**, or preferred value.

To illustrate closed response loops and homeostasis, let's apply the concept to a simple nonbiological example. Think about an aquarium whose heater is programmed to maintain the water temperature (the regulated variable) at 30 °C (Fig. 1.11). The room temperature is 25 °C. The desired water temperature (30 °C) is the *setpoint* for the regulated variable.

Assume that initially the aquarium water is at room temperature, 25 °C. When you turn the control box on, you set the response loop in motion. The thermometer (sensor) registers a temperature of 25 °C. It sends this information through a wire (input signal) to the control box (integrating center). The control box is programmed to evaluate the incoming temperature signal, compare it with the setpoint for the system (30 °C), and "decide" whether a response is needed to bring the water temperature up to the setpoint. The control box sends a signal through another wire (output signal) to the heater (the target), which turns on and starts heating the water (response). This sequence—from stimulus to response—is the response loop.

This aquarium example involves a variable (temperature) controlled by a single control system (the heater). We can also describe a system that is under dual control. For example, think of a house that has both heating and air conditioning. The owner would like the house to remain at 70 °F (about 21 °C). On chilly autumn mornings, when the temperature in the house falls, the heater turns on to warm the house. Then, as the day warms up, the heater is no longer needed and turns off. When the sun heats the house above the setpoint, the air conditioner turns on to cool the house back to 70 °F. The heater and air conditioner have *antagonistic control* over house temperature because they work in opposition to each other. Similar situations occur in the human body when two branches of the nervous system or two different hormones have opposing effects on a single target.

Concept Check

3. What is the drawback of having only a single control system (a heater) for maintaining aquarium water temperature in some desired range?

Feedback Loops Modulate the Response Loop

The response loop is only the first part of many reflexes. For example, in the aquarium just described, the sensor sends temperature information to the control box, which recognizes that the water is too cold. The control box responds by turning on the heater to warm the water. Once the response starts, what keeps the heater from sending the temperature up to, say, 50 °C?

The answer is a **feedback loop,** where the response "feeds back" to influence the input portion of the pathway. In the aquarium example, turning on the heater increases the temperature of the water. The sensor continuously monitors the temperature and sends that information to the control box. When the control box gets feedback that the temperature has warmed up to the maximum acceptable value, it shuts off the heater, ending the reflex response.

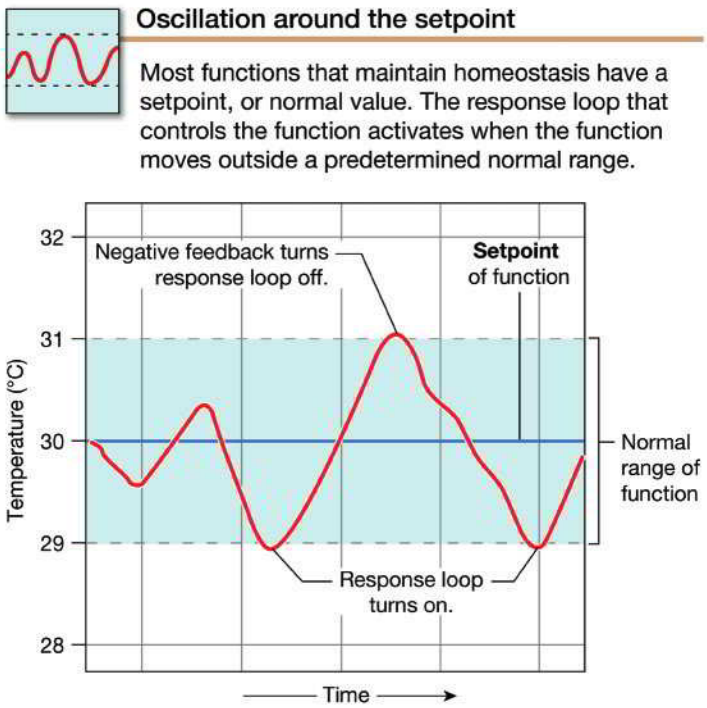
Negative Feedback Loops Are Homeostatic

For most reflexes, feedback loops are homeostatic—that is, designed to keep the system at or near a setpoint so that the regulated variable is relatively stable. How well an integrating center succeeds in maintaining stability depends on the *sensitivity* of the system. In the case of our aquarium, the control box is programmed to have a sensitivity of ±1 °C. If the water temperature drops from 30 °C to 29.5 °C, it is still within the acceptable range, and no response occurs. If the water temperature drops below 29 °C (30 − 1), the control box turns the heater on (**FIG. 1.12**). As the water heats up, the control box constantly receives information about the water temperature from the sensor. When the water reaches 31 °C (30 ± 1), the upper limit for the acceptable range, the feedback loop causes the control box to turn the heater off. The water then gradually cools off until the cycle starts all over again. The end result is a regulated variable that *oscillates* {*oscillare*, to swing} around the setpoint.

In physiological systems, some sensors are more sensitive than others. For example, the sensors that trigger reflexes to conserve water activate when blood concentration increases only 3% above the acceptable range, but the sensors for low oxygen in the blood will not respond until oxygen has decreased by 40%.

A pathway in which the response opposes or removes the signal is known as **negative feedback** (**FIG. 1.13a**). Negative feedback loops *stabilize* the regulated variable and thus aid the system in maintaining homeostasis. In the aquarium example, the heater warms the water (the response) and removes the

Fig. 1.12 Oscillation around the setpoint



stimulus (low water temperature). With loss of the stimulus for the pathway, the response loop shuts off. *Negative feedback loops can restore the usual state but cannot prevent the initial disturbance.*

Positive Feedback Loops Are Not Homeostatic

A few reflex pathways are not homeostatic. In a **positive feedback loop,** the response *reinforces* the stimulus rather than decreasing or removing it. In positive feedback, the response sends the regulated variable even farther from its usual value. This initiates a vicious cycle of ever-increasing response and sends the system temporarily out of control (Fig. 1.13b). Because positive feedback escalates the response, this type of feedback requires some intervention or event outside the loop to stop the response.

One example of a positive feedback loop involves the hormonal control of uterine contractions during childbirth (**FIG. 1.14**). When the baby is ready to be delivered, it drops lower in the uterus and begins to put pressure on the *cervix,* the opening of the uterus. Sensory signals from the cervix to the brain cause release of the hormone *oxytocin,* which causes the uterus to contract and push the baby's head even harder against the cervix, further stretching it. The increased stretch causes more oxytocin release, which causes more contractions that push the baby harder against the cervix. This cycle continues until finally the baby is delivered, releasing the stretch on the cervix and stopping the positive feedback loop.

Concept Check

4. Does the aquarium heating system in Figure 1.11 operate using positive feedback or negative feedback?

Feedforward Control Allows the Body to Anticipate Change

Negative feedback loops can stabilize a function and maintain it within an acceptable range but are unable to prevent the change that triggered the reflex in the first place. A few reflexes have evolved that enable the body to predict that a change is about to occur and start the response loop in anticipation of the change. These anticipatory responses are called **feedforward control.**

Fig. 1.13 Negative and positive feedback

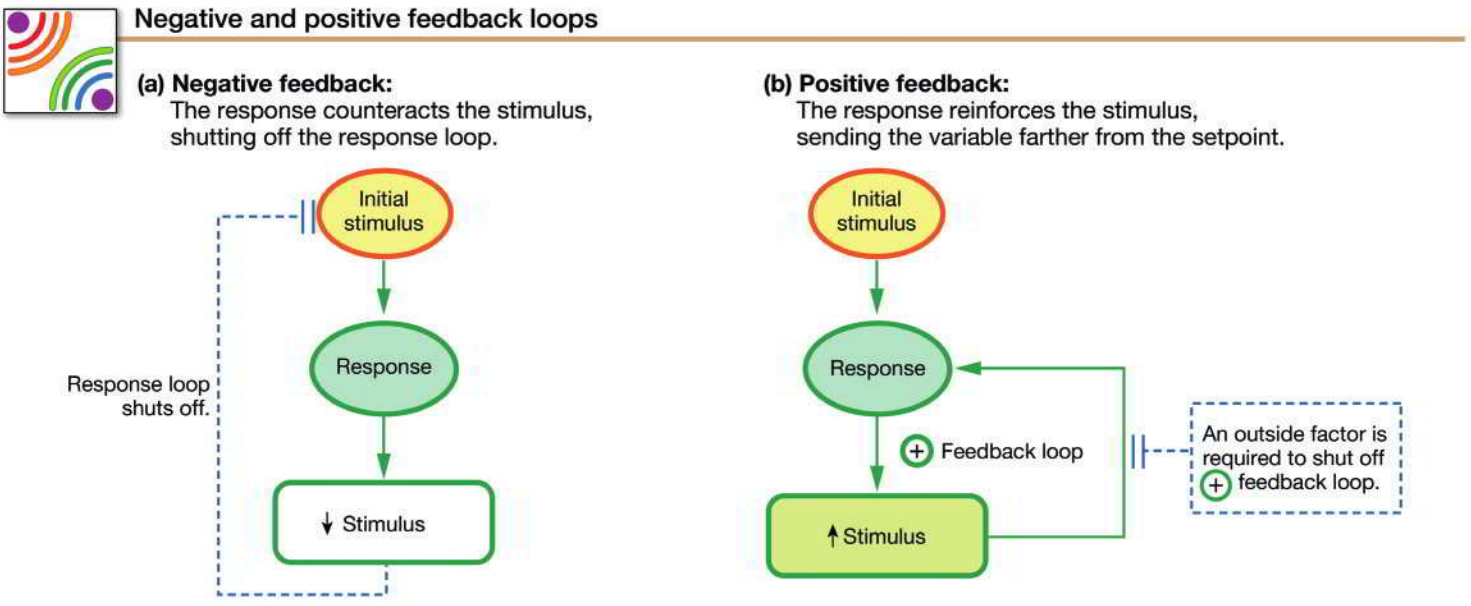
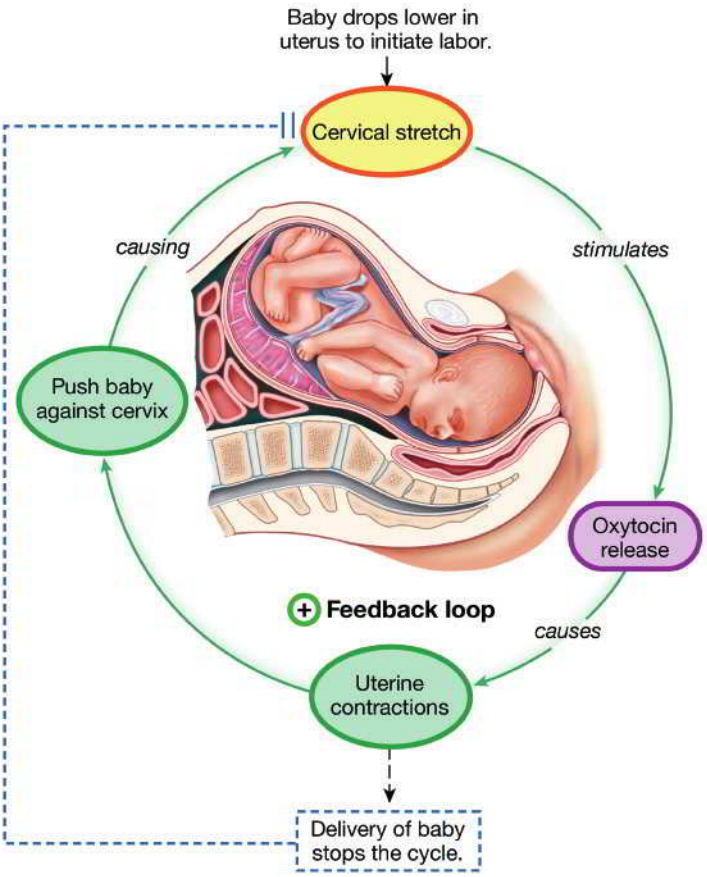


Fig. 1.14 A positive feedback loop



An easily understood physiological example of feedforward control is the salivation reflex. The sight, smell, or even the thought of food is enough to start our mouths watering in expectation of eating the food. This reflex extends even further, because the same stimuli can start the secretion of hydrochloric acid as the stomach anticipates food on the way. One of the most complex feedforward reflexes appears to be the body's response to exercise discussed in Chapter 25.

Biological Rhythms Result from Changes in a Setpoint

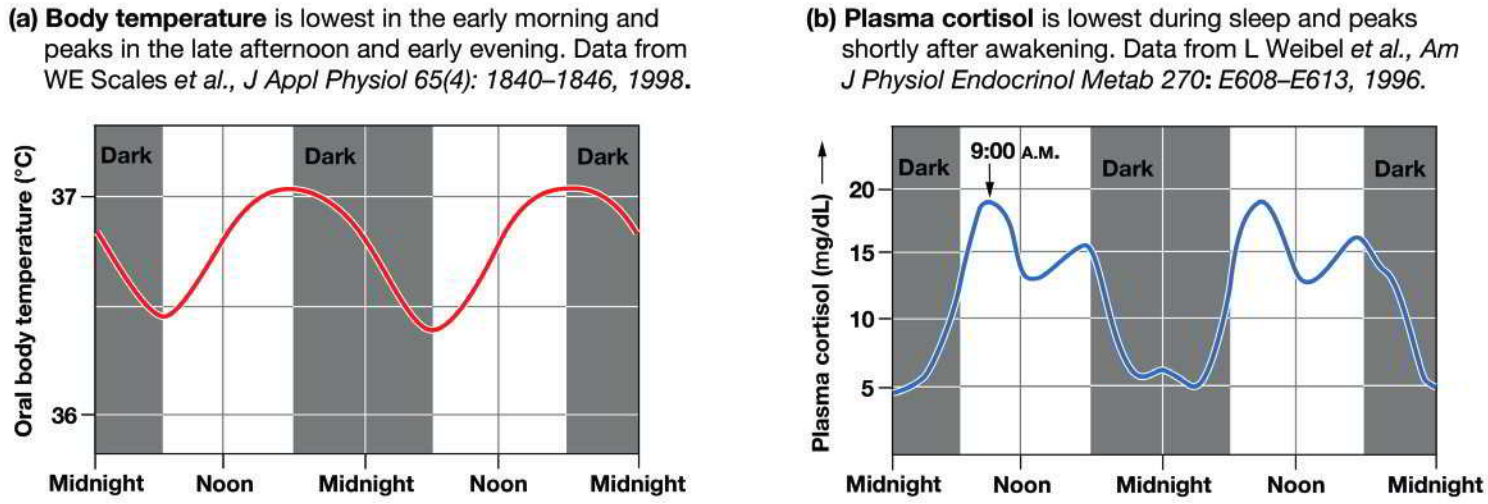
As discussed earlier, each regulated variable has an acceptable range within which it can vary without triggering a correction. In physiological systems, the setpoints for many regulated variables are different from person to person, or may change for the same individual over a period of time. Factors that influence an individual's setpoint for a given variable include normal biological rhythms, inheritance, and the conditions to which the person has become accustomed.

Regulated variables that change predictably and create repeating patterns or cycles of change are called **biological rhythms**, or *biorhythms*. The timing of many biorhythms coincides with a predictable environmental change, such as daily light–dark cycles or the seasons. Biological rhythms reflect changes in the setpoint of the regulated variable.

For example, all animals exhibit some form of daily biological rhythm, called a **circadian rhythm** {*circa*, about + *dies*, day}. Humans have circadian rhythms for many body functions, including blood pressure, body temperature, and metabolic processes. For example, body temperature peaks in the late afternoon and declines dramatically in the early hours of the morning (**FIG. 1.15a**). Have you ever been studying late at night and noticed that you feel cold? This is not because of a drop in environmental temperature but because your thermoregulatory reflex has turned down your internal thermostat.

One of the interesting correlations between circadian rhythms and behavior involves body temperature. Researchers found that self-described "morning people" have temperature rhythms that cause body temperature to climb before they wake

Fig. 1.15 Circadian rhythms in humans



up in the morning, so that they get out of bed prepared to face the world. On the other hand, "night people" may be forced by school and work schedules to get out of bed while their body temperature is still at its lowest point, before their bodies are prepared for activity. These night people are still going strong and working productively in the early hours of the morning, when the morning people's body temperatures are dropping and they are fast asleep.

Many hormones in humans have blood concentrations that fluctuate predictably in a 24-hour cycle. Cortisol, growth hormone, and the sex hormones are among the most noted examples. A cortisol concentration in a 9:00 AM sample might be nearly twice as high as one taken in the early afternoon (Fig. 1.15b).

If a patient has a suspected abnormality in hormone secretion, it is therefore important to know when hormone levels are measured. A concentration that is normal at 9:00 AM is high at 2:00 PM. One strategy for avoiding errors due to circadian fluctuations is to collect information for a full day and calculate an average value over 24 hours. For example, cortisol secretion is estimated indirectly by measuring all urinary cortisol metabolites excreted in 24 hours.

What is the adaptive significance of functions that vary with a circadian rhythm? Our best answer is that biological rhythms create an anticipatory response to a predictable environmental variable. There are seasonal rhythms of reproduction in many organisms. These rhythms are timed so that the offspring have food and other favorable conditions to maximize survival.

Circadian rhythms cued by the light–dark cycle may correspond to rest-activity cycles. These rhythms allow our bodies to anticipate behavior and coordinate body processes accordingly. You may hear people who are accustomed to eating dinner at 6:00 PM say that they cannot digest their food if they wait until 10:00 PM to eat because their digestive system has "shut down" in anticipation of going to bed.

Some variability in setpoints is associated with changing environmental conditions rather than biological rhythms. The adaptation of physiological processes to a given set of environmental conditions is known as **acclimatization** when it occurs naturally. If the process takes place artificially in a laboratory setting, it is called **acclimation**. Each winter, people in the upper latitudes of the northern hemisphere go south in February, hoping to escape the bitter subzero temperatures and snows of the northern climate. As the northerners walk around in 40 °F (about 4 °C) weather in short-sleeve shirts, the southerners, all bundled up in coats and gloves, cannot understand why: the weather is cold! The difference in behavior is due to different temperature acclimatization, a difference in the setpoint for body temperature regulation that is a result of prior conditioning.

Biorhythms and acclimatization are complex processes that scientists still do not completely understand. Some rhythms arise from special groups of cells in the brain and are reinforced by information about the light–dark cycle that comes in through the eyes. Some organs outside the nervous system generate their own rhythms of protein synthesis and breakdown. Research in simpler animals such as flies is helping explain the molecular basis for biological rhythms. We discuss the cellular and molecular basis for circadian rhythms in Chapter 10.

Running Problem 1.5

Most of the articles Hiro found in PubMed and Google Scholar seemed to be focused on detailed descriptions of experiments. "Is there any way to find papers that are not so complicated?" he asked Jennifer.

"Well, when I'm trying to learn about a new topic, I look for review articles, which are summaries of recent research. Both Google Scholar and PubMed have options that let you limit your results to show only review articles." Hiro went back to PubMed and Google Scholar to see if this would help him find the information he was looking for.

Jennifer had also mentioned using artificial intelligence to answer the question. "But you need to be cautious and always verify what an AI program tells you." Hiro went to ChatGPT (chat.openai.com) and typed "What does research say about taking probiotics?"

Q6: *On the Google Scholar and PubMed pages with results from the last 5 years, select the option for review articles. Now how many results are there?*

Q7: *Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*

1.6 The Science of Physiology

How do we know what we know about the physiology of the human body? The first descriptions of physiology came from simple observations. But physiology is an experimental science, one in which researchers generate **hypotheses** {*hypotithenai*, to assume; singular *hypothesis*}, or logical guesses, about how events take place. They test their hypotheses by designing experiments to collect evidence that supports or disproves their hypotheses, and they publish the results of their experiments in the scientific literature. Healthcare providers look in the scientific literature for evidence from these experiments to help guide their clinical decision-making. Critically evaluating the scientific evidence in this manner is a practice known as *evidence-based medicine*. Observation and experimentation are the key elements of **scientific inquiry.**

Good Scientific Experiments Must Be Carefully Designed

A common type of biological experiment either removes or alters some variable that the investigator thinks is an essential part of an observed phenomenon. That altered variable is the **independent variable.** For example, a biologist notices that birds at a feeder seem to eat more in the winter than in the summer. She generates a hypothesis that cold temperatures cause birds to increase their food intake. To test her hypothesis, she designs an experiment in

which she keeps birds at different temperatures and monitors how much food they eat. In her experiment, temperature, the manipulated element, is the independent variable. Food intake, which is hypothesized to be dependent on temperature, becomes the **dependent variable.**

Concept Check

5. Students in the laboratory run an experiment in which they drink different volumes of water and measure their urine output in the hour following drinking. What are the independent and dependent variables in this experiment?

An essential feature of any experiment is an experimental **control.** A control group is usually a duplicate of the experimental group in every respect except that the independent variable is not changed from its initial value. Ideally, all other conditions are kept identical in the control and experimental groups, and those factors are considered **controlled variables**. For example, in the bird-feeding experiment, the control group would be a set of birds maintained at a warm summer temperature but otherwise treated exactly like the birds held at cold temperatures. The purpose of the control group is to ensure that any observed changes are due to the manipulated variable and not to changes in some other variable. For example, suppose that in the bird-feeding experiment food intake increased after the investigator changed to a different food. Unless she had a control group that was also fed the new food, the investigator could not determine whether the increased food intake was due to temperature or to the fact that the new food was more palatable. The type of food fed to the birds would be a controlled variable.

During an experiment, the investigator carefully collects information, or **data** {plural; singular *datum*, a thing given}, about the effect that the manipulated (independent) variable has on the observed (dependent) variable. Once the investigator feels that she has sufficient information to draw a conclusion, she begins to analyze the data. Analysis can take many forms and usually includes statistical analysis to determine if apparent differences are statistically significant. A common format for presenting data is a graph (**FIG. 1.16**).

If one experiment supports the hypothesis that cold causes birds to eat more, then the experiment should be repeated to ensure that the results were not an unusual one-time event. This step is called **replication.** When the data support a hypothesis in multiple experiments, the hypothesis may become a working **model.** A model with substantial evidence from multiple investigators supporting it may become a **scientific theory.**

Most information presented in textbooks like this one is based on models that scientists have developed from the best available experimental evidence. On occasion, investigators publish new experimental evidence that does not support a current model. In that case, the model must be revised to fit the available evidence. For this reason, you may learn a physiological "fact" while using this textbook, but in 10 years that "fact" may be inaccurate because of what scientists have discovered in the interval.

For example, in 1970, students learned that the cell membrane was a "butter sandwich," a structure composed of a layer of fats sandwiched between two layers of proteins. In 1972, however, scientists presented a very different model of the membrane, in which globules of proteins float within a double layer of fats. As a result, students who had learned the butter sandwich model had to revise their mental model of the membrane.

Where do our scientific models for human physiology come from? We have learned much of what we know from experiments on animals ranging from fruit flies and squid to rats. In many instances, the physiological processes in such animals are either identical to those taking place in humans or else similar enough that we can extrapolate from the animal model to humans. It is important to use nonhuman models because experiments using human subjects can be difficult to perform.

However, not all studies done on animals can be applied to humans. For example, an antidepressant drug that Europeans had used safely for years was undergoing stringent testing required by the U.S. Food and Drug Administration before it could be sold in this country. When beagle dogs were given the drug for a period of months, the dogs started dying from heart problems. Scientists were alarmed until further research showed that beagles have a unique genetic makeup that causes them to break down the drug into a more toxic substance. The drug was perfectly safe in other breeds of dogs and in humans, and it was subsequently approved for human use.

The Results of Human Experiments Can Be Difficult to Interpret

Many reasons make it difficult to carry out physiological experiments in humans, including variability, psychological factors, and ethical considerations.

Variability

Human populations have tremendous genetic and environmental **variability.** It has been traditional in medicine to talk about "normal values" for body functions, but what is "normal" for one person may not be "normal" for someone else. When possible, it is better to use the word *typical* or *healthy* although you will still encounter *normal* in tables and discussions of variables that can be quantified, such as blood glucose concentrations. Physiology books usually present *average* values for many physiological variables, such as blood pressure, but these average values simply represent a number that falls somewhere near the middle of a wide range of values.

The variability found in human populations can make it difficult to show significant differences between experimental and control groups in a human experiment. Ideally, an investigator would have to include a large number of identical subjects in a study. However, getting two groups of people who are *identical* in every respect is impossible. Instead, the researcher must attempt to recruit subjects who are *similar* in as many aspects as possible. You may have seen newspaper advertisements requesting research volunteers: "Healthy males between 18 and 25,

Fig. 1.16 Focus on . . . Graphing

Focus on . . . Graphing

Graphs are pictorial representations of the relationship between two (or more) variables, plotted in a rectangular region. Graphs present a large amount of numerical data in a small space, emphasize comparisons between variables, or show trends over time.

A viewer can extract information much more rapidly from a graph than from a table of numbers or from a written description. A well-constructed graph should contain (in very abbreviated form) everything the reader needs to know about the data, including the purpose of the experiment, how the experiment was conducted, and the results.

All scientific graphs have common features.

The horizontal axis is called the **x-axis**.

The vertical axis is called the **y-axis**.

The intersection of the two axes is called the **origin**. The origin usually, but not always, has a value of zero for both axes.

The simplest way to know what most graphs mean is the substitute the labels on the X and Y axes into the following sentence:

The effect of [X] on [Y]

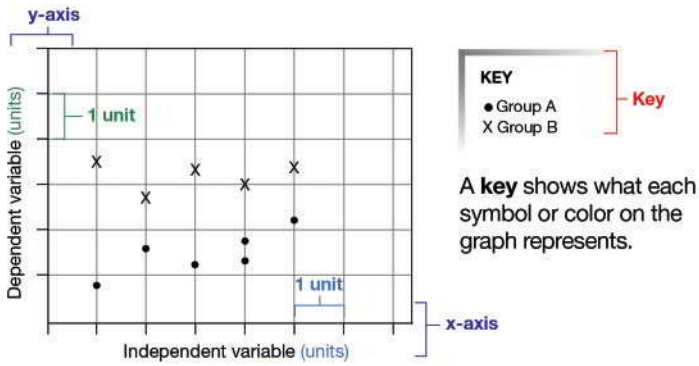
The x-axis shows values of the variable manipulated by the experimenter. This is called the **independent variable**.

The y-axis shows the variable measured by the experimenter. It is called the **dependent variable**.

If the experimental design is valid and the hypothesis is correct, changes in the independent variable (x-axis) will cause changes in the dependent variable (y-axis).

In other words, y is a function of x, or mathematically, y = f(x).

A graph should have a **title** (usually put above the graph) or **legend** below the graph. These describe what the graph represents.



A **key** shows what each symbol or color on the graph represents.

Each axis of a graph is divided into units represented by evenly spaced tick marks on the axis.

Each axis has a label that tells

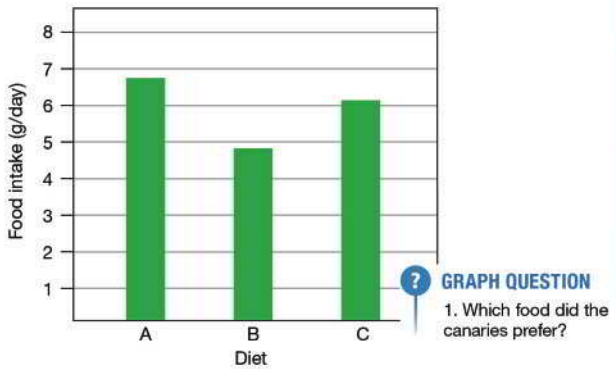
- what variable the axis represents (time, temperature, amount of food consumed)
- the units of the axis (days, degrees Celsius, grams per day).

Most graphs you will encounter in physiology display data either as bars (bar graphs or histograms), as lines (line graphs), or as dots (scatter plots). Some typical types of graphs are shown here.

Here's one approach to reading graphs:

1. Read the title and legend. These are a capsule summary of the graph's contents.
2. Read the axis labels and put them into the sentence
   The effect of [X] on [Y].
3. Look for trends in the graph. Are lines horizontal or do they have a slope? Are bars the same height or different heights?

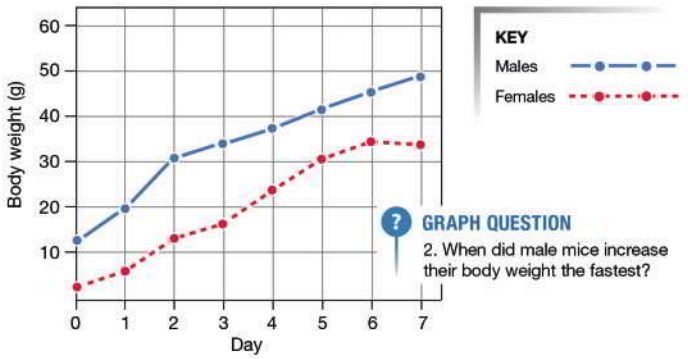
Bar graphs are used when the independent variables are distinct entities. Each bar represents a different variable. The bars are lined up side by side so that they can easily be compared with one another. Scientific bar graphs traditionally have vertical bars.



Canaries were fed one of three diets and their food intake was monitored for three weeks.

Line graphs are used when the independent variable on the x-axis is a continuous phenomenon, such as time, temperature, or weight.

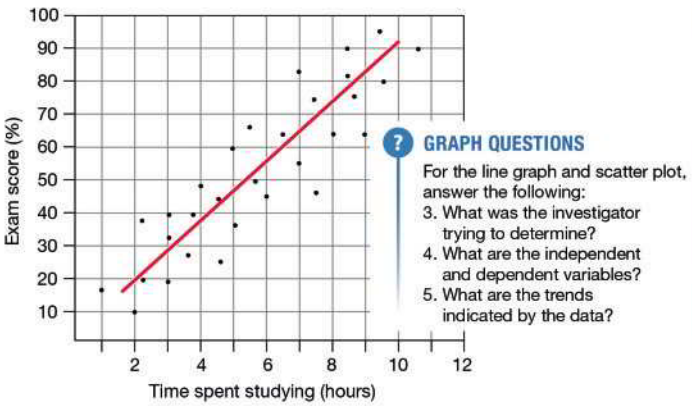
- Each point on the graph represents the average of a set of observations.
- Because the independent variable is a continuous function, the points can be connected with a line (point-to-point connections or a mathematically calculated "best fit" line or curve).
- The slope of the line between two points represents the rate at which the variable changed.
- Connecting the points with lines allows the reader to **interpolate**, or estimate values between the measured values.



Male and female mice were fed a standard diet and weighed daily.

Scatter plots show the relationship between two variables, such as time spent studying for an exam and performance on that exam.

- Usually each point on the plot represents one member of a test population.
- Individual points on a scatter plot are never connected by a line, but a "best fit" line or curve may indicate a trend in the data.



Student scores were directly related to the amount of time they spent studying.

Try It!

Graphing

Students in a physiology laboratory collected heart rate data on one another. In each case, heart rate was measured first for the subject at rest and again after the subject had exercised for 5 minutes using a step test.

Data from the experiment are shown in the table.

Subject	Sex	Age	Resting heart rate (beats/min)	Post exercise heart rate (beats/min)
1	M	20	58	90
2	M	21	62	110
3	F	19	70	111
4	M	20	64	95
5	F	20	85	120
6	F	19	72	98
7	F	21	73	101

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Describe two observations you can make from the data.

(c) Draw one graph that illustrates both findings you described in (b). Label each axis with the correct variable.

(*Hint:* Excel is a simple way to make graphs from data in tables. Excel calls graphs "charts.")

nonsmokers, within 10% of ideal body weight, to participate in a study. . . .” Researchers must take into account the variability inherent in even a select group of humans when doing experiments with human subjects. This variability may affect the researcher’s ability to interpret the significance of data collected on that group.

One way to reduce variability within a test population, whether human or animal, is to do a **crossover study.** In a crossover study, each individual acts both as experimental subject and as control. Thus, the individual’s responses to the treatment can be compared to the same subject's control value. This method is particularly effective when there is wide variability within a population.

For example, in a test of blood pressure medication, investigators might divide subjects into two groups. Group A takes an inactive substance called a **placebo** (from the Latin for “I shall be pleasing”) for the first half of the experiment, then changes to the experimental drug for the second half. Group B starts with the experimental drug, and then changes to the placebo. This scheme enables the researcher to assess the effect of the drug on each individual. In other words, subjects act as their own control. Statistically, the data analysis can use methods that look at the changes within each individual rather than at changes in the collective group data.

Psychological Factors

Another significant variable in human studies is the psychological aspect of administering a treatment. If you give someone a pill and tell the person that it will help alleviate some problem, there is a strong possibility that the pill will have exactly that effect, even if it contains only sugar or an inert substance. This well-documented phenomenon is called the **placebo effect.** Similarly, if you warn people that a drug they are taking may have specific adverse side effects, those people will report a higher incidence of the side effects than a similar group of people who were not warned. This phenomenon is called the **nocebo effect,** from the Latin *nocere,* to do harm. The placebo and nocebo effects show the ability of our minds to alter the physiological functioning of our bodies.

In setting up an experiment with human subjects, we must try to control for the placebo and nocebo effects. The simplest way to do this is with a **blind study,** in which the subjects do not know whether they are receiving the treatment or the placebo. Even this precaution can fail, however, if the researchers assessing the subjects know which type of treatment each subject is receiving. The researchers’ expectations of what the treatment will or will not do may color their measurements or interpretations.

To avoid this outcome, researchers often use **double-blind studies.** A third party, not involved in the experiment, is the only one who knows which group is receiving the experimental treatment and which group is receiving the control treatment. The most sophisticated experimental design for minimizing psychological effects is the **double-blind crossover study.** In this type of study, the control group in the first half of the experiment becomes the experimental group in the second half, and vice versa, but no one involved knows who is taking the active treatment.

Ethical Considerations

Ethical questions arise when humans are used as experimental subjects, particularly when the subjects are people suffering from a disease or other illness. Is it ethical to withhold a new and promising treatment from the control group? A noteworthy example occurred some years ago when researchers were testing the efficacy of a treatment for dissolving blood clots in heart attack victims. The survival rate among the treated patients was so much higher that testing was halted so that members of the control group could also be given the experimental drug.

In contrast, tests on some anticancer agents have shown that the experimental treatments were less effective in stopping the spread of cancer than were the standard treatments used by the controls. Was it ethical to undertreat patients in the experimental group by depriving them of the more effective current medical practice? Most studies now are evaluated continually over the course of the study to minimize the possibility that subjects will be harmed by their participation.

In 2002, a trial on hormone replacement therapy in postmenopausal women was halted early when investigators realized that women taking a pill containing two hormones were developing cardiovascular disease and breast cancer at a higher rate than women on placebo pills. On the other hand, the women receiving hormones also had *lower* rates of colon cancer and bone fractures. The investigators performed a *risk-benefit analysis* and decided that the risks associated with taking the hormones exceeded the potential benefits, so they stopped the study. To learn more about this clinical trial and the pros and cons of hormone replacement therapy, visit MedlinePlus, a website of the U.S. National Library of Medicine.

Human Studies Can Take Many Forms

Almost daily, the newspapers carry articles about clinical trials studying the efficacy of drugs or other medical treatments. Many different aspects of experimental design can affect the validity and applicability of the results of these trials. For example, some trials are carried out for only a limited time on a limited number of people, such as studies conducted for the U.S. Food and Drug Administration’s drug-approval process. In several instances in recent years, drugs approved as a result of such studies have later been withdrawn from the market when extended use of the drug by larger populations uncovered adverse side effects, including deaths.

Longitudinal studies are designed to be carried out for a long period of time. One of the most famous longitudinal studies is the Framingham Heart Study, started in 1948 and still ongoing. Framingham is a **prospective study** {*prospectus*, outlook, looking forward} that recruited healthy people and has been following them for years to identify factors that contribute to the development of cardiovascular disease. This study has already made important contributions to healthcare, and it continues today with the adult children and grandchildren of the original participants.

Additional study designs you may encounter in the literature include cross-sectional and retrospective studies. **Cross-sectional studies** survey a population for the prevalence of a disease or condition. Data from cross-sectional studies identify trends to be

investigated further, such as whether age group or socioeconomic status is associated with a higher risk of developing the condition being surveyed. **Retrospective studies** {*retro*, backward + *spectare*, to look} match groups of people who all have a particular disease to a similar but healthy control group. The goal of these studies is to determine whether development of the disease can be associated with a particular variable.

Often, the results of one or more published studies do not agree with the conclusions of other published studies. In some cases, the reason for the disagreement turns out to be a limitation of the experimental design, such as a small number of subjects who may not be representative of larger populations. In other cases, the disagreement may be due to small but potentially significant differences in the experimental designs of the different studies.

One way scientists attempt to resolve contradictory results is to perform a **meta-analysis** of the data {*meta-*, at a higher level}. A meta-analysis combines all the data from a group of similar studies and uses sophisticated statistical techniques to extract significant trends or findings from the combined data. For example, multiple studies have been done to assess whether glucosamine and chondroitin, two dietary supplements, can improve degenerative joint disease. However, the individual studies had small numbers of subjects (<50) and used different dosing regimens. A meta-analysis using statistical methods is one way to compare the results from these studies.[7]

The difficulty of using human subjects in experiments is one of the reasons scientists use animals to develop many of our scientific models. Since the 1970s, physiological research has increasingly augmented animal experimentation with techniques developed by cellular biologists and molecular geneticists. As we have come to understand the fundamentals of chemical signaling and communication in the body, we have unlocked the mysteries of many processes. In doing so, we also have come closer to being able to treat many diseases by correcting their cause rather than simply treating their symptoms.

More and more, medicine is turning to therapies based on interventions at the molecular level. A classic example is the treatment of cystic fibrosis (CF), an inherited disease in which the mucus of the lungs and digestive tract is unusually thick. For many years, patients with this condition had few treatment options, and most died at a young age. However, basic research into the mechanisms by which salt and water move across cell membranes provided clues to the underlying cause of cystic fibrosis: a defective protein in the membrane of certain cells. The newest treatments for CF now improve the function of the defective protein, and life expectancy of people with CF is close to that of the general population. Without the basic research into how cells and tissues carry out their usual tasks, however, this treatment would never have been developed. Some of the most exciting therapies coming to medicine are interventions targeting gene mutations that result in disease. In late 2023, the U.S. Food and Drug Administration approved two new treatments correcting the gene mutation that causes the abnormal hemoglobin associated with sickle cell disease.

As you read this book and learn what we know about how the human body works, keep in mind that many of the ideas presented are not hard facts – they simply describe models that represent our current understanding and therefore are subject to change. As we learned during the COVID-19 pandemic, scientific knowledge is constantly and rapidly changing. There are still many questions in physiology waiting for investigators to find the answers.

Running Problem 1.6 Conclusion: What to Believe?

After reading a few of the review articles Hiro found while searching, he called Jennifer back. “Hey! Those were great suggestions, but I just need something simple. Is there some place that a nonmedical person should go to learn about probiotics?”

“I send my friends to MedlinePlus (www.medlineplus.gov) when they need basic information,” Jennifer answered. Hiro repeated his search once more in MedlinePlus and found himself back where he had started, with links to the probiotics articles on the NCCIH website. “All these sites are saying we don’t have enough information yet to know whether probiotics are helpful,” Hiro decided.

Most people today begin their quest for information by searching the internet. Be cautious! Anyone can make a website or video and publish it on the web. There is no screening process comparable to peer review in scientific journals, and the reader of a website must decide how valid the information on the site is. Websites published by recognized universities and nonprofit organizations are likely to have good information, but you should view an article about probiotics on a health food store web page with a skeptical eye unless the article cites published peer-reviewed research.

The best websites for health information are sponsored by organizations that are part of the scientific and healthcare communities, such as the National Institutes of Health (NIH), nonprofit groups dedicated to supporting research on a particular disease (e.g., The American Diabetes Association, diabetes.org), or clinics and universities where scientists and physicians are actively investigating causes and treatments for diseases. Treat commercial websites that end in **.com* with extra caution.

Check your answers to the questions against the information in the table below.

Question		Answer and Commentary
Q1:	*Rank these 10 results from most to likely to have good information, and explain how you chose your rankings.*	1. Best: The NIH websites that are written by scientists. *www.nccih.nih.gov, www.ods.od.nih.gov* 2. *mayoclinic.org* and *health.harvard.edu* are vetted by health professionals at medical schools 3. *webmd.com* and *healthline.com* are commercial sites with the potential for bias in favor of advertisers. 4. *en.wikipedia.org*: Wikipedia is a crowd-sourced website and sometimes contains information that is not accurate. 5. *seed.com, amazon.com,* and *ritual.com* are all commercial websites whose goal is to sell products.
Q2:	*What is the mission of NCCIH?*	The ABOUT page says the mission of NCCIH is to provide authoritative, science-based information on the use, safety, and efficacy of products used in complementary and integrative healthcare practices.
Q3:	*What does NCCIH say about whether probiotics are helpful and about whether they are safe?*	The "What you need to know" factsheet[8] on probiotics includes a warning about the risks of giving probiotics to premature infants. The section on effectiveness of probiotics says that although a lot is known, there are still unanswered questions about how probiotics work and when they might be unsafe.
Q4:	*Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from his simple Google search.*	The Google Scholar search returns over 860,000 results and the PubMed search yields more than 46,000 results.
Q5:	*Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*	For the last 5 years, the Google Scholar search returns more than 32,000 results and the PubMed search has more than 23,000 results.
Q6:	*On the Google Scholar and PubMed pages with results from the last 5 years, select the option for reviews. Now how many results are there?*	For reviews in the last 5 years, the Google Scholar search has more than 21,000 results and the PubMed search has about 5,000 results.
Q7:	*Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*	The responses of an AI program might differ slightly each time a question is asked, but in January 2024, ChatGPT returned the following answer: *As of my last knowledge update in January 2022, research on probiotics was ongoing, and findings were mixed regarding their overall benefits.* The answer continued to point out that the topic is complex and that there might be more recent information based on better evidence.

Citing Resources

Whenever you use someone else's material, even if it is just for a class project, you should cite your source. If you put a photo from the web into a PowerPoint slide, be sure to include the URL. If you paraphrase something written, acknowledge where you learned the information. Copying or paraphrasing material from another source without acknowledging that source is academic dishonesty.

There are many different citation format styles. PubMed allows you to choose between AMA (American Medical Association), APA (American Psychological Association), MLA (Modern Language Association), and NLM (National Library of Medicine) styles when downloading references. Two useful websites for learning about citation styles are *Scientific Style and Format*[9], published by the Council of Science Editors, and Purdue University's Online Writing Lab, Purdue OWL (owl.purdue.edu).

Citing Web Sources

Unlike formally published resources like scientific journals, web pages are not permanent and frequently disappear or move. Here is one suggested format for citing information from a website:

Author/Editor (if known). Revision or copyright date (if available). Title of web page [Publication medium]. Publisher of webpage. *URL* [Date accessed].

Example:

Patton G (editor). 2005. Biological Journals and Abbreviations. [Online]. National Cancer Institute. *http://home.ncifcrf.gov/research/bja* [accessed April 10, 2005].

Citing Publications

Citation formats for papers in research journals vary but will usually include the following elements (with the punctuation shown):

Author(s). Article title. *Journal Name* volume (issue): inclusive pages, year of publication. DOI.

Example:

Echevarria M, Ilundain AA. Aquaporins. *J Physiol Biochem* 54(2): 107–118, 1998.

Many articles now have a unique DOI (digital object identifier) number. These are alphanumeric codes that provide a permanent link to the article on the Internet, so that even if a website changes names, you will still be able to find the article.

Helpful Hints

- If you access a published journal on the web, you should give the print citation and DOI, not the URL of the website.

- Journal names are abbreviated using standard abbreviations that you can look up online[10]. One-word titles, such as *Science,* are never abbreviated. For example, the *American Journal of Physiology* is abbreviated as *Am J Physiol*.
- Journals group their publications into volumes that correspond to a certain period of time (a year, six months, etc.). The first publication of a given volume is designated issue 1, the second is issue 2, and so on. In the citation *J Physiol Biochem* 54(2): 107–118, 1998, you know that this was volume 54, issue 2.
- Word-for-word quotations placed within quotation marks are rarely used in scientific writing.
- When paraphrasing in written work, acknowledge the source this way:

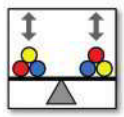
Some rare forms of epilepsy are known to be caused by mutations in ion channels (Mulley *et al*., 2003).

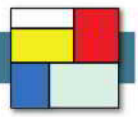
When a paper has three or more authors, we usually use the abbreviation *et al*.—from the Latin *et alii*, meaning "and others"—to save space in the body of the text. All authors' names are given in the full citation, which is usually included within a References section at the end of the paper.

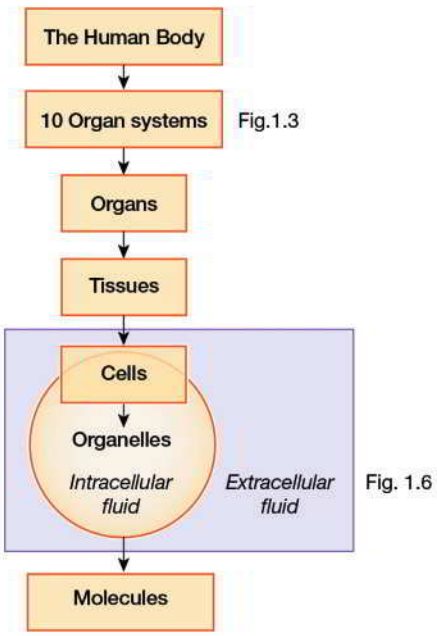
Chapter Summary

Chapter 1 has introduced you to the physiology you will be learning about as you continue through this book. The eight core concepts discussed here and in the other chapters in Unit 1 will provide you with a solid foundation for your studies.

Core Concepts in Physiology

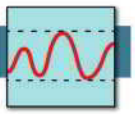
Core Concept	Structure-function	Molecular interactions	Compartmentation	Energy	Gradients	Communication	Homeostasis	Mass balance
Icon								

Levels of Organization 



Homeostasis

Fig. 1.5

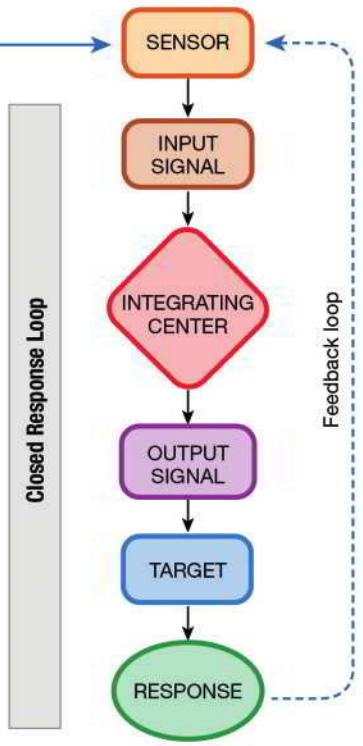


Maintenance of a relatively stable internal environment depends on

Table 1.1

10 Regulated Variables

- Some reflexes are not for homeostasis. Fig. 1.14
- Setpoints that initiate a response loop can vary. Fig. 1.15
- Negative feedback loops help maintain homeostasis. Fig. 1.11
- Positive feedback is not homeostatic. Fig. 1.13
- Feedforward reflexes anticipate a change.



Mass Balance

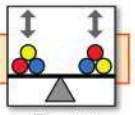
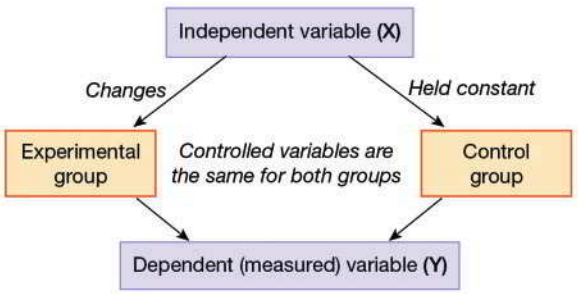


Fig. 1.7

- To maintain a steady state, input must equal output.
- Steady state is not the same as equilibrium.
- A disequilibrium can exist in a steady state. Fig. 1.8

The Science of Physiology

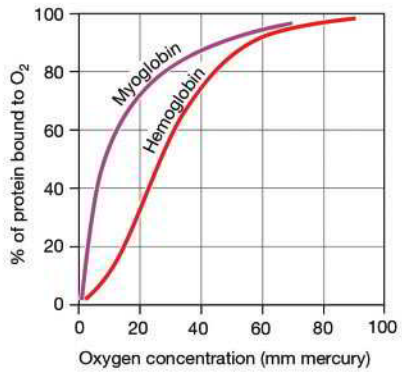
Scientific Experiments



Graphical display of data

Fig. 1.16

The effect of **X** on **Y**



Human Experiments

Complex because of

- Variability among individuals
  - What is "normal"?
- Psychological factors
  - Placebo and nocebo effects
- Ethical considerations
  - Risk-benefit analysis
  - Side effects
  - Undertreating

Types of Studies

- Blind and double-blind
- Crossover studies
- Prospective and retrospective
- Cross-sectional

Links to Resources

[1]DR Richardson. A survey of students' notions of body function as teleologic or mechanistic. *Advan Physiol Educ* 258: 8–10, Jun 1990. https://doi.org/10.1152/advances.1990.258.6.S8

[2]SR Smith et al. Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: a 6-wk translational research study. *Am J Physiol Endocrinol Metab* 293: E620–E627, 2007. https://doi.org/10.1152/ajpendo.00217.2007

[3]*Scientific Foundations for Future Physicians*. Howard Hughes Medical Institute (HHMI) and the Association of American Medical Colleges (AAMC), 2009. https://store.aamc.org/scientific-foundations-for-future-physicians-pdf.html

[4]*Vision and Change: A Call to Action*. National Science Foundation (NSF) and American Association for the Advancement of Science (AAAS). 2011.

[5]C Bernard. *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* (Vol. 1, p. 113), Paris: J.-B. Baillière, 1885. https://www.biodiversitylibrary.org/item/97313#page/151/mode/1up

[6]WB Cannon. Organization for physiological homeostasis. *Physiol Rev* 9: 399–443, 1929. nvc https://doi.org/10.1152/physrev.1929.9.3.399

[7]S Wandel et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *Br Med J* 341: c4675–c4676, 2010. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941572/

[8]*What you need to know* factsheet https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know#

[9]Scientific Style and Format https://www.scientificstyleandformat.org/Welcome.html

[10]https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/

[11]JB Moseley et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *The N Engl J Med* 347: 81–88, 2002. https://doi.org/10.1056/NEJMoa013259

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. Define physiology. Describe the relationship between physiology and anatomy.
2. Name the different levels of organization in the biosphere.
3. Name the 10 systems of the body and give their major function(s).
4. What does "Physiology is an integrative science" mean?
5. Define homeostasis. Name some regulated variables that are maintained through homeostasis.
6. Name eight core concepts in physiology.
7. Put the following parts of a reflex in the correct order for a physiological response loop: input signal, integrating center, output signal, response, sensor, stimulus, target.
8. The name for daily fluctuations of body functions such as blood pressure, temperature, and metabolic processes is a(n) _____.

Level Two Reviewing Concepts

9. **Mapping exercise:** Make a large map showing the organization of the human body. Show all levels of organization in the body (see Fig. 1.2) and all 10 organ systems. Try to include functions of all components on the map and remember that some structures may share functions. (*Hint:* Start with the human body as the most important term. You may also draw the outline of a body and make your map using it as the basis.)
10. Distinguish between the items in each group of terms.
    (a) tissues and organs
    (b) x-axis and y-axis on a graph
    (c) dependent and independent variables
    (d) teleological and mechanistic approaches
    (e) the internal and external environments for a human
    (f) blind, double-blind, and crossover studies
    (g) the target and the sensor in a control system
11. Name as many organs or body structures that connect directly with the external environment as you can.
12. Which organ systems are responsible for coordinating body function? For protecting the body from outside invaders? Which systems exchange material with the external environment, and what do they exchange?
13. Explain the differences among positive feedback, negative feedback, and feedforward mechanisms. Under what circumstances would each be advantageous?

Level Three Problem Solving

14. A group of biology majors went to a mall and asked passersby, "Why does blood flow?" These are some of the answers they received. Which answers are teleological and

which are mechanistic? (Not all answers are correct, but they can still be classified.)

(a) Because of gravity

(b) To bring oxygen and food to the cells

(c) Because if it didn't flow, we would die

(d) Because of the pumping action of the heart

15. Although dehydration is one of the most serious physiological obstacles that land animals must overcome, there are others. Think of as many as you can, and think of various strategies that different terrestrial animals have to overcome these obstacles. (*Hint:* Think of humans, insects, and amphibians; also think of as many different terrestrial habitats as you can.)

Level Four Quantitative Problems

16. A group of students wanted to see what effect a diet deficient in vitamin D would have on the growth of baby guppies. They fed the guppies a diet low in vitamin D and measured fish body length every third day for three weeks. Their data looked like this:

Day	0	3	6	9	12	15	18	21
Average body length (mm)	6	7	9	12	14	16	18	21

(a) What was the dependent variable and what was the independent variable in this experiment?

(b) What was the control in this experiment?

(c) Make a fully labeled graph with a legend, using the data in the table.

(d) During what time period was growth slowest? Most rapid? (Use your graph to answer this question.)

17. You performed an experiment in which you measured the volumes of nine slices of potato, then soaked the slices in solutions of different salinities for 30 minutes. At the end of 30 minutes, you again measured the volumes of the nine slices. The changes you found were:

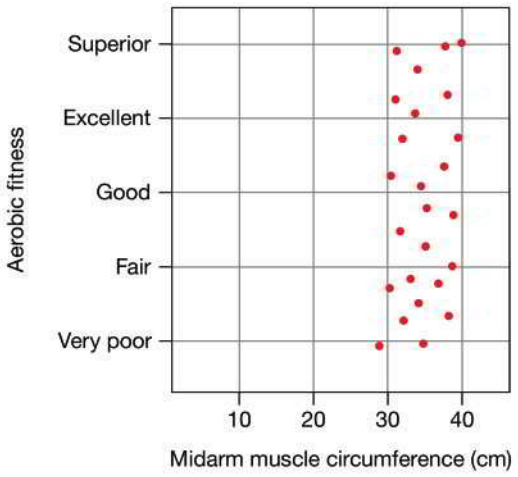
Percent Change in Volume after 30 Minutes			
Solution	**Sample 1**	**Sample 2**	**Sample 3**
Distilled water	10%	8%	11%
1% salt (NaCl)	0%	−0.5%	1%
9% salt (NaCl)	−8%	−12%	−11%

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Can you tell from the information given whether or not there was a control in this experiment? If there was a control, what was it?

(c) Graph the results of the experiment using the most appropriate type of graph.

18. At the end of the semester, researchers measured an intermediate-level class of 25 male weight lifters for aerobic fitness and midarm muscle circumference. The relationship between those two variables is graphed here.



(a) What kind of graph is this?

(b) What question were the investigators asking?

(c) In one sentence, summarize the relationship between the two variables plotted on the graph.

19. Answer the questions after the following article summary.

A study[11] was carried out on human volunteers to see whether two procedures performed during arthroscopic surgery {*arthro-*, joint + *scopium*, to look at} are effective in relieving knee pain associated with osteoarthritis, or degenerative joint disease {*osteon*, bone + *arthro* −, joint + *−itis*, inflammation}. The volunteers were up to 75 years old and were recruited from a Veterans Affairs Medical Center. They were 93% male and 60% white. One-third of the subjects had placebo operations—that is, they were given anesthesia and their knees were cut open, but the remainder of the treatment procedure was not done. The other two-thirds of the subjects had one of the two treatment procedures performed. Subjects were followed for two years. They answered questions about their knee pain and function and were given an objective walking and stair-climbing test. At the end of the study, the results showed no significant difference in knee function or perception of pain between subjects getting one of the standard treatments and those getting the placebo operation.

(a) Do you think it is ethical to perform placebo surgeries on humans who are suffering from a painful condition, even if the subjects are informed that they might receive the placebo operation and not the standard treatment?

(b) Give two possible explanations for the decreased pain reported by the placebo operation subjects.

(c) Analyze and critique the experimental design of this study. Are the results of this study applicable to everyone with knee pain?

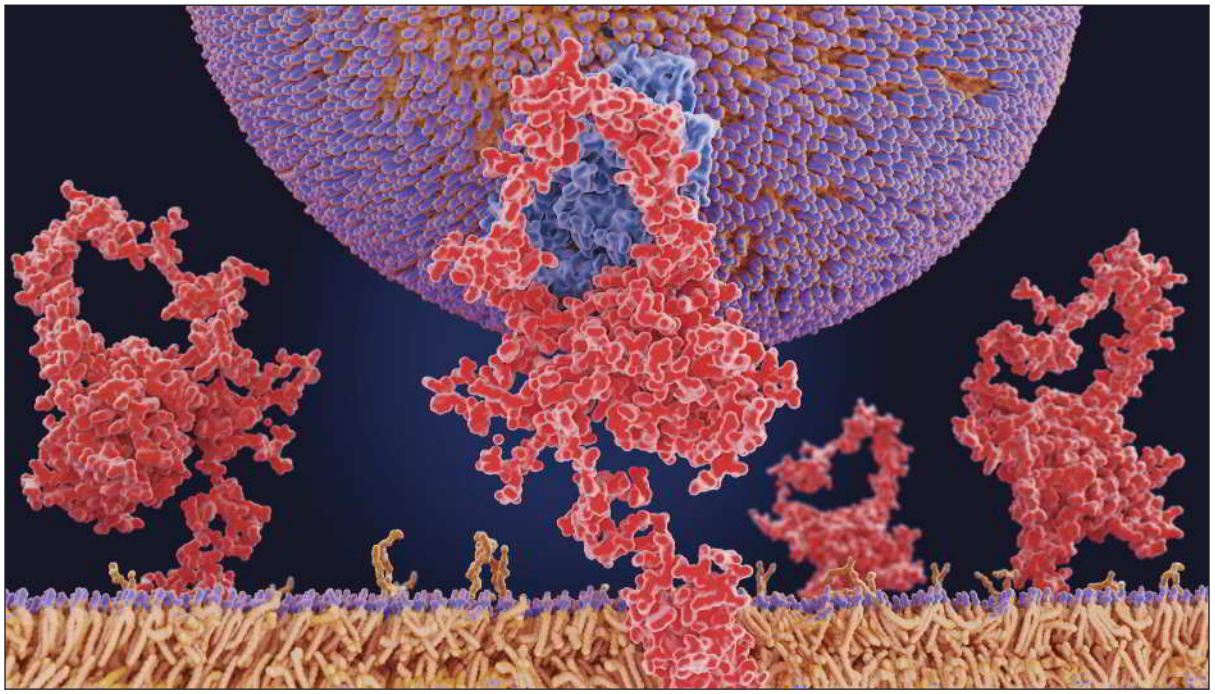
(d) Was this study a blind, double-blind, or double-blind crossover design?

(e) Why do you think the investigators felt it was necessary to include a placebo operation in this study?

Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

2

Molecular Interactions



LDL particle binding to the LDL receptor

Science regards man as an aggregation of atoms temporarily united by a mysterious force called the life-principle.

H. P. Blavatsky, 1877. In Isis Unveiled: A Master-Key to the Mysteries of Ancient and Modern Science and Theology, *Vol. I: Science*

Chapter 2 focuses on the core concept of Molecular Interactions, going from subatomic particles up to complex macromolecules that are responsible for many aspects of physiological function.

The first two sections of the chapter may be a review, depending on your background. Use the REVIEW figures to check your understanding of chemistry and biochemistry.

Section 2.3 focuses on protein binding, one of the key molecular interactions that govern physiological processes. The principles of protein binding apply to membrane transporters and signal receptors as well as to enzymes, so learning the basic patterns here is important.

Molecular Interactions

Learning Outcomes

2.1 Molecules and Bonds

- **LO 2.1.1** Compare and contrast the composition, structure, and functions of the four major groups of biomolecules.
- **LO 2.1.2** Describe four important biological roles of electrons.
- **LO 2.1.3** Describe and compare the different types of covalent and noncovalent bonds.

2.2 Noncovalent Interactions

- **LO 2.2.1** Contrast the structure and solubility of polar and nonpolar molecules.
- **LO 2.2.2** Describe the covalent and noncovalent interactions that contribute to molecular shape, and explain how molecular shape is related to molecular function.
- **LO 2.2.3** Define pH in words and mathematically, and explain the differences between acids, bases, and buffers.

2.3 Protein Interactions

- **LO 2.3.1** List nine important functions of proteins in the body.
- **LO 2.3.2** Explain the meanings of affinity, specificity, saturation, and competition in protein-ligand binding.
- **LO 2.3.3** Explain the different methods by which modulators alter protein binding or protein activity.

Nearly 100 years ago two scientists, Aleksander Oparin in Russia and John Haldane in England, speculated on how life might have arisen on a primitive Earth whose atmosphere consisted mainly of hydrogen, water, ammonia, and methane. Their theories were put to the test in 1953, when a 23-year-old scientist named Stanley Miller combined these molecules in a closed flask and boiled them for a week while periodically discharging flashes of electricity through them, simulating lightning. At the end of his test, Miller found amino acids had formed in the flask. With this simple experiment, he had shown that it was possible to create organic molecules, usually associated with living creatures, from nonliving inorganic precursors.

Miller's experiments were an early attempt to solve one of the biggest mysteries of biology: How did a collection of chemicals first acquire the complex properties that we associate with living creatures? We still do not have an answer to this question. Numerous scientific theories have been proposed, ranging from life arriving by meteor from outer space to molecules forming in deep ocean hydrothermal vents. No matter what their origin, the molecules associated with living organisms have the ability to organize themselves into compartments, replicate themselves, and act as *catalysts* to speed up reactions that would otherwise proceed too slowly to be useful.

The human body is far removed from the earliest life forms, but we are still a collection of chemicals—dilute solutions of dissolved and suspended molecules enclosed in compartments with lipid-protein walls. Strong links between atoms, known as **chemical bonds**, store and transfer energy to support life functions. Weaker interactions between and within molecules create distinctive molecular shapes and allow biological molecules to interact reversibly with each other.

This chapter introduces some of the fundamental principles of molecular interactions that you will encounter repeatedly in your study of physiology. The human body is more than 50% water, and because most of its molecules are dissolved in this water, we will review the properties of aqueous solutions. If you would like to refresh your understanding of the key features of **atoms**, chemical bonds, and biomolecules, you will find a series of one- and two-page review features that encapsulate biochemistry as it pertains to physiology. You can test your knowledge of basic chemistry and biochemistry with a special review quiz at the end of the chapter.

Running Problem 2.1: Chromium Supplements

"Lose weight while gaining muscle," the ads promise. "Prevent heart disease." "Stabilize blood sugar." What is this miracle substance? It's chromium picolinate, a nutritional supplement being marketed to consumers looking for a quick fix. Does it work, though, and is it safe? Some athletes, like Malik—the star running back on the college football team—swear by it. Malik takes 500 micrograms of chromium picolinate daily. Many researchers, however, are skeptical and feel that the necessity for and safety of chromium supplements have not been established.

2.1 Molecules and Bonds

There are more than 100 known elements on Earth, but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are considered *major* **essential elements**. Some additional *minor essential elements* (trace elements) are required in minute amounts, but there is no universal agreement on which trace elements are essential for cell function in humans. The **periodic table** shows the major and commonly accepted minor essential elements.

Most Biomolecules Contain Carbon, Hydrogen, and Oxygen

Molecules that contain carbon are known as **organic molecules,** because it was once thought that they all existed in or were derived from plants and animals. Organic molecules associated with living organisms are also called **biomolecules.** There are four major groups of biomolecules: carbohydrates, lipids, proteins, and nucleotides.

The body uses carbohydrates, lipids, and proteins for energy and as the building blocks of cellular components. The fourth group, the **nucleotides**, includes DNA, **RNA**, ATP, and cyclic AMP. DNA and RNA are the structural components of genetic

material. **ATP** (adenosine triphosphate) and related molecules carry energy, while **cyclic AMP** (adenosine monophosphate; cAMP) and related compounds regulate metabolism.

Each group of biomolecules has a characteristic composition and molecular structure. **Lipids** are mostly carbon and hydrogen (**FIG. 2.1**). **Carbohydrates** are primarily carbon, hydrogen, and oxygen, in the ratio CH_2O (**FIG. 2.2**). **Proteins** and nucleotides contain nitrogen in addition to carbon, hydrogen, and oxygen (**FIGS. 2.3** and **2.4**). Two **amino acids**, the building blocks of proteins, also contain sulfur.

Fig. 2.1 REVIEW Biochemistry of Lipids

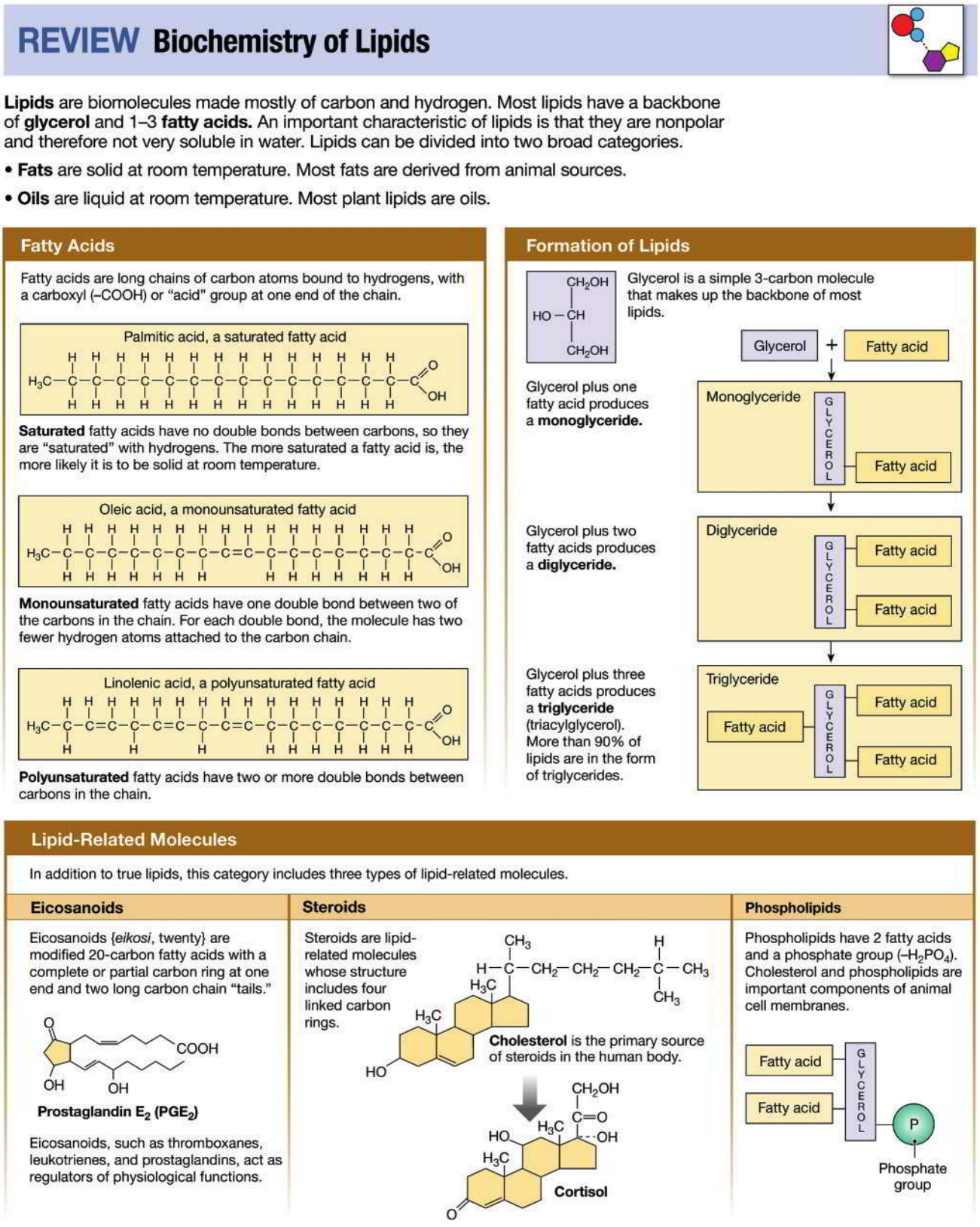


Fig. 2.2 REVIEW Biochemistry of Carbohydrates

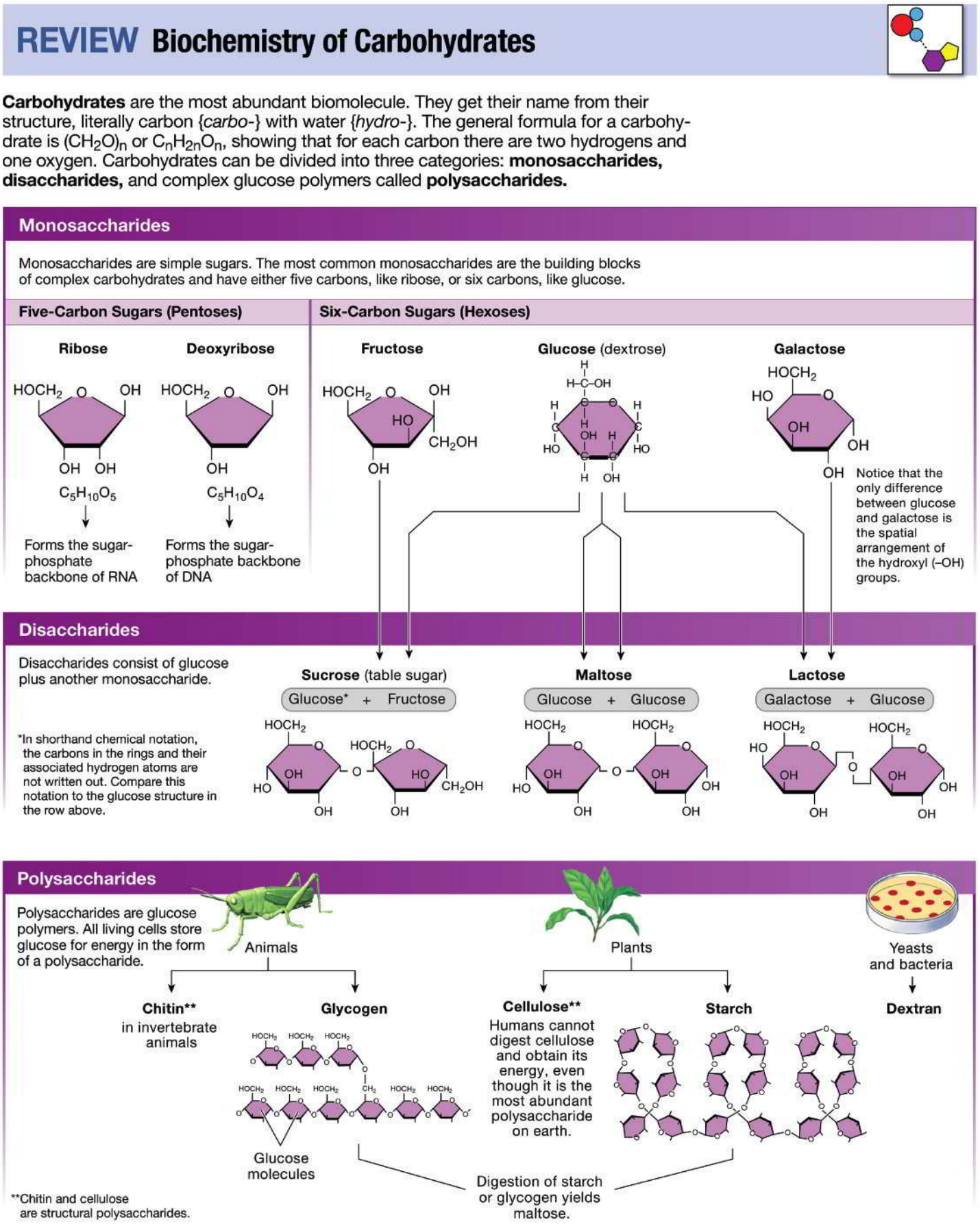


Fig. 2.3 REVIEW Biochemistry of Proteins

REVIEW Biochemistry of Proteins

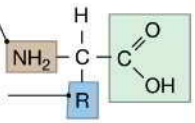
Proteins are polymers of smaller building-block molecules called **amino acids.**

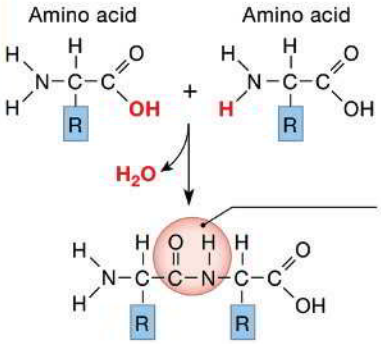
Amino Acids

All amino acids have a carboxyl group (–COOH), an amino group ($–NH_2$), and a hydrogen attached to the same carbon. The fourth bond of the carbon attaches to a variable "R" group.

The nitrogen (N) in the amino group makes proteins our major dietary source of nitrogen.

The R groups differ in their size, shape, and ability to form hydrogen bonds or ions. Because of the different R groups, each amino acid reacts with other molecules in a unique way.





In a **peptide bond,** the amino group of one amino acid joins the carboxyl group of the other, with the loss of water.

Amino Acids in Natural Proteins

Twenty different amino acids commonly occur in natural proteins. The human body can synthesize most of them, but at different stages of life some amino acids must be obtained from diet and are therefore considered *essential amino acids*. Some physiologically important amino acids are listed below.

Amino Acid	Three-Letter Abbreviation	One-Letter Symbol
Arginine	Arg	R
Aspartic acid (aspartate)*	Asp	D
Cysteine	Cys	C
Glutamic acid (glutamate)*	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Tryptophan	Trp	W
Tyrosine	Tyr	Y

*The suffix -ate indicates the anion form of the acid.

Note:

A few amino acids do not occur in proteins but have important physiological functions.

- *Homocysteine*: a sulfur-containing amino acid that in excess is associated with heart disease
- *γ-amino butyric acid* (gamma-amino butyric acid) or *GABA*: a chemical made by nerve cells
- *Creatine*: a molecule that stores energy when it binds to a phosphate group

Structure of Peptides and Proteins

Primary Structure

The 20 protein-forming amino acids assemble into polymers called peptides. The sequence of amino acids in a peptide chain is called the **primary structure.** Just as the 26 letters of our alphabet combine to create different words, the 20 amino acids can create an almost infinite number of combinations.

Peptides range in length from two to two million amino acids:

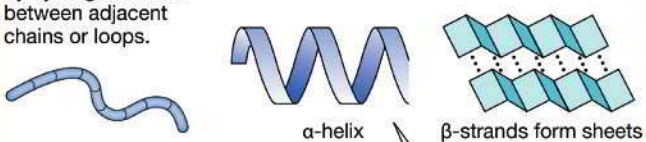
- **Oligopeptide** {*oligo-*, few}: 2–9 amino acids
- **Polypeptide:** 10–100 amino acids
- **Proteins:** >100 amino acids

Sequence of amino acids

Secondary Structure

Secondary structure is created primarily by hydrogen bonds between adjacent chains or loops.

Covalent bond angles between amino acids determine secondary structure.



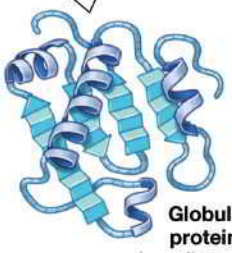
α-helix

β-strands form sheets

Tertiary Structure

Tertiary structure is the protein's three-dimensional shape.

Fibrous proteins
(usually insoluble)
Collagen

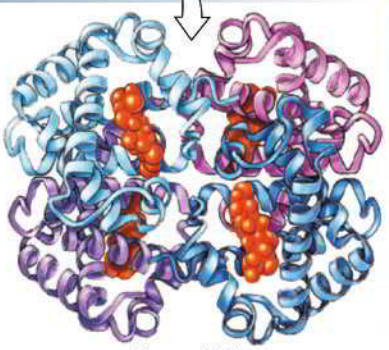


Globular proteins
(usually soluble)

Tertiary structures can be a mix of secondary structures. Beta-sheets are shown as flat ribbon arrows and alpha helices are shown as ribbon coils.

Quaternary Structure

Multiple subunits combine with noncovalent bonds. Hemoglobin molecules are made from four globular protein subunits.



Hemoglobin

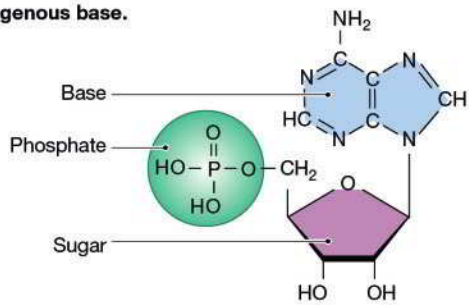
Fig. 2.4 REVIEW Nucleotides and Nucleic Acids

REVIEW Nucleotides and Nucleic Acids

Nucleotides are biomolecules that play an important role in energy and information transfer. Single nucleotides include the energy-transferring compounds **ATP** (adenosine triphosphate) and **ADP** (adenosine diphosphate), as well as **cyclic AMP,** a molecule important in the transfer of signals between cells. **Nucleic acids** (or nucleotide polymers) such as **RNA** and **DNA** store and transmit genetic information.

Nucleotide

A nucleotide consists of (1) one or more phosphate groups, (2) a 5-carbon sugar, and (3) a carbon-nitrogen ring structure called a **nitrogenous base.**



consists of

Nitrogenous Bases

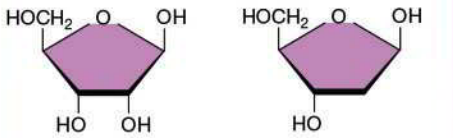
Purines have a double ring structure.

Pyrimidines have a single ring.

Adenine (A) | Guanine (G) | Cytosine (C) | Thymine (T) | Uracil (U)

Five-Carbon Sugars

Ribose | **Deoxyribose** {*de-*, without; *oxy-*, oxygen}



Phosphate

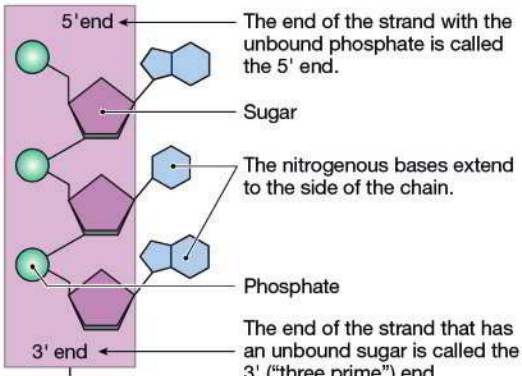
Adenine + Ribose → Adenosine

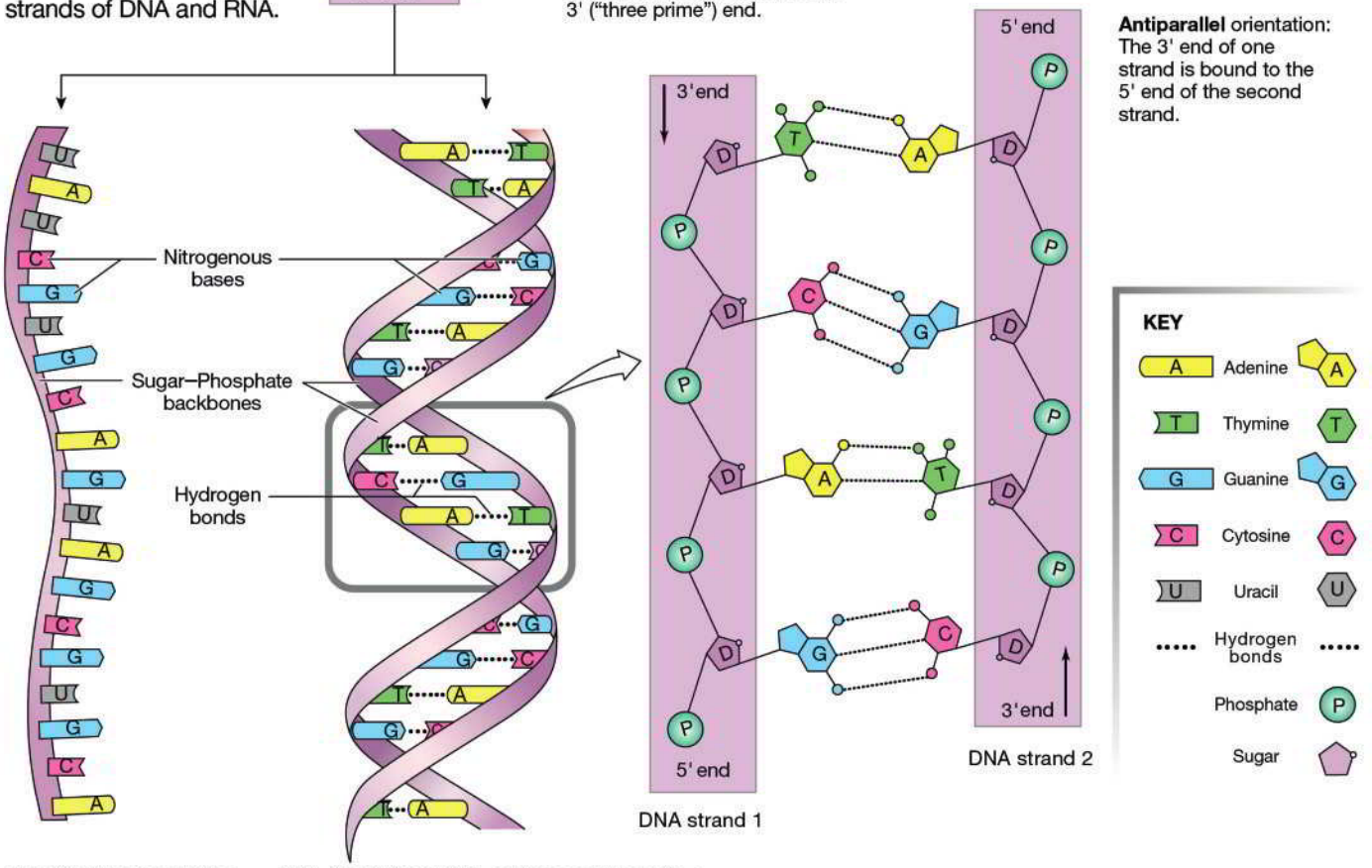
Single Nucleotide Molecules

Single nucleotide molecules have two critical functions in the human body: (1) Capture and transfer energy in high-energy electrons or phosphate bonds, and (2) aid in cell-to-cell communication.

Nucleotide	*consists of*	Base	+	Sugar	+	Phosphate Groups	+	Other Component	Function
ATP	=	Adenine	+	Ribose	+	3 phosphate groups			Energy capture and transfer
ADP	=	Adenine	+	Ribose	+	2 phosphate groups			
NAD	=	Adenine	+	2 Ribose	+	2 phosphate groups	+	Nicotinamide	
FAD	=	Adenine	+	Ribose	+	2 phosphate groups	+	Riboflavin	
cAMP	=	Adenine	+	Ribose	+	1 phosphate group			Cell-to-cell communication

Nucleic acids (nucleotide polymers) function in information storage and transmission. The sugar of one nucleotide links to the phosphate of the next, creating a chain of alternating sugar–phosphate groups. The sugar–phosphate chains, or backbone, are the same for every nucleic acid molecule. Nucleotide chains form strands of DNA and RNA.





RNA (ribonucleic acid) is a single-strand nucleic acid with ribose as the sugar in the backbone, and four bases—adenine, guanine, cytosine, and uracil.

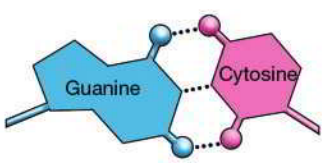
DNA (deoxyribonucleic acid) is a double helix, a three-dimensional structure that forms when two DNA strands link through hydrogen bonds between complementary base pairs. Deoxyribose is the sugar in the backbone, and the four bases are adenine, guanine, cytosine, and thymine.

Base-Pairing

Bases on one strand form hydrogen bonds with bases on the adjoining strand. This bonding follows very specific rules:

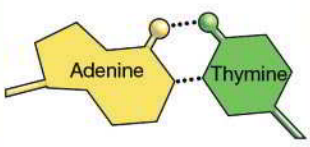
- Because purines are larger than pyrimidines, space limitations always pair a purine with a pyrimidine.
- Guanine (G) forms three hydrogen bonds with cytosine (C).
- Adenine (A) forms two hydrogen bonds with thymine (T) or uracil (U).

Guanine-Cytosine Base Pair



More energy is required to break the triple hydrogen bonds of G≡C than the double bonds of A=T or A=U.

Adenine-Thymine Base Pair



Not all biomolecules are pure protein, pure carbohydrate, or pure lipid, however. **Conjugated proteins** are protein molecules combined with another kind of biomolecule. For example, proteins combine with lipids to form **lipoproteins.** Lipoproteins are found in cell membranes and in the blood, where they act as carriers for less soluble molecules, such as cholesterol.

Glycosylated molecules are molecules to which a carbohydrate has been attached. Proteins combined with carbohydrates form **glycoproteins.** Lipids bound to carbohydrates become **glycolipids.** Glycoproteins and glycolipids, like lipoproteins, are important components of cell membranes [Fig. 3.2].

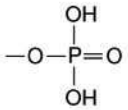
Many biomolecules are **polymers,** large molecules made up of repeating units {*poly-*, many + *-mer*, a part}. For example, **glycogen** and **starch** are both **glucose** polymers. They differ in the way the glucose molecules attach to each other, as you can see at the bottom of Figure 2.2.

Some combinations of elements, known as **functional groups,** occur repeatedly in biological molecules. The atoms in a functional group tend to move from molecule to molecule as a single unit. For example, *hydroxyl groups*, –OH, common in many biological molecules, are added and removed as a group rather than as single hydrogen or oxygen atoms. **Amino groups**, $-NH_2$, are the signature of amino acids. The phosphate group, $-H_2PO_4$, plays a role in many important cell processes, such as energy transfer and protein regulation. Addition of a phosphate group is called *phosphorylation*; removal of a phosphate group is **dephosphorylation**.

The most common functional groups are listed in **TABLE 2.1**.

Table 2.1 Common Functional Groups

Notice that oxygen, with two electrons to share, sometimes forms a double bond with another atom.

	Shorthand	Bond Structure
Amino	$-NH_2$	
Carboxyl (acid)	—COOH	
Hydroxyl	—OH	—O—H
Phosphate	$-H_2PO_4$	

Concept Check

1. List three major essential elements found in the human body.
2. What is the general formula of a carbohydrate?
3. What is the chemical formula of an amino group? Of a carboxyl group?

Electrons Have Four Important Biological Roles

An atom of any element has a unique combination of protons and electrons that determines the element's properties (**FIG. 2.5**). We are particularly interested in the electrons because they play four important roles in physiology:

1. **Covalent bonds.** The arrangement of electrons in the outer energy level (*shell*) of an atom determines an element's ability to bind with other elements. Electrons shared between atoms form strong covalent bonds that bind atoms together to form molecules
2. **Ions.** If an atom or molecule gains or loses one or more electrons, it acquires an electrical charge and becomes an **ion.** Ions are the basis for electrical signaling in the body. Ions may be single atoms, like the sodium ion Na^+ and chloride ion Cl^-. Other ions are combinations of atoms, such as the bicarbonate ion HCO_3^-. Important ions of the body are listed in **TABLE 2.2**.
3. **High-energy electrons.** The electrons in certain atoms can capture energy from their environment and transfer it to other atoms. This allows the energy to be used for synthesis, movement, and other life processes. The released energy may also be emitted as radiation. For example, bioluminescence in fireflies is visible light emitted by high-energy electrons returning to their normal low-energy state.
4. **Free radicals.** Free radicals are unstable molecules with an unpaired electron. They are thought to contribute to aging and to the development of certain diseases, such as some cancers. Free radicals and high-energy electrons are discussed in Chapter 23.

The role of electrons in molecular bond formation is discussed in the next section. There are four common bond types, two strong and two weak. Covalent and ionic bonds are strong bonds because they require significant amounts of energy to make or break. Hydrogen bonds and van der Waals forces are weaker bonds that require much less energy to break. Interactions between molecules with different bond types are responsible for energy use and transfer in metabolic reactions as well as a variety of other reversible interactions.

Table 2.2 Important Ions of the Body

Cations		Anions	
Na^+	Sodium	Cl^-	Chloride
K^+	Potassium	HCO_3^-	Bicarbonate
Ca^{2+}	Calcium	HPO_4^{2-}	Phosphate
H^+	Hydrogen	SO_4^{2-}	Sulfate
Mg^{2+}	Magnesium		

Covalent Bonds between Atoms Create Molecules

Molecules form when atoms share pairs of electrons, one electron from each atom, to create **covalent bonds.** These strong bonds require the input of energy to break them apart. It is possible to predict how many covalent bonds an atom can form by knowing how many unpaired electrons are in its outer shell, because an atom is most stable when all of its electrons are paired (**FIG. 2.6**).

For example, a hydrogen atom has one unpaired electron and one empty electron place in its outer shell. Because hydrogen has only one electron to share, it always forms one covalent bond, represented by a single line (—) between atoms. Oxygen has six electrons in an outer shell that can hold eight. That means oxygen can form two covalent bonds and fill its outer shell with electrons. If adjacent atoms share two pairs of electrons rather than just one pair, a **double bond,** represented by a double line (=), results. If two atoms share three pairs of electrons, they form a triple bond.

Running Problem 2.2

What is chromium picolinate? Chromium (Cr) is an essential element that has been linked to normal glucose metabolism. In the diet, chromium is found in brewer's yeast, broccoli, mushrooms, and apples. Because chromium in food and in chromium chloride supplements is poorly absorbed from the digestive tract, a scientist developed and patented the compound chromium picolinate. Picolinate, derived from amino acids, enhances chromium uptake at the intestine. The recommended adequate intake (AI) of chromium for men ages 19–50 is 35 μg/day. (For women, it is 25 μg/day.) As we've seen, Malik takes more than 10 times this amount.

Q1: *Locate chromium on the periodic table of the elements. What is chromium's atomic number?* ***Atomic mass****? How many electrons does one atom of chromium have?*

Q2: *Which elements close to chromium are also essential elements?*

Polar and Nonpolar Molecules

Some molecules develop regions of partial positive and negative charge when the electron pairs in their covalent bonds are not evenly shared between the linked atoms. When electrons are shared unevenly, the atom(s) with the stronger attraction for electrons develops a slight negative charge (indicated by δ^-), and the atom(s) with the weaker attraction for electrons develops a slight positive charge (δ^+). These molecules are called **polar molecules** because they can be said to have positive and negative ends, or poles. Certain elements, particularly nitrogen and oxygen, have a strong attraction for electrons and are often found in polar molecules.

A good example of a polar molecule is water (H_2O). The larger and stronger oxygen atom pulls the hydrogen electrons toward itself (Fig. 2.6b). This pull leaves the two hydrogen atoms of the molecule with a partial positive charge, and the single oxygen atom with a partial negative charge from the unevenly shared electrons. Note that the net charge for the entire water molecule is zero. The polarity of water makes it a good solvent, and all life as we know it is based on **aqueous solutions**, with water as the solvent.

A **nonpolar molecule** is one whose shared electrons are distributed so evenly that there are no regions of partial positive or negative charge. For example, molecules composed mostly of carbon and hydrogen, such as the **fatty acid** shown in Figure 2.6a, tend to be nonpolar. This is because carbon does not attract electrons as strongly as oxygen does. As a result, the carbons and hydrogens share electrons evenly, and the molecule has no regions of partial charge.

Noncovalent Bonds Facilitate Reversible Interactions

Ionic bonds, hydrogen bonds, and van der Waals forces are noncovalent bonds. They play important roles in many physiological processes, including pH, molecular shape, and the reversible binding of molecules to each other.

Ionic Bonds

Ions form when one atom has such a strong attraction for electrons that it pulls one or more electrons completely away from another atom. For example, a chlorine atom needs only one electron to fill the last of eight places in its outer shell, so it pulls an electron from a sodium atom, which has only one weakly held electron in its outer shell (Fig. 2.6c). The atom that gains electrons acquires one negative charge (−1) for each electron added, so the chlorine atom becomes a chloride ion Cl^-. Negatively charged ions are called **anions**.

An atom that gives up electrons has one positive charge (+1) for each electron lost. For example, the sodium atom becomes a sodium ion Na^+. Positively charged ions are called **cations**.

Ionic bonds, also known as *electrostatic attractions*, result from the attraction between ions with opposite charges. (Remember the basic principle of electricity that says that opposite charges attract and like charges repel.) In a crystal of table salt, the solid form of ionized NaCl, ionic bonds between alternating Na^+ and Cl^- ions hold the ions in a neatly ordered structure.

Hydrogen Bonds

A **hydrogen bond** is a weak attractive force between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. No electrons are gained, lost, or shared in a hydrogen bond. Instead, the oppositely charged regions in polar molecules are attracted to each other. Hydrogen bonds may occur between atoms in neighboring molecules or between atoms in different parts of the same molecule. For example, one water molecule may hydrogen-bond with as many as four other water molecules. As a result, the molecules line up with their neighbors in a somewhat ordered fashion (Fig. 2.6d).

Hydrogen bonding between molecules is responsible for the **surface tension** of water. Surface tension is the attractive force between water molecules that causes water to form spherical

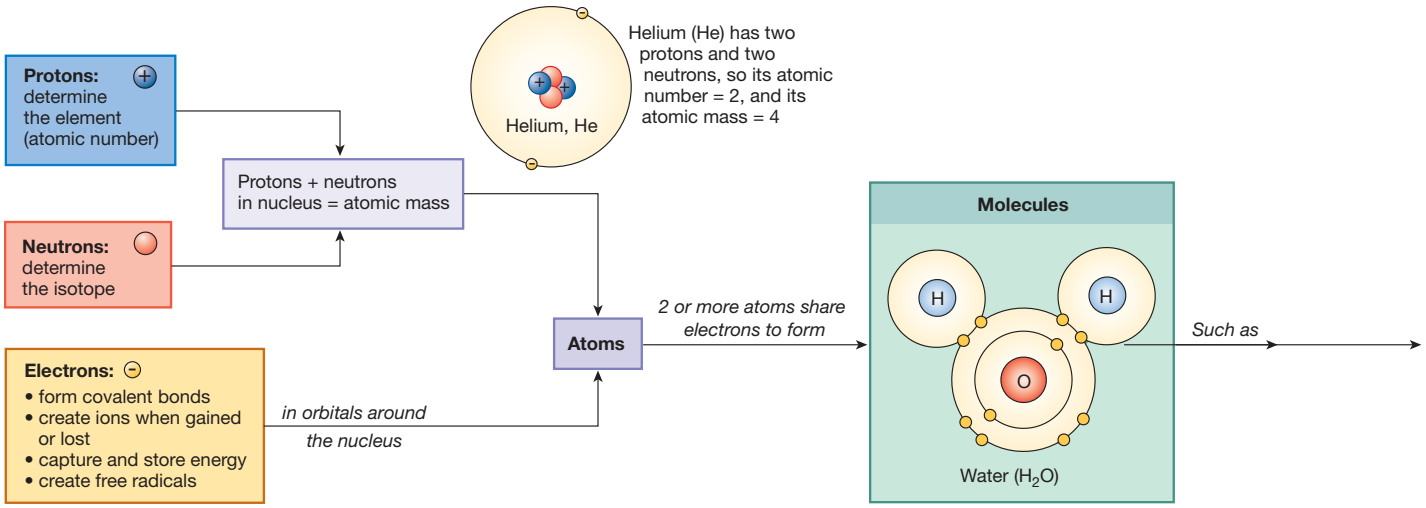
Fig. 2.5 REVIEW Atoms and Molecules

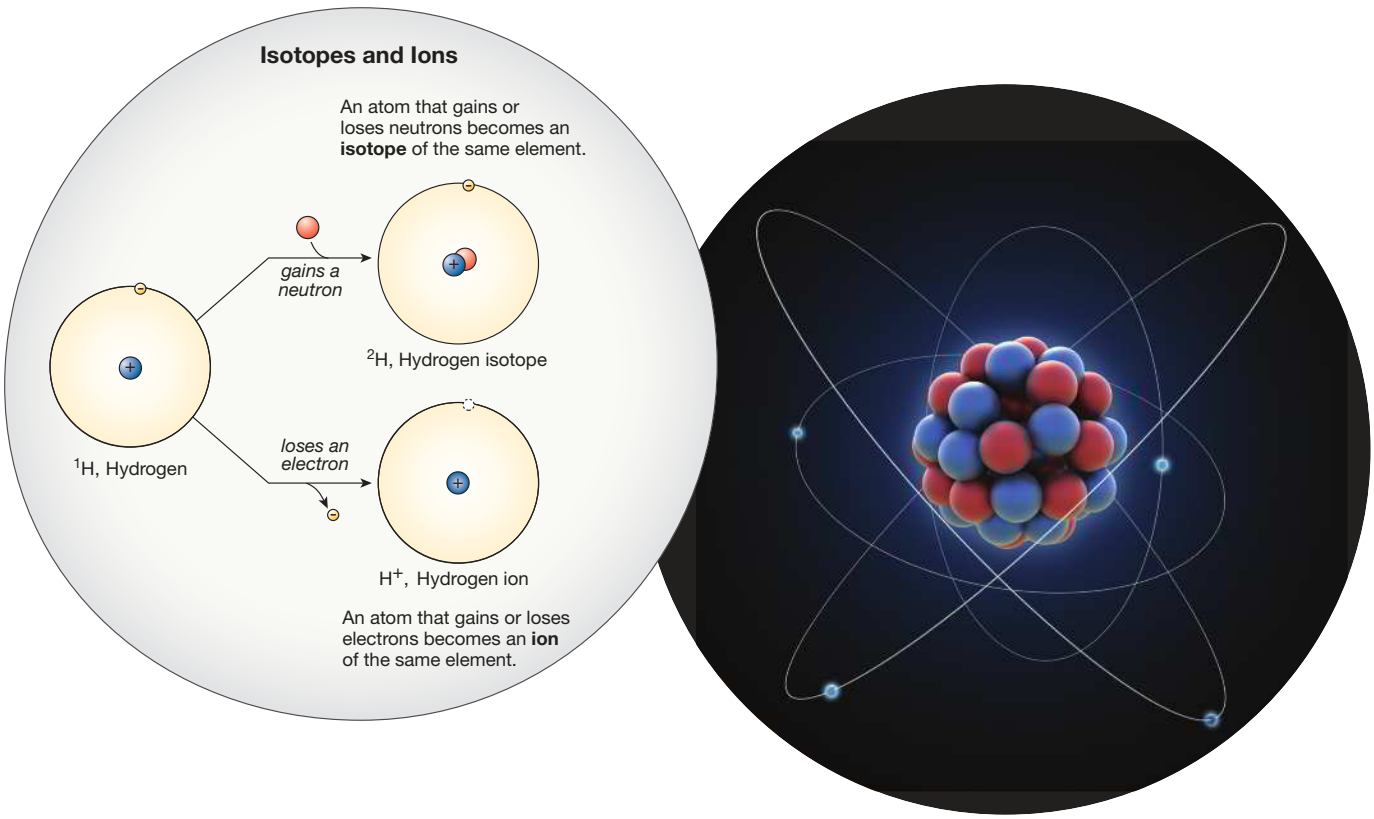
REVIEW Atoms and Molecules

Elements are the simplest type of matter. There are over 100 known elements,* but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are *major essential elements*. An additional 19 *minor essential elements* are required in trace amounts. The smallest particle of any element is an **atom** {*atomos*, indivisible}. Atoms link by sharing electrons to form molecules.

Major Essential Elements	Minor Essential Elements
H, C, O, N, Na, Mg, K, Ca, P, S, Cl	Li, F, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Y, I, Zr, Nb, Mo, Tc, Ru, Rh, La

* A periodic table of the elements can be found inside the back cover of the book.





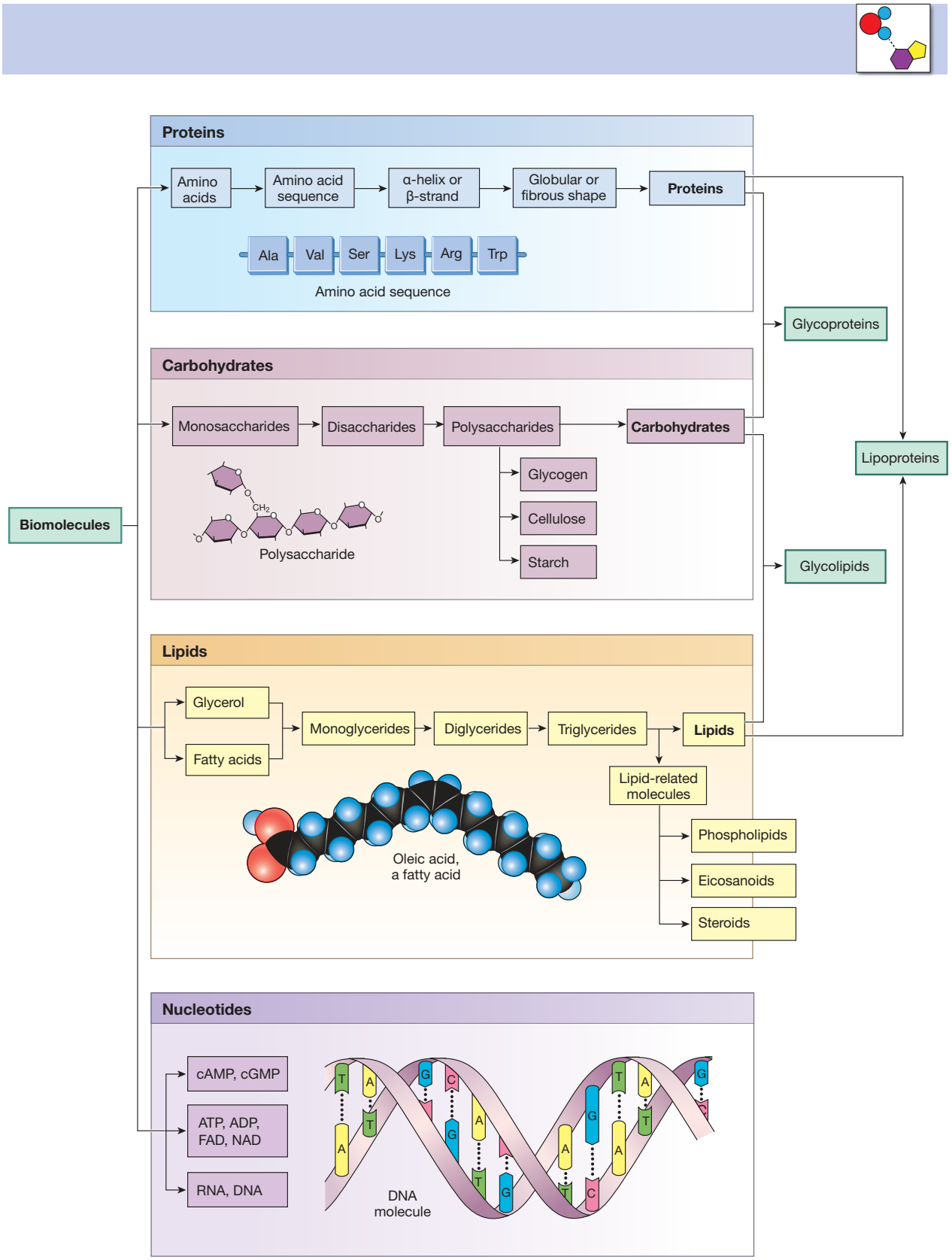
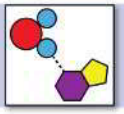


Fig. 2.6 REVIEW Molecular Bonds

REVIEW Molecular Bonds



When two or more atoms link by sharing electrons, they make units known as **molecules.** The transfer of electrons from one atom to another or the sharing of electrons by two atoms is a critical part of forming **bonds,** the links between atoms.

Bonds

Covalent Bonds

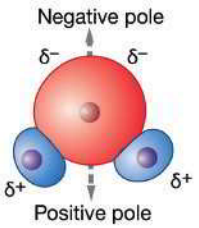
Covalent bonds result when atoms share electrons. These bonds require the most energy to make or break.

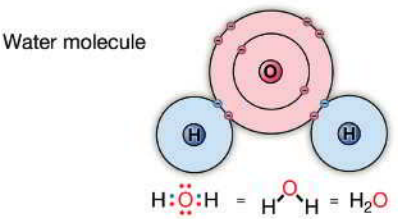
(a) Nonpolar Molecules

Nonpolar molecules have an even distribution of electrons. For example, molecules composed mostly of carbon and hydrogen tend to be nonpolar.

(b) Polar Molecules

Polar molecules have regions of partial charge (δ+ or δ−). The most important example of a polar molecule is water.

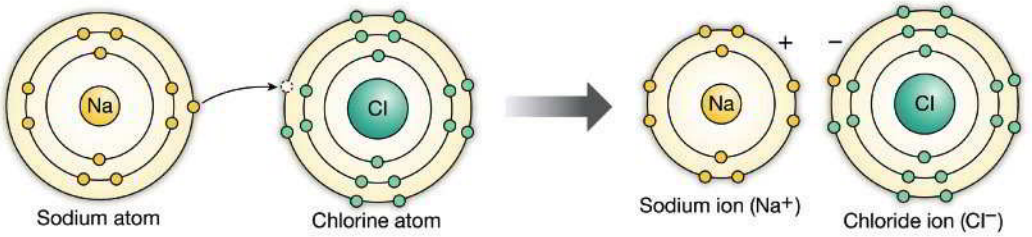




Noncovalent Bonds

(c) Ionic Bonds

Ionic bonds are electrostatic attractions between ions. A common example is sodium chloride.

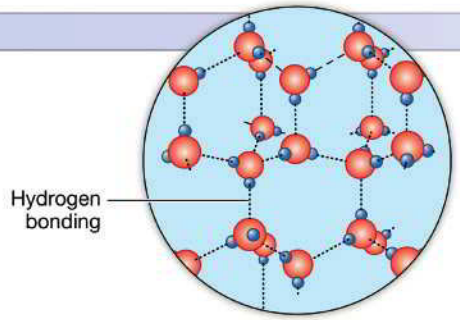


Sodium gives up its one weakly held electron to chlorine, creating sodium and chloride ions, Na^+ and Cl^-.

The sodium and chloride ions both have stable outer shells that are filled with electrons. Because of their opposite charges, they are attracted to each other and, in the solid state, the ionic bonds form a sodium chloride (NaCl) crystal.

(d) Hydrogen Bonds

Hydrogen bonds form between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. So, for example, the polar regions of adjacent water molecules allow them to form hydrogen bonds with one another.



Hydrogen bonding between water molecules is responsible for the surface tension of water.

(e) Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between atoms.

droplets when falling or to bead up when spilled onto a nonabsorbent surface (Fig. 2.6d). The high cohesiveness {*cohaesus*, to cling together} of water is due to hydrogen bonding and makes it difficult to stretch or deform, as you may have noticed in trying to pick up a wet glass that is "stuck" to a slick table top by a thin film of water. The surface tension of water influences lung function (described in Chapter18).

Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between the nucleus of any atom and the electrons of nearby atoms. Two atoms that are weakly attracted to each other by van der Waals forces move closer together until they are so close that their electrons begin to repel one another. Consequently, van der Waals forces allow atoms to pack closely together and occupy a minimum amount of space. A single van der Waals attraction between atoms is very weak.

Running Problem 2.3

One advertising claim for chromium is that it improves the transfer of glucose—the simple sugar that cells use to fuel all their activities—from the bloodstream into cells. In people with diabetes mellitus, cells are unable to take up glucose from the blood efficiently. It seemed logical, therefore, to test whether the addition of chromium to the diet would enhance glucose uptake in people with diabetes. In one Chinese study, diabetic patients receiving 500 micrograms (μg) of chromium picolinate twice a day showed significant improvement in their glucose uptake, but patients receiving 100 micrograms or a placebo did not.

Q3: *If people have a chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*

Q4: *From the results of the Chinese study, can you conclude that all people with diabetes suffer from a chromium deficiency?*

Concept Check

4. Are electrons in an atom or molecule most stable when they are paired or unpaired?
5. When an atom of an element gains or loses one or more electrons, it is called a(n) _____ of that element.
6. Match each type of bond with its description:

(a) covalent bond	1. weak attractive force between hydrogen and oxygen or nitrogen
(b) ionic bond	2. formed when two atoms share one or more pairs of electrons
(c) hydrogen bond	3. weak attractive force between atoms
(d) van der Waals force	4. formed when one atom loses one or more electrons to a second atom

2.2 Noncovalent Interactions

Many different kinds of noncovalent interactions can take place between and within molecules as a result of the four different types of bonds. For example, the charged, uncharged, or partially charged nature of a molecule determines whether that molecule can dissolve in water. Covalent and noncovalent bonds determine molecular shape and function. Finally, noncovalent interactions allow proteins to associate reversibly with other molecules, creating functional pairings such as enzymes and substrates, or signal receptors and molecules.

Hydrophilic Interactions Create Biological Solutions

Life as we know it is established on water-based, or *aqueous*, **solutions** that resemble dilute seawater in their ionic composition. The adult human body is about 60% water. Na^+, K^+, and Cl^- are the main ions in body fluids, with other ions making up a lesser proportion. All molecules and cell components are either dissolved or suspended in these solutions. For these reasons, it is useful to understand the properties of solutions, which are reviewed in **FIGURE 2.7**.

The degree to which a molecule is able to dissolve in a **solvent** is the molecule's **solubility:** the more easily a molecule dissolves, the higher its solubility. Water, the biological solvent, is polar, so molecules that dissolve readily in water are polar or ionic molecules whose positive and negative regions readily interact with water. For example, if NaCl crystals are placed in water, polar regions of the water molecules disrupt the ionic bonds between sodium and chloride, which causes the crystals to dissolve (**FIG. 2.8a**). Molecules that are soluble in water are said to be **hydrophilic** {*hydro-*, water + *-philic*, loving}.

In contrast, molecules such as oils that do not dissolve well in water are said to be **hydrophobic** {*-phobic*, hating}. Hydrophobic substances are usually nonpolar molecules that cannot form hydrogen bonds with water molecules. The lipids (fats and oils) are the most hydrophobic group of biological molecules.

When placed in an aqueous solution, lipids do not dissolve. Instead they separate into distinct layers. One familiar example is salad oil floating on vinegar in a bottle of salad dressing. Before hydrophobic molecules can dissolve in body fluids, they must combine with a hydrophilic molecule that will carry them into solution.

For example, **cholesterol**, a common animal fat, is a hydrophobic molecule. Fat from a piece of meat dropped into a glass of warm water will float to the top, undissolved. In the blood, cholesterol will not dissolve unless it binds to special water-soluble carrier molecules. You may know the combination of cholesterol with its hydrophilic carriers as **HDL-cholesterol** and LDL-cholesterol, the "good" and "bad" forms of cholesterol associated with heart disease.

Some molecules, such as the **phospholipids**, have both polar and nonpolar regions (Fig. 2.8b). This dual nature allows them to associate both with each other (hydrophobic interactions) and

Fig. 2.7 REVIEW Solutions

REVIEW Solutions

Life as we know it is established on water-based, or aqueous, solutions that resemble dilute seawater in their ionic composition. The human body is 60% water. Sodium, potassium, and chloride are the main ions in body fluids. All molecules and cell components are either dissolved or suspended in these saline solutions. For these reasons, the properties of solutions play a key role in the functioning of the human body.

Terminology

A **solute** is any substance that dissolves in a liquid. The degree to which a molecule is able to dissolve in a solvent is the molecule's solubility. The more easily a solute dissolves, the higher its **solubility**.

A **solvent** is the liquid into which solutes dissolve. In biological solutions, water is the universal solvent.

A **solution** is the combination of solutes dissolved in a solvent. The **concentration** of a solution is the amount of solute per unit volume of solution.

Concentration = solute amount/volume of solution

Expressions of Solute Amount

- **Mass** (weight) of the solute before it dissolves. Usually given in grams (g) or milligrams (mg).
- **Molecular mass** is calculated from the chemical formula of a molecule. This is the mass of one molecule, expressed in atomic mass units (amu) or, more often, in daltons (Da), where 1 amu = 1 Da.

Molecular mass = SUM [atomic mass of each element × the number of atoms of each element]

Example

What is the molecular mass of glucose, $C_6H_{12}O_6$?

Answer

Element	# of Atoms	Atomic Mass of Element
Carbon	6	12.0 amu × 6 = 72
Hydrogen	12	1.0 amu × 12 = 12
Oxygen	6	16.0 amu × 6 = 96

Molecular mass of glucose = 180 amu (or Da)

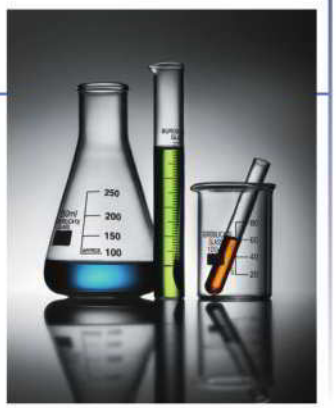
- **Moles** (mol) are an expression of the number of solute molecules, without regard for their weight. One mole = 6.02×10^{23} atoms, ions, or molecules of a substance. One mole of a substance has the same number of particles as one mole of any other substance, just as a dozen eggs has the same number of items as a dozen roses.
- **Gram molecular weight.** In the laboratory, we use the molecular mass of a substance to measure out moles. For example, one mole of glucose (with 6.02×10^{23} glucose molecules) has a molecular mass of 180 Da and weighs 180 grams. The molecular mass of a substance expressed in grams is called the gram molecular weight.
- **Equivalents** (Eq) are a unit used for ions, where 1 equivalent = molarity of the ion × the number of charges the ion carries. The sodium ion, with its charge of +1, has one equivalent per mole. The hydrogen phosphate ion (HPO_4^{2-}) has two equivalents per mole. Concentrations of ions in the blood are often reported in milliequivalents per liter (mEq/L).

FIGURE QUESTIONS

1. What are the two components of a solution?
2. The concentration of a solution is expressed as:
   (a) amount of solvent/volume of solute
   (b) amount of solute/volume of solvent
   (c) amount of solvent/volume of solution
   (d) amount of solute/volume of solution
3. Calculate the molecular mass of water, H_2O.
4. How much does a mole of KCl weigh?

Expressions of Volume

Volume is usually expressed as liters (L) or milliliters (mL) {*milli-*, 1/1000}. A volume convention common in medicine is the deciliter (dL), which is 1/10 of a liter, or 100 mL.



Prefixes

deci- (d)	1/10	1×10^{-1}
milli- (m)	1/1000	1×10^{-3}
micro- (μ)	1/1,000,000	1×10^{-6}
nano- (n)	1/1,000,000,000	1×10^{-9}
pico- (p)	1/1,000,000,000,000	1×10^{-12}

Useful Conversions

- 1 liter of water weighs 1 kilogram (kg) {*kilo-*, 1000}
- 1 kilogram = 2.2 pounds

Expressions of Concentration

- **Percent solutions.** In a laboratory or pharmacy, scientists cannot measure out solutes by the mole. Instead, they use the more conventional measurement of weight. The solute concentration may then be expressed as a percentage of the total solution, or percent solution. A 10% solution means 10 parts of a solute per 100 parts of total solution. Weight/volume solutions, used for solutes that are solids, are usually expressed as g/100 mL solution or mg/dL. An out-of-date way of expressing mg/dL is mg% where % means per 100 parts or 100 mL. A concentration of 20 mg/dL could also be expressed as 20 mg%.

Example

Solutions used for intravenous (IV) infusions are often expressed as percent solutions. How would you make 500 mL of a 5% dextrose (glucose) solution?

Answer

5% solution = 5 g glucose dissolved in water to make a final volume of 100 mL solution.

5 g glucose/100 mL = ? g/500 mL

25 g glucose with water added to give a final volume of 500 mL

- **Molarity** is the number of moles of solute in a liter of solution, and is abbreviated as either mol/L or M. A one molar solution of glucose (1 mol/L, 1 M) contains 6.02×10^{23} molecules of glucose per liter of solution. It is made by dissolving one mole (180 grams) of glucose in enough water to make one liter of solution. Typical biological solutions are so dilute that solute concentrations are usually expressed as **millimoles** per liter (mmol/L or mM).

Example

What is the molarity of a 5% dextrose solution?

Answer

5 g glucose/100 mL = 50 g glucose/1000 mL (or 1 L)

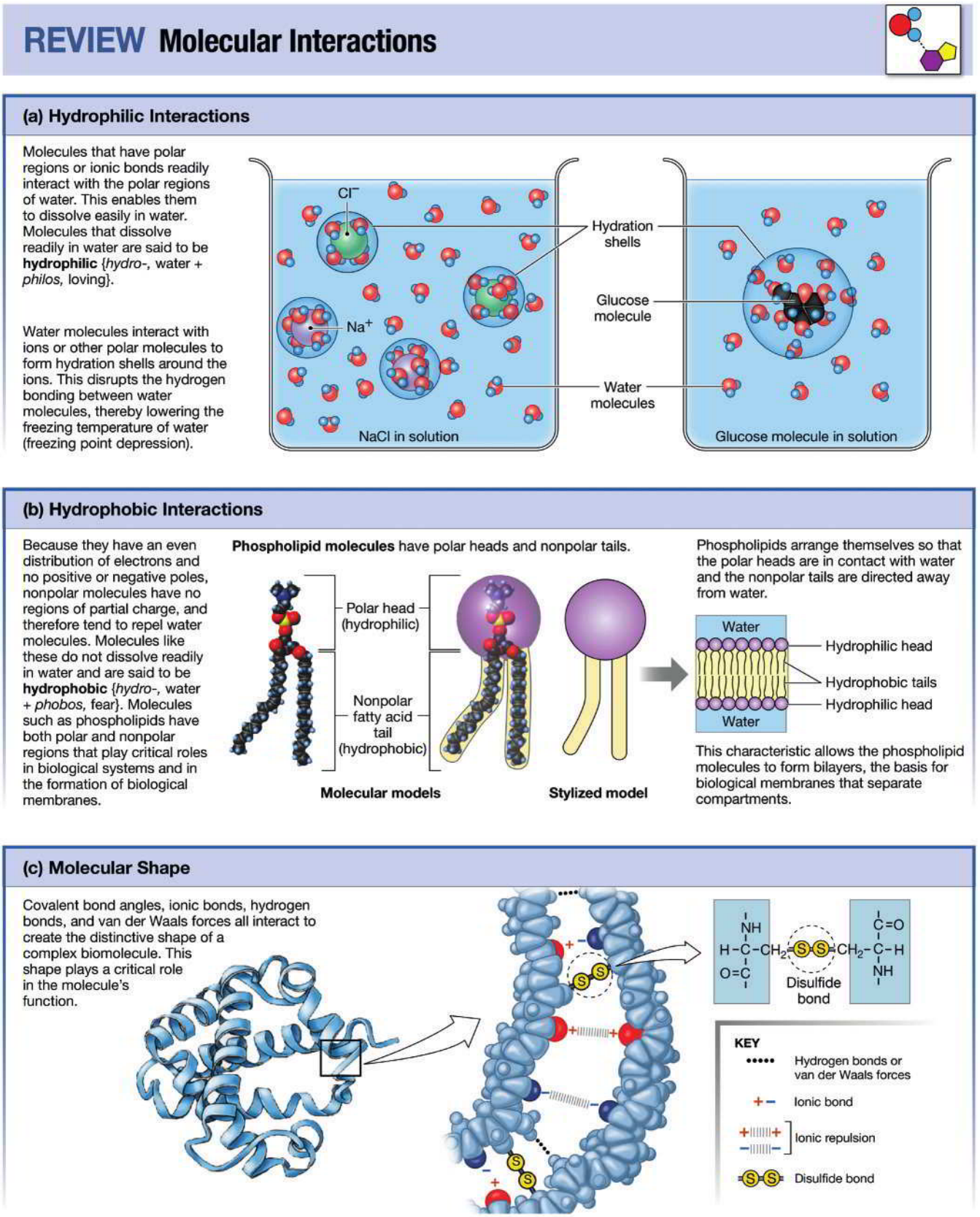
1 mole glucose = 180 g glucose

50 g/L × 1 mole/180 g = 0.278 moles/L or 278 mM

FIGURE QUESTIONS

5. Which solution is more concentrated: a 100 mM solution of glucose or a 0.1 M solution of glucose?
6. When making a 5% solution of glucose, why don't you measure out 5 grams of glucose and add it to 100 mL of water?

Fig. 2.8 REVIEW Molecular Interactions



with polar water molecules (hydrophilic interactions). Phospholipids are the primary component of biological membranes.

Concept Check

7. Which dissolve more easily in water, polar molecules or nonpolar molecules?
8. A molecule that dissolves easily is said to be hydro__ic.
9. Why does table salt (NaCl) dissolve in water?

Molecular Shape Is Related to Molecular Function

A molecule's shape is closely related to its function. Molecular bonds—both covalent bonds and weak bonds—play a critical role in determining molecular shape. The three-dimensional shape of a molecule is difficult to show on paper, but many molecules have characteristic shapes due to the angles of covalent bonds between the atoms. For example, the two hydrogen atoms of the water molecule shown in Figure 2.6b are attached to the oxygen with a bond angle of 104.5°. Double bonds in long carbon chain fatty acids cause the chains to kink or bend, as shown by the three-dimensional model of oleic acid in Figure 2.5.

Weak noncovalent bonds also contribute to molecular shape. The complex double helix of a **DNA** molecule, shown in Figure 2.4, results both from covalent bonds between adjacent **nitrogenous bases** in each strand and the hydrogen bonds connecting the two strands of the helix.

Proteins have the most complex and varied shapes of all the biomolecules. Their shapes are determined both by the sequence of amino acids in the protein chain (the **primary structure of a protein**) plus varied noncovalent interactions as long **polypeptide** chains loop and fold back on themselves. The stable **secondary structures** of proteins are formed by covalent bond angles between amino acids in the polypeptide chain.

The two common protein **secondary structures** are the **α – helix (alpha-helix)** spiral and the zigzag shape of **β – sheets (beta-sheet)** (Fig. 2.3). Adjacent β-*strands* in the polypeptide chain associate into sheetlike structures held together by hydrogen bonding, shown as dotted lines (. . .) in Figure 2.3. The sheet configuration is very stable and occurs in many proteins destined for structural uses. Proteins with other functions may have a mix of β-strands and α-helices. Protein secondary structure is illustrated by ribbon diagrams (or Richardson diagrams), with beta-sheets shown as flat arrows and α-helices as ribbon spirals (Fig. 2.3).

The **tertiary structure** of a protein is its three-dimensional shape, created through spontaneous folding as the result of covalent bonds and noncovalent interactions. Proteins are categorized into two large groups based on their shape: globular and fibrous (see Fig. 2.3). **Globular proteins** can be a mix of α-helices, β-sheets, and amino acid chains that fold back on themselves. The result is a complex tertiary structure that may contain pockets, channels, or protruding knobs. The tertiary structure of globular proteins arises partly from the angles of covalent bonds between amino acids and partly from hydrogen bonds, van der Waals forces, and ionic bonds that stabilize the molecule's shape.

In addition to covalent bonds between adjacent amino acids, covalent **disulfide bonds** (S–S) play an important role in the shape of many globular proteins (Fig. 2.8c). The amino acid *cysteine* contains sulfur as part of a *sulfhydryl group* (–SH). Two cysteines in different parts of the polypeptide chain can bond to each other with a disulfide bond that pulls the sections of chain together.

Fibrous proteins can be β-strands or long chains of α-helices. Fibrous proteins are usually insoluble in water and form important structural components of cells and tissues. Examples of fibrous proteins include *collagen*, found in many types of connective tissue, such as skin, and *keratin*, found in hair and nails.

Hydrogen Ions in Solution Can Alter Molecular Shape

Hydrogen bonding is an important part of molecular shape. However, free hydrogen ions, H^+, in solution can also participate in hydrogen bonding and van der Waals forces. If free H^+ disrupts a molecule's noncovalent bonds, the molecule's shape, or *conformation*, can change. A change in shape may alter or destroy the molecule's ability to function.

Running Problem 2.4

Chromium is found in several ionic forms. The chromium usually found in biological systems and in dietary supplements is the cation Cr^{3+}. This ion is called trivalent because it has a net charge of $+3$. The hexavalent cation, Cr^{6+}, with a charge of $+6$, is used in industry, such as in the manufacturing of stainless steel and the chrome plating of metal parts.

Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*

The concentration of free H^+ in body fluids, or *acidity*, is measured in terms of **pH. FIGURE 2.9** reviews the chemistry of pH and shows a pH scale with the pH values of various substances. The typical pH of blood in the human body is 7.40, slightly alkaline. Regulation of the body's pH within a narrow range is critical because a blood pH more acidic than 7.00 ($pH < 7.00$) or more alkaline than 7.70 ($pH > 7.70$) is incompatible with life.

Where do hydrogen ions in body fluids come from? Some of them come from the separation of water molecules (H_2O) into H^+ and OH^- ions. Others come from **acids,** molecules that release H^+ when they dissolve in water (Fig. 2.9). Many of the molecules made during metabolism are acids. For example, acid is made in the body from CO_2 (carbon dioxide) and water.

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

Note that when the hydrogen is part of the water molecule, it does not contribute to acidity. *Only free H^+ contributes to the hydrogen ion concentration.*

We are constantly adding acid to the body through metabolism, so how does the body maintain an acceptable pH? One

Fig. 2.9 REVIEW pH

REVIEW pH

Acids and Bases

An **acid** is a molecule that contributes H^+ to a solution.

- The carboxyl group, –COOH, is an acid because in solution it tends to lose its H^+:

$$R\text{–}COOH \longrightarrow R\text{–}COO^- + H^+$$

A **base** is a molecule that decreases the H^+ concentration of a solution by combining with free H^+.

- Molecules that produce hydroxide ions, OH^-, in solution are bases because the hydroxide combines with H^+ to form water:

$$R\text{–}OH \longrightarrow R^+ + OH^- \longrightarrow OH^- + H^+ \longrightarrow H_2O$$

- Another molecule that acts as a base is ammonia, NH_3. It reacts with a free H^+ to form an ammonium ion:

$$NH_3 + H^+ \longrightarrow NH_4^+$$

pH

The concentration of H^+ in body fluids is measured in terms of **pH.**

- The expression pH stands for "power of hydrogen."

(1) $pH = -\log [H^+]$

This equation is read as "pH is equal to the negative log of the hydrogen ion concentration." Square brackets are shorthand notation for "concentration" and by convention, concentration is expressed in Eq/L.

- Using the rule of logarithms that says $-\log x = \log(1/x)$, pH equation (1) can be rewritten as:

(2) $pH = \log (1/[H^+])$

This equation shows that pH is inversely related to H^+ concentration. In other words, as the H^+ concentration goes up, the pH goes down.

Example

What is the pH of a solution whose hydrogen ion concentration $[H^+]$ is 10^{-7} Eq/L?

Answer

$pH = -\log [H^+]$
$pH = -\log [10^{-7}]$

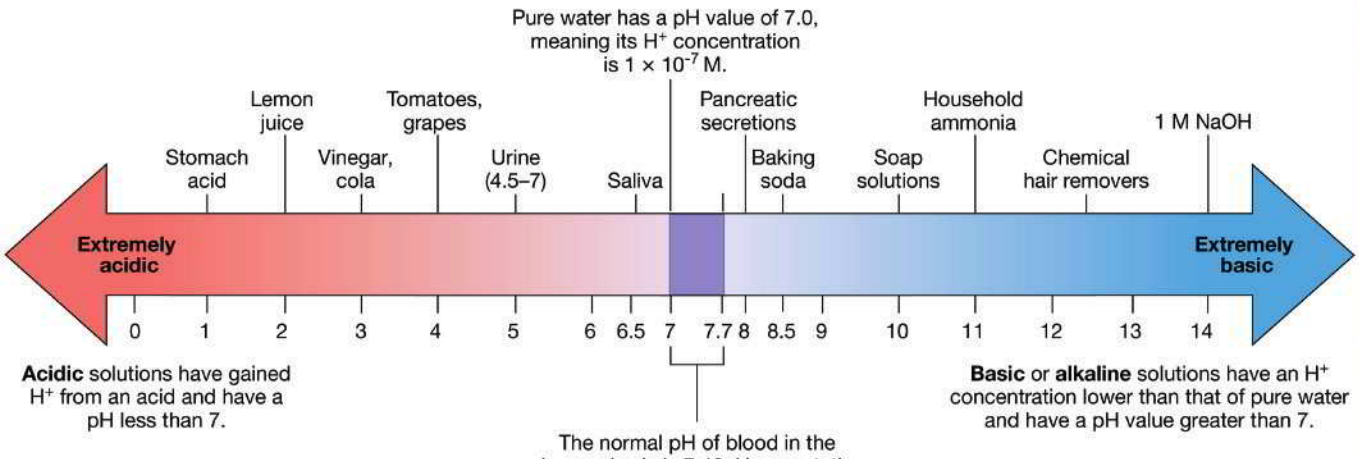
Using the rule of logs, this can be rewritten as

$pH = \log (1/10^{-7})$

Using the rule of exponents that says $1/10^x = 10^{-x}$

$pH = \log 10^7$

the log of 10^7 is 7, so the solution has a pH of 7.



The pH of a solution is measured on a numeric scale between 0 and 14. The pH scale is logarithmic, meaning that a change in pH value of 1 unit indicates a 10-fold change in $[H^+]$. For example, if a solution changes from pH 8 to pH 6, there has been a 100-fold (10^2 or 10 × 10) increase in $[H^+]$.

FIGURE QUESTIONS

1. When the body becomes more acidic, does pH increase or decrease?
2. How can urine, stomach acid, and saliva have pH values outside the pH range that is compatible with life and yet be part of the living body?

answer is buffers. A **buffer** is any substance that moderates changes in pH. Many buffers contain anions that have a strong attraction for H^+ molecules. When free H^+ is added to a buffer solution, the buffer's anions bond to the H^+, thereby minimizing any change in pH.

The bicarbonate anion, HCO_3^-, is an important buffer in the human body. The following equation shows how a sodium bicarbonate solution acts as a buffer when hydrochloric acid (HCl) is added. When placed in plain water, hydrochloric acid separates, or dissociates, into H^+ and Cl^- and creates a high H^+ concentration (low pH). When HCl dissociates in a sodium bicarbonate solution, however, some of the bicarbonate ions combine with some of the H^+ to form undissociated carbonic acid. "Tying up" the added H^+ in this way keeps the free H^+ concentration of the solution from changing significantly and minimizes the pH change.

$$\underset{\text{Hydrochloric acid}}{H^+ + Cl^-} + \underset{\text{Sodium bicarbonate}}{HCO_3^- + Na^+} \rightleftharpoons \underset{\text{Carbonic acid}}{H_2CO_3} + \underset{\text{Sodium chloride (table salt)}}{Cl^- + Na^+}$$

Concept Check

10. To be classified as an acid, a molecule must do what when dissolved in water?
11. pH is an expression of the concentration of what in a solution?
12. When pH goes up, acidity goes _____.

2.3 Protein Binding Interactions

Noncovalent molecular interactions occur between proteins and many different biomolecules. For example, biological membranes are formed by the noncovalent associations of proteins and phospholipids. And glycoproteins join glycolipids in cell membranes to create a "sugar coat" on cell surfaces that assists cell **aggregation** {*aggregare*, to join together} and adhesion {*adhaerere*, to stick}.

Proteins play important roles in so many cell functions that we can consider them the "workhorses" of the body. Most proteins fall into nine broad categories:

1. **Enzymes.** Some proteins act as **enzymes,** biological catalysts that speed up chemical reactions. Enzymes are crucial players in metabolism and you will learn more about their properties in Chapter 4.
2. **Membrane transporters.** Proteins in cell membranes help substances move between the intracellular and extracellular compartments. These proteins may form channels in the cell membrane, or they may bind to ions and molecules and carry them through the membrane. Membrane transporters are discussed in detail in Chapter 5.
3. **Signal molecules.** Some proteins and smaller **peptides** act as hormones and other signal molecules. Signal molecules are described in Chapters 6 and 8.
4. **Receptors.** Proteins that bind signal molecules and initiate cellular responses are called *receptors*. Receptors are discussed along with signal molecules in Chapter 6.
5. **Binding proteins.** These proteins, found mostly in the extracellular fluid, bind to and transport molecules throughout the body. Examples you may be familiar with include cholesterol-binding lipoproteins such as LDL (low-density lipoprotein) and the oxygen-transporting protein *hemoglobin* found inside red blood cells.
6. **Immunoglobulins.** These extracellular immune proteins, also called *antibodies*, help protect the body from foreign invaders and substances. Immune functions are discussed in Chapter 7.
7. **Motor proteins.** Motor proteins use energy from ATP to create movement. Examples include *myosin* that plays a role in muscle contraction, proteins that propel cilia and flagella, and protein fibers inside cells that move organelles and help in cell division.
8. **Structural proteins.** Fibrous proteins play an important role in creating the shape and structure of cells, tissues, and organs, as you will learn in Chapter 3. Some of the key structural proteins include *collagen*, *keratin*, and *elastin*.
9. **Regulatory proteins.** Regulatory proteins turn cell processes on and off or up and down. For example, the regulatory proteins known as *transcription factors* bind to DNA and alter gene expression and protein synthesis. The details of regulatory proteins can be found in cell biology textbooks.

Although proteins are quite diverse in shape and function, they share one common feature: they all bind to other molecules through noncovalent interactions. The interaction takes place at a location on the protein molecule called the **binding site.** The binding site depends on the three-dimensional shape of the protein, and its properties can be altered or *modulated* by factors that affect protein structure. The unique shapes of different binding sites give rise to three important properties of protein binding that are discussed below: specificity, affinity, and competition.

Running Problem 2.5

The hexavalent form of chromium used in industry is known to be toxic to humans. In 1992, officials at California's Hazard Evaluation System and Information Service warned that inhaling chromium dust, mist, or fumes placed chrome and stainless steel workers at increased risk for lung cancer. Officials found no risk to the public from normal contact with chrome surfaces or stainless steel. In 1995 and 2002, a possible link between the biological trivalent form of chromium (Cr^{3+}) and cancer came from *in vitro* studies {*vitrum*, glass—that is, a test tube} in which mammalian cells were kept alive in tissue culture. In these experiments, cells exposed to moderately high levels of chromium picolinate developed potentially cancerous changes.[1, 2]

Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*

Any molecule or ion that binds to another molecule is called a **ligand** {*ligare*, to bind or tie}. Ligands that bind to enzymes and membrane transporters are usually called **substrates** {*sub-*, below + *stratum*, a layer}. Proteins can also be ligands. Protein signal molecules bind to receptors, and protein transcription factors bind to DNA. Immunoglobulins bind ligands called *antigens*, but the immunoglobulin-antigen complex itself can then become a ligand [Fig. 7.8].

Proteins Are Selective about the Molecules They Bind

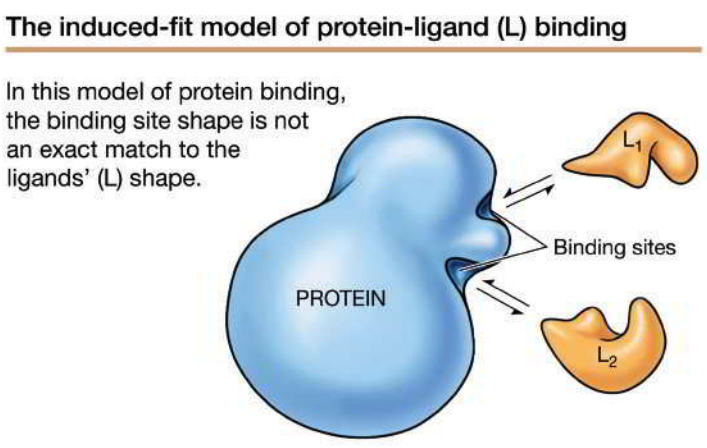
The ability of a protein to bind to a particular ligand or a group of related ligands is called **specificity.** Some proteins are very specific about the ligands they bind, while others bind to whole groups of molecules. For example, the enzymes known as **peptidases** bind to polypeptide ligands and break apart their **peptide bonds**, no matter which two amino acids are joined by those bonds. For this reason the action of peptidases is not very specific. In contrast, **aminopeptidases** also break peptide bonds but are more specific. They will bind to only one end of a protein chain (the end with an unbound amino group) and can act only on the last peptide bond in the chain.

Ligand binding requires **molecular complementarity**. In other words, the ligand and the protein binding site must be complementary, or compatible. In protein binding, when the ligand and protein come close to each other, noncovalent interactions between the ligand and the protein's binding site allow the two molecules to bind. From studies of enzymes and other binding proteins, scientists have discovered that a protein's binding site and the shape of its ligand do not need to fit one another exactly. When the binding site and the ligand come close to each other, they begin to interact through hydrogen and ionic bonds and van der Waals forces. The protein's binding site then changes shape (*conformation*) to fit more closely to the ligand. This is known as the **induced-fit model of protein-ligand interaction** and is shown in **FIGURE 2.10**.

When one protein binds to several related ligands, the related ligands that compete for the binding sites are said to be **competitors.** Competition between ligands is a universal property of protein binding. Competing ligands that mimic each other's actions are called **agonists** {*agonist*, contestant}. Agonists may occur in nature, such as *nicotine*, the chemical found in tobacco, which mimics the activity of the neurotransmitter *acetylcholine* by binding to the same receptor protein. Agonists can also be synthesized using what scientists learn from the study of protein–ligand binding sites.

Competing ligands that bind to the protein and block the binding site without causing a response are **antagonists**, also called inhibitors. Antagonists act like someone slipping into the front of a box office line to chat with their friend, the cashier. They are not interested in buying a ticket, but prevent the people waiting in line from getting their tickets. The ability of agonist and antagonist molecules to mimic or decrease the activity of naturally occurring ligands has led to the development of many drugs.

Fig. 2.10 The induced-fit model of protein-ligand (L) binding



Isoforms

Closely related proteins whose function is similar but whose affinity for ligands differs are called **isoforms** of one another. For example, the oxygen-transporting protein *hemoglobin* has multiple isoforms. One hemoglobin molecule has a **quaternary structure** consisting of four subunits (see Fig. 2.3). In the developing fetus, the hemoglobin isoform has two α (alpha) chains and two γ (gamma) chains that make up the four subunits. Shortly after birth, fetal hemoglobin molecules are broken down and replaced by adult hemoglobin. The adult hemoglobin isoform retains the two α chain isoforms but has two β (beta) chains in place of the γ chains. Both adult and fetal isoforms of hemoglobin bind oxygen, but the fetal isoform has a higher affinity for oxygen. This makes it more efficient at picking up oxygen across the placenta.

Protein-Binding Reactions Are Reversible

The degree to which a protein is attracted to a particular ligand is called the protein's **affinity** for the ligand. If a protein has a high affinity for a given ligand, the protein is more likely to bind to that ligand than to other ligands for which the protein has lower affinity.

Protein binding to a ligand can be written using the same notation that we use to represent chemical reactions:

$$P + L \rightleftharpoons PL$$

where P is the protein, L is the ligand, and PL is the bound protein-ligand complex. The double arrow indicates that binding is reversible.

Reversible binding reactions reach a state of **equilibrium**, where the rate of binding ($P + L \rightarrow PL$) is exactly equal to the rate of unbinding, or *dissociation* ($P + L \leftarrow PL$) When a reaction is at equilibrium, the ratio of the product concentration, or protein-ligand complex [PL], to the reactant concentrations [P][L] is always the same. This ratio is called the **equilibrium constant** K_{eq}, and it applies to all reversible chemical reactions:

$$K_{eq} = \frac{[PL]}{[P][L]}$$

The square brackets [ ] around the letters indicate concentrations of the protein, ligand, and protein-ligand complex.

In protein-binding reactions, the equilibrium constant K_{eq} is a quantitative representation of the protein's binding affinity for the ligand: high affinity for the ligand means a larger K_{eq}.[3] If one protein binds to several related ligands, a comparison of their K_{eq} values tells us which ligand is more likely to bind to the protein.

Binding Reactions Obey the Law of Mass Action

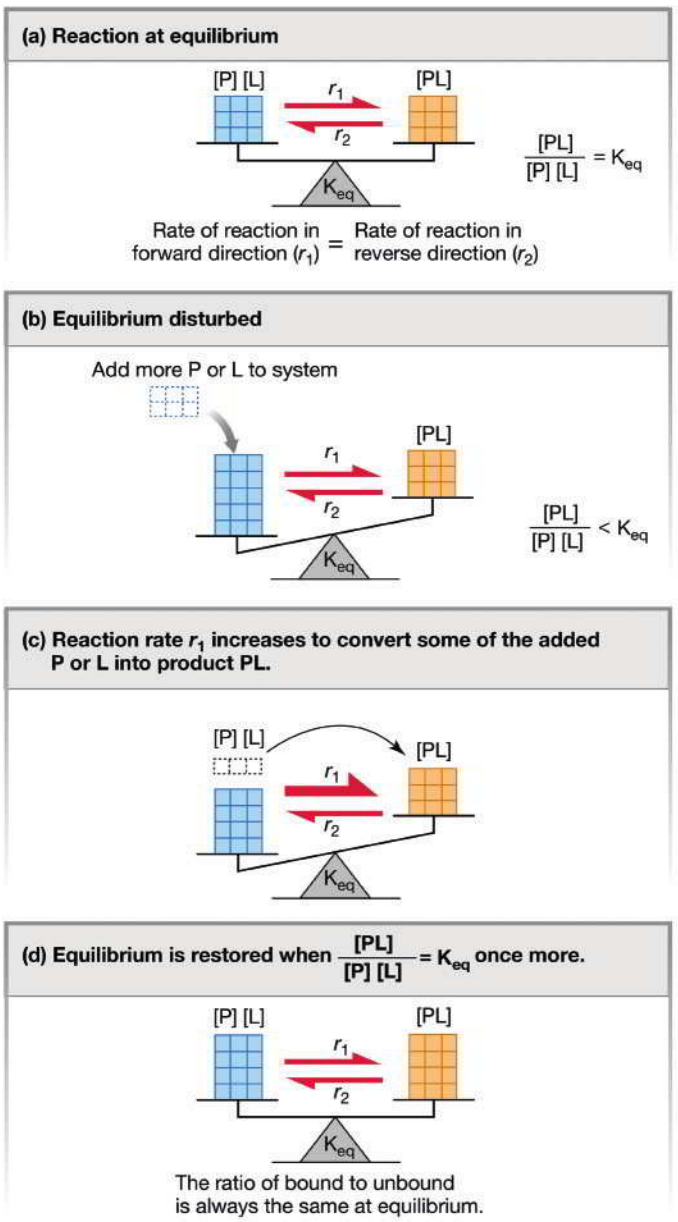
Reversible reactions at equilibrium have a constant ratio of bound protein to free protein and ligand. However, equilibrium is not a static state. In the living body, concentrations of protein or ligand change constantly through synthesis, breakdown, or movement from one compartment to another. So what restores equilibrium when it is disturbed?

When the concentration of protein or ligand changes, the reaction follows the **law of mass action**, which you may have learned in chemistry as *Le Châtelier's principle*. The law of mass action says that reaction rates are proportional to the concentration of the reactants. If the concentration of one of the participants changes, the reaction rates will increase or decrease to restore the equilibrium condition.

An example of this is shown in **FIGURE. 2.11**, which begins with a reaction at equilibrium (Fig 2.11a). The equilibrium is disturbed when more protein or ligand is added to the system (Fig. 2.11b). Now the ratio of [PL] to [P][L] differs from the K_{eq}. In response, the rate of the binding reaction increases to convert some of the added P or L into the bound protein-ligand complex (Fig. 2.11c). As the ratio approaches its equilibrium value again, the rate of the forward reaction slows until finally the system reaches the equilibrium ratio once more (Fig. 2.11d). [P], [L], and [PL] have all increased over their initial values, but the equilibrium ratio has been restored.

One example of this principle at work is the transport of **steroid** hormones in the blood. Steroids are hydrophobic, so more than 99% of steroid hormone in the blood is bound to carrier proteins. The equilibrium ratio [PL]/[P][L] is 99% bound:1% unbound hormone. However, only the unbound or "free" hormone can cross the cell membrane and enter cells. As unbound hormone leaves the blood, the equilibrium ratio is disturbed. The binding proteins then release some of the bound hormone until the 99:1 ratio is again restored. The same principle applies to enzymes and metabolic reactions. Changing the concentration of one participant in a chemical reaction has a chain-reaction effect that alters the concentrations of other participants in the reaction.

Fig. 2.11 The law of mass action



Concept Check

13. Consider the carbonic acid reaction, which is reversible:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

If the concentration of carbon dioxide in the body increases, what happens to the pH?

14. A researcher is trying to design a drug to bind to a particular cell receptor protein. Candidate molecule A has a K_{eq} of 0.9 for the receptor. Molecule B has a K_{eq} of 4.3. Which molecule has the most potential to be successful as the drug?

Running Problem 2.6

Malik has been taking chromium picolinate because he heard that it would increase his strength and muscle mass. Then a friend told him that the Food and Drug Administration (FDA) said there was no evidence to show that chromium would help build muscle. In one study,[4] a group of researchers gave high daily doses of chromium picolinate to football players during a two-month training period. By the end of the study, the players who took chromium supplements had not increased muscle mass or strength any more than players who did not take the supplement.

Use Google Scholar (*http://scholar.google.com*) and search for *chromium picolinate AND muscle*. Look for articles on body composition or muscle strength in humans before you answer the next question.

Q7: *Based on the papers you found, the Hallmark et al. study (which did not support enhanced muscle development from chromium supplements), and the studies that suggest that chromium picolinate might cause cancer, do you think that Malik should continue taking chromium picolinate?*

Multiple Factors Alter Protein Binding

A protein's affinity for a ligand is not always constant. Chemical and physical factors can alter, or *modulate*, binding affinity or can even eliminate it totally. Some proteins must be activated before they have a functional binding site. In this section we discuss some of the processes that have evolved to allow activation, modulation, and inactivation of protein binding. **TABLE 2.3** summarizes the different types of activation and modulation.

Activation

Some proteins are synthesized in the cell in an inactive state. Before these proteins can become active, enzymes must chop off one or more portions of the protein molecule (**FIG. 2.12a**). Protein hormones (a type of signal molecule) and enzymes are two groups that commonly undergo such *proteolytic activation* {*lysis*, to release}. The inactive forms of these proteins are often identified with the prefix *pro-* {before}: prohormone, proenzyme, proinsulin, for example. Some inactive enzymes have the suffix *-ogen* added to the name of the active enzyme instead, as in **trypsinogen**, the inactive form of trypsin.

The activation of some proteins requires the presence of a **cofactor,** which is an ion or small organic functional group. Cofactors must attach to the protein before the binding site is able to bind to a ligand (Fig. 2.12b). Ionic cofactors include Ca^{2+}, Mg^{2+}, and Fe^{2+}. Many enzymes do not function without their cofactors.

Table 2.3 Factors That Affect Protein Binding

Essential for Binding Activity	
Cofactors	Required for ligand binding at binding site
Proteolytic activation	Converts inactive to active form by removing part of molecule. Examples: digestive enzymes, protein hormones
Modulators and Factors That Alter Binding or Activity	
Competitive inhibitor	Competes directly with ligand by binding reversibly to active site
Irreversible inhibitor	Binds to binding site and cannot be displaced by competition
Allosteric modulator	Binds to protein away from binding site and changes activity; may be inhibitors or activators
Covalent modulator	Binds covalently to protein and changes its activity. Example: phosphate groups
pH and temperature	Alter three-dimensional shape of protein by disrupting hydrogen or S–S bonds; may be irreversible if protein becomes denatured

Modulation

The ability of a protein to bind a ligand and initiate a response can be altered by various factors, including temperature, pH, and molecules that interact with the protein. **Chemical modulators** are molecules that bind to proteins and alter their binding ability or their activity. Chemical modulators can be classified in several ways:

- By whether they enhance or inhibit the protein's activity,
- By whether their effect is reversible or irreversible,
- By where they bind to the protein (at the binding site or to another part of the protein), and
- By how they bind to the protein (noncovalent interactions or covalent bonds).

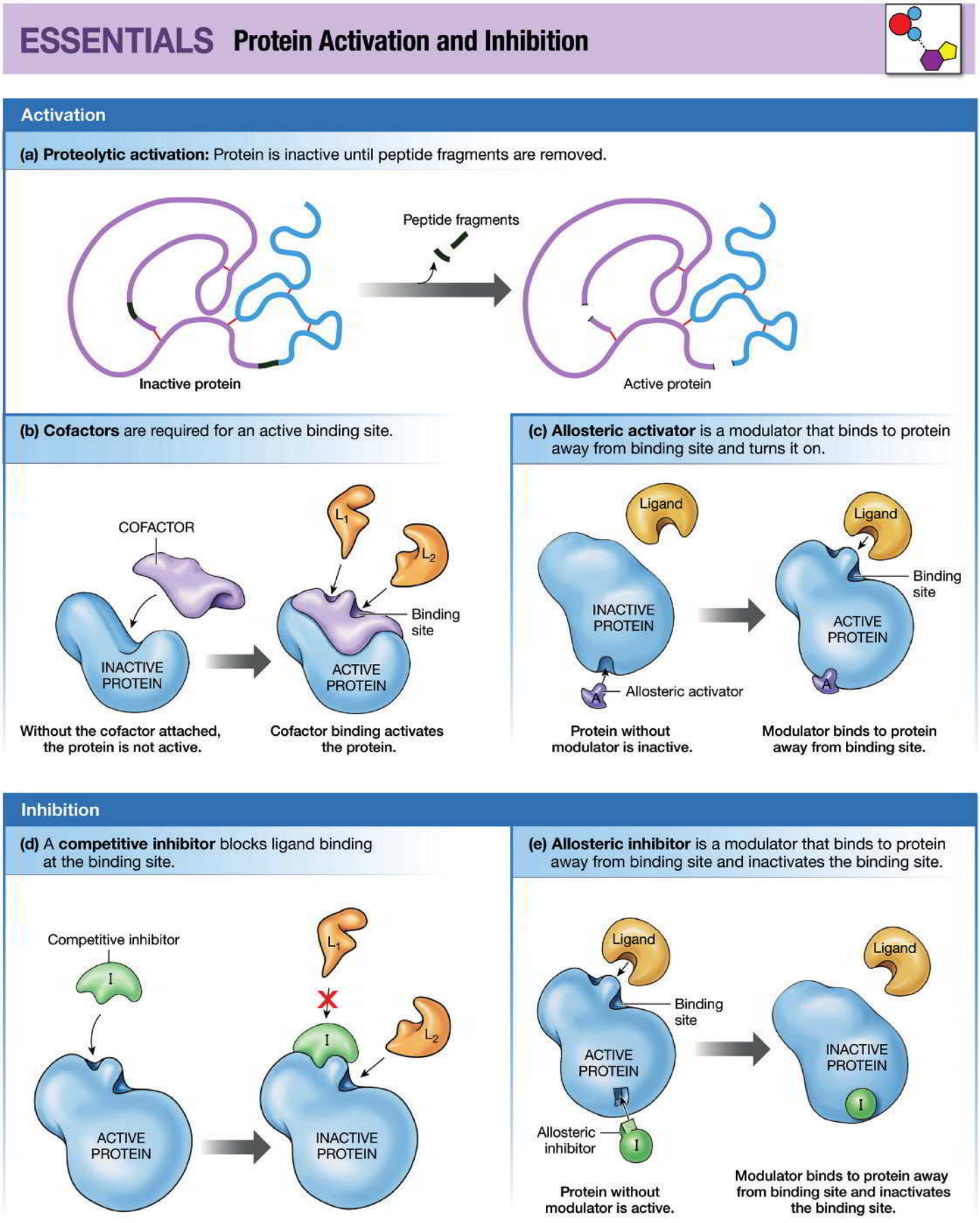
Inhibitors are chemical modulators that bind to a protein and decrease or stop its activity. The action of inhibitors may be reversible (competitive inhibitors) or irreversible (irreversible antagonists). **Competitive inhibitors** are reversible antagonists that compete with the typical ligand for the binding site (Fig. 2.12d). The degree of inhibition depends on the relative concentrations of the competitive inhibitor and the customary ligand, as well as on the protein's affinities for the ligand and inhibitor. The binding of competitive inhibitors is reversible: increasing the concentration of the customary ligand can displace the competitive inhibitor and decrease the inhibition.

Irreversible antagonists, on the other hand, bind tightly to the protein and cannot be displaced by competition. Antagonist drugs have proven useful for treating many conditions. For example, tamoxifen, an estrogen receptor antagonist, is used in the treatment of hormone-dependent cancers of the breast.

Allosteric modulators {*allos*, other + *stereos*, solid (as a shape)} bind to a protein at a regulatory site away from the binding site, and by doing so change the shape of the binding site. The effects of allosteric modulators may be reversible or irreversible. *Allosteric inhibitors* are antagonists that decrease the affinity of the binding site for the ligand and inhibit protein activity (Fig. 2.12e). *Allosteric activators* increase the probability of protein-ligand binding and enhance protein activity (Fig. 2.12c). For example, the oxygen-binding ability of hemoglobin changes with allosteric modulation by carbon dioxide, H^+ and several other factors [Fig. 19.9].

Covalent modulators are atoms or functional groups that bind covalently to proteins and alter the proteins' properties. Like allosteric modulators, covalent modulators may either increase or decrease a protein's binding ability or its activity. One of the most common covalent modulators is the phosphate group. Many proteins in the cell are activated or inactivated when a phosphate group forms a covalent bond with them, a process known as

Fig. 2.12 ESSENTIALS Protein Activation and Inhibition



phosphorylation. Phosphorylation can be reversed by enzymes that break the covalent bond.

One of the best known covalent inhibitor drugs is the antibiotic penicillin. Alexander Fleming discovered this compound in 1928, when he noticed that *Penicillium* mold inhibited bacterial growth in a petri dish. By 1938, researchers had extracted the active ingredient penicillin from the mold and used it to treat infections in humans. But it was not until 1965 that researchers figured out exactly how the antibiotic works. Penicillin is an irreversible antagonist that binds covalently to a key bacterial protein by mimicking the normal ligand. Because penicillin forms unbreakable bonds with the protein, the protein is irreversibly inhibited. Without the protein, the bacterium is unable to make a rigid cell wall. Without a rigid cell wall, the bacterium swells, ruptures, and dies.

Physical Factors

Physical conditions such as temperature and pH (acidity) can have dramatic effects on protein structure and function. Small changes in pH or temperature act as modulators to increase or decrease the activity of proteins such as enzymes (**FIG. 2.13a**). However, once these physical factors exceed some critical value, they disrupt the noncovalent bonds holding the protein in its tertiary conformation. The protein loses its shape and, along with that, its activity. When the protein loses its conformation, it is said to be *denatured*.

If you have ever fried an egg, you have watched this transformation happen to the egg white proteins as they change from a slithery clear state to a firm white state. Hydrogen ions in high enough concentration to be called acids have a similar effect on protein structure. During preparation of ceviche, a popular dish in several Latin American countries, raw fish is marinated in lime juice. The acidic lime juice contains hydrogen ions that disrupt hydrogen bonds in the muscle proteins of the fish, causing the proteins to become denatured. As a result, the meat becomes firmer and opaque, just as it would if it were cooked with heat.

In a few cases, protein activity can be restored if the original temperature or pH returns. The protein then resumes its original shape as if nothing had happened. Usually, however, denaturation produces a permanent loss of activity. There is certainly no way to unfry an egg or uncook a piece of fish. The potentially disastrous influence of temperature and pH on proteins is one reason these variables are so closely regulated by the body.

Concept Check

15. Match each chemical to its action(s).

(a) Allosteric modulator	**1.** Bind away from the binding site
(b) Competitive inhibitor	**2.** Bind to the binding site
(c) Covalent modulator	**3.** Inhibit activity only
	4. Inhibit or enhance activity

The Body Regulates the Amount of Protein in Cells

The final characteristic of proteins in the human body is that the amount of a given protein varies over time, often in a regulated fashion. The body has mechanisms that enable it to monitor whether it needs more or less of certain proteins. Complex signaling pathways, many of which themselves involve proteins, direct particular cells to make new proteins or to break down (*degrade*) existing proteins. This programmed production of new proteins (receptors, enzymes, and membrane transporters, in particular) is called **up-regulation.** Conversely, the programmed removal of proteins is called **down-regulation.** In both instances, the cell is directed to make or remove proteins to alter its response.

The amount of protein present in a cell has a direct influence on the magnitude of the cell's response. For example, the graph in Figure 2.13b shows the results of an experiment in which the amount of ligand is held constant while the amount of protein is varied. As the graph shows, an increase in the amount of protein present causes an increase in the response.

As an analogy, think of the checkout lines in a supermarket. Imagine that each cashier is an enzyme, the waiting customers are ligand molecules, and people leaving the store with their purchases are products. One hundred customers can be checked out faster when there are 25 lines open than when there are only 10 lines. Likewise, in an enzymatic reaction, the presence of more protein molecules (enzyme) means that more binding sites are available to interact with the ligand molecules. As a result, the ligands are converted to products more rapidly.

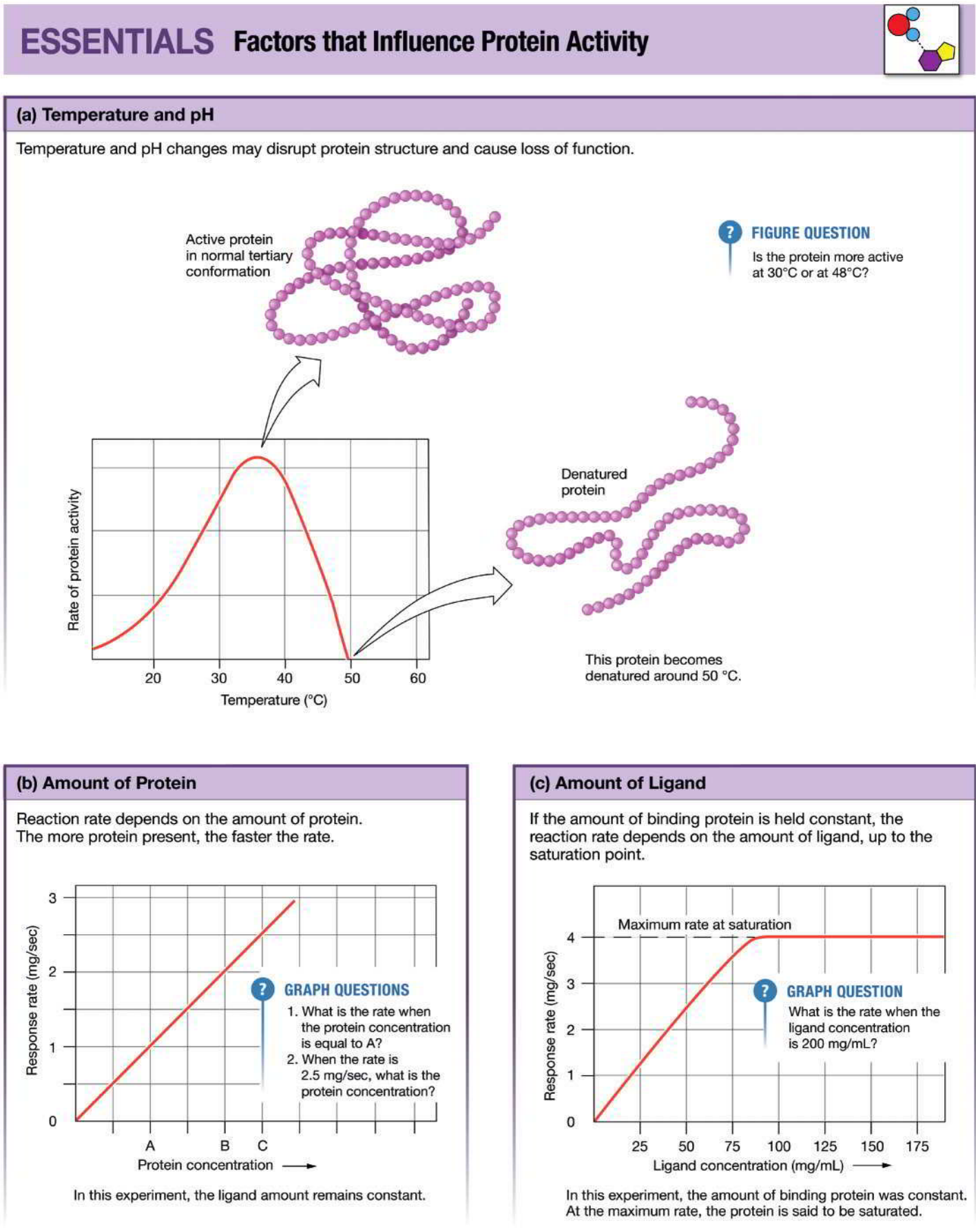
Regulating protein concentration is an important strategy that cells use to control their physiological processes. Cells alter the amount of a protein by influencing both its synthesis and its breakdown. If protein synthesis exceeds breakdown, protein accumulates and the reaction rate increases. If protein breakdown exceeds synthesis, the amount of protein decreases, as does the reaction rate. Even when the amount of protein is constant, there is still a steady turnover of protein molecules.

Reaction Rate Can Reach a Maximum

If the concentration of a protein in a cell is constant, then the concentration of the ligand determines the magnitude of the response. Fewer ligands activate fewer proteins, and the response is low. As ligand concentrations increase, so does the magnitude of the response, up to a maximum where all protein binding sites are occupied.

Figure 2.13c shows the results of a typical experiment in which the protein concentration is constant but the concentration of ligand varies. At low ligand concentrations, the response rate is directly proportional to the ligand concentration. Once the concentration of ligand molecules exceeds a certain level, the protein molecules have no more free binding sites. The proteins are fully occupied, and the rate reaches a maximum value. This condition is known as **saturation.** Saturation applies to enzymes, membrane transporters, receptors, binding proteins, and immunoglobulins.

Fig. 2.13 ESSENTIALS Factors That Influence Protein Activity



An analogy to saturation appeared in the early days of television on the *I Love Lucy* show and can be viewed today by searching YouTube (https://www.youtube.com/watch?v=AnHiAWlrYQc). Lucille Ball's character was working at the conveyor belt of a candy factory, wrapping chocolates to go into a candy box. Initially, the belt moved slowly, and she had no difficulty wrapping the candy. Gradually, the belt brought candy to her more rapidly, and she had to increase her wrapping speed to keep up. Finally, the belt brought candy to her so fast that she could not wrap it all because she was working at her maximum rate. That was Lucy's saturation point.

In conclusion, you have now learned about the important and nearly universal properties of proteins: shape-function relationships, ligand binding, specificity, competition, activation/inhibition, and saturation. You will revisit these concepts many times as you work through the organ systems of the body.

Concept Check

16. What happens to the rate of an enzymatic reaction as the amount of enzyme present decreases?
17. What happens to the rate of an enzymatic reaction when the enzyme has reached saturation?

Running Problem 2.7 Conclusion: Chromium Supplements

In this running problem, you learned that claims of chromium picolinate's ability to enhance muscle mass have not been supported by evidence from controlled scientific experiments. You also learned that studies suggest that the biological trivalent form of chromium may damage cells. In 2022 the NIH *Chromium Fact Sheet for Health Professionals*[5] says evidence indicates chromium may not be an essential nutrient as previously believed and there is insufficient research at this time to support its use as a nutritional supplement. Now compare your answers with those in the summary table.

Question	Facts	Integration and Analysis
Q1: *What is chromium's atomic number? Atomic mass? How many electrons does one atom of chromium have?*	Reading from the table, chromium (Cr) has an atomic number of 24 and an average atomic mass of 52. Atomic number is the number of protons in one atom. An atom has equal numbers of protons and electrons.	The atomic number of chromium is 24; therefore, one atom of chromium has 24 protons and 24 electrons.
Q2: *Which elements close to chromium are also essential elements?*	Molybdenum, manganese, and iron.	N/A
Q3: *If people have chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*	Chromium helps move glucose from blood into cells.	If chromium is absent or lacking, less glucose would leave the blood and blood glucose would be higher than normal.
Q4: *From the result of the Chinese study, can you conclude that all people with diabetes suffer from chromium deficiency?*	Higher doses of chromium supplements lowered elevated blood glucose levels, but lower doses have no effect. This is only one study, and no information is given about similar studies elsewhere.	We have insufficient evidence from the information presented to draw a conclusion about the role of chromium deficiency in diabetes.
Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*	For each electron lost from an ion, a positively charged proton is left behind in the nucleus of the ion.	The hexavalent ion of chromium, Cr^{6+}, has six unmatched protons and therefore has lost six electrons. The trivalent ion, Cr^{3+}, has lost three electrons.
Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*	The hexavalent form is used in industry and, when inhaled, has been linked to an increased risk of lung cancer. Enough studies have shown an association that California's Hazard Evaluation System and Information Service has issued warnings to chromium workers. Evidence to date for toxicity of trivalent chromium in chromium picolinate comes from studies done on isolated cells in tissue culture.	Although the toxicity of Cr^{6+} is well established, the toxicity of Cr^{3+} has not been conclusively determined. Studies performed on cells in vitro may not be applicable to humans. Additional studies need to be performed in which animals are given reasonable doses of chromium picolinate for an extended period of time.
Q7: *Based on the study that did not support enhanced muscle development from chromium supplements and the studies that suggest that chromium picolinate might cause cancer, do you think Malik should continue taking picolinate?*	No research evidence supports a role for chromium picolinate in increasing muscle mass or strength in humans. Other research suggests that chromium picolinate may cause cancerous changes in isolated cells.	The evidence presented suggests that for Malik, there is no benefit from taking chromium picolinate, and there may be risks. Using risk–benefit analysis, the evidence supports stopping the supplements. However, the decision is Malik's personal responsibility. He should keep himself informed of new developments that would change the risk–benefit analysis.

Chemistry Review Quiz

Use this quiz to see what areas of chemistry and basic biochemistry you might need to review. The title above each set of questions refers to a review figure on this topic. Answers are in Appendix A.

Atoms and Molecules (Fig. 2.5)

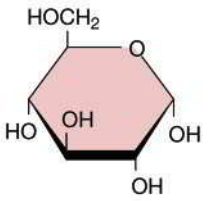
Match each subatomic particle in the left column with all the phrases in the right column that describe it. A phrase may be used more than once.

1. electron	(a) one has atomic mass of 1 amu
2. neutron	(b) found in the nucleus
3. proton	(c) negatively charged
	(d) changing the number of these in an atom creates a new element
	(e) adding or losing these makes an atom into an ion
	(f) gain or loss of these makes an isotope of the same element
	(g) determine(s) an element's atomic number
	(h) contribute(s) to an element's atomic mass

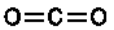
4. Isotopes of an element have the same number of _____ and _____, but differ in their number of _____. Unstable isotopes emit energy called _____.
5. Name the element associated with each of these symbols: C, O, N, and H.
6. Write the one- or two-letter symbol for each of these elements: phosphorus, potassium, sodium, sulfur, calcium, and chlorine.
7. Use the periodic table of the elements to answer the following questions:
   (a) Which element has 30 protons?
   (b) How many electrons are in one atom of calcium?
   (c) Find the atomic number and average atomic mass of iodine.
   (d) What is the letter symbol for iodine?
8. A magnesium ion, Mg^{2+}, has (*gained/lost*) two (*protons/ neutrons/ electrons*).
9. H^+ is also called a proton. Why is it given that name?
10. Use the periodic table of the elements to answer the following questions about an atom of sodium.
    (a) How many electrons does the atom have?
    (b) What is the electrical charge of the atom?
    (c) How many neutrons does the average atom have?
    (d) If this atom loses one electron, it would be called a(n) *anion/cation*.
    (e) What would be the electrical charge of the substance formed in (d)?
    (f) Write the chemical symbol for the ion referred to in (d).
    (g) What does the sodium atom become if it loses a proton from its nucleus?
    (h) Write the chemical symbol for the atom referred to in (g).

11. Write the chemical formulas for each molecule depicted. Calculate the molecular weight of each molecule.

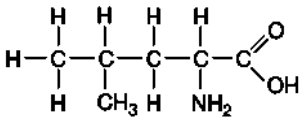
(a)



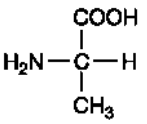
(b)



(c)



(d)



Lipids (Fig. 2.1)

12. Match each lipid with its best description.

(a) triglyceride	**1. most common form of lipid in the body**
(b) eicosanoid	**2. liquid at room temperature, usually from plants**
(c) steroid	**3. important component of cell membrane**
(d) oil	**4. structure composed of carbon rings**
(e) phospholipids	**5. modified 20-carbon fatty acid**

13. Use the chemical formulas given to decide which of the following fatty acids is most **unsaturated**:
    (a) $C_{18}H_{36}O_2C_{18}H_{36}O_2$
    (b) $C_{18}H_{34}O_2$
    (c) $C_{18}H_{30}O_2$

Carbohydrates (Fig. 2.2)

14. Match each carbohydrate with its description.

(a) starch	1. monosaccharide
(b) chitin	2. disaccharide, found in milk
(c) glucose	3. storage form of glucose for animals
(d) lactose	4. storage form of glucose for plants
(e) glycogen	5. structural polysaccharide of invertebrates

Proteins (Fig. 2.3)

15. Match these terms pertaining to proteins and amino acids:

(a) the building blocks of proteins	1. essential amino acids
(b) must be included in our diet	2. primary structure
(c) protein catalysts that speed the rate of chemical reactions	3. amino acids
	4. globular proteins
(d) sequence of amino acids in a protein	5. enzymes
(e) protein chains folded into a ball-shaped structure	6. tertiary structure
	7. fibrous proteins

16. What aspect of protein structure allows proteins to have more versatility than lipids or carbohydrates?
17. Peptide bonds form when the _____ group of one amino acid joins the _____ of another amino acid.

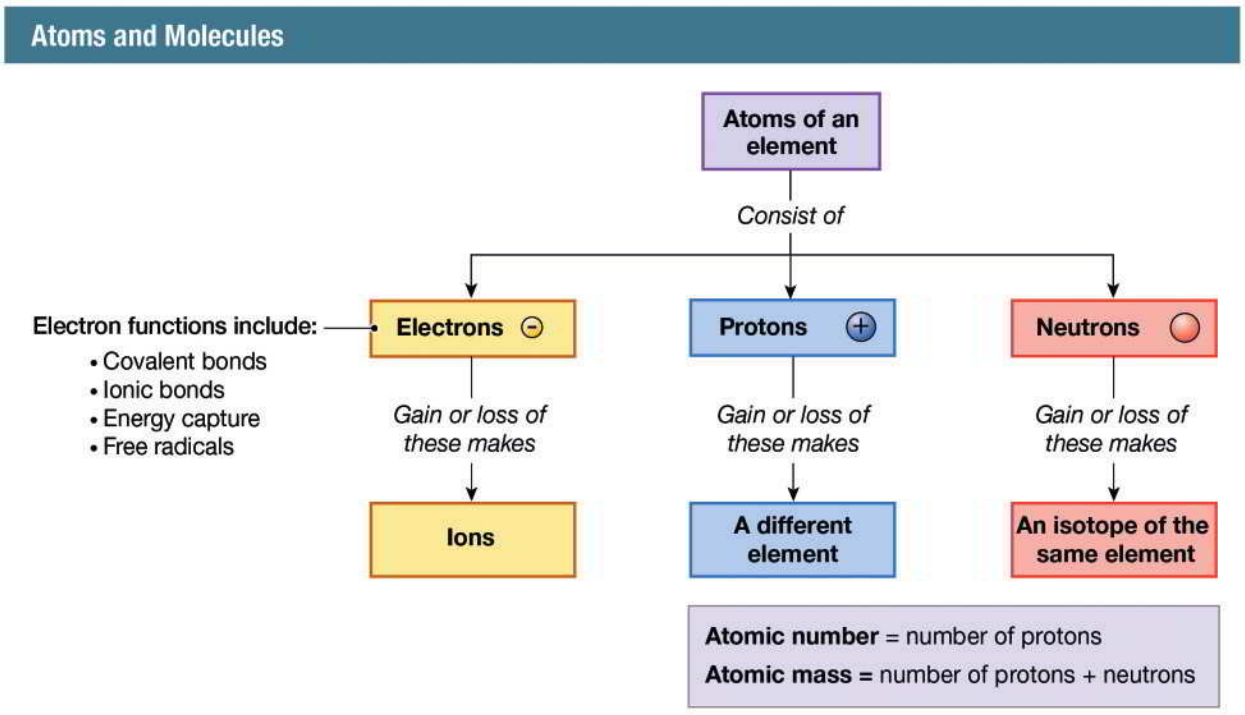
Nucleotides (Fig. 2.4)

18. List the three components of a nucleotide.
19. Compare the structure of DNA with that of RNA.
20. Distinguish between purines and pyrimidines.

Chapter Summary

This chapter has focused on the core concept of molecular interactions. Key ideas that will occur repeatediy in your study of physiology include:

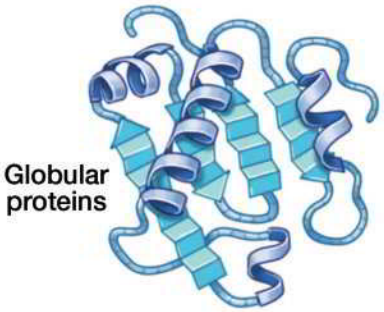
- The four main classes of **biomolecules**, their building blocks and variations. Fig. 2.1-2.4
- Key elements, **functional groups**, and **ions**. Tbl. 2.1, 2.2, Fig. 2.5
- The importance of **noncovalent interactions** in molecular shape and **solubility**. Fig. 2.6, 2.8
- **Solutions** and how to express concentration. Fig. 2.7
- Acids, bases, and **pH** Fig. 2.9
- The importance of **protein binding interactions** that play a role in nearly every physiological process. Fig. 2.8, 2.10



Functional Categories of Proteins

- Enzymes
- Membrane transporters
- Signal molecules
- Receptors
- Binding proteins
- Immunoglobulins
- Molecular motors
- Structural proteins
- Regulatory proteins

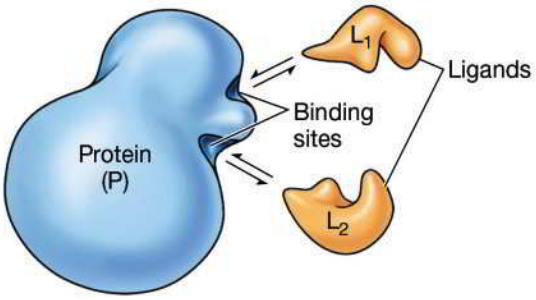
Fibrous proteins

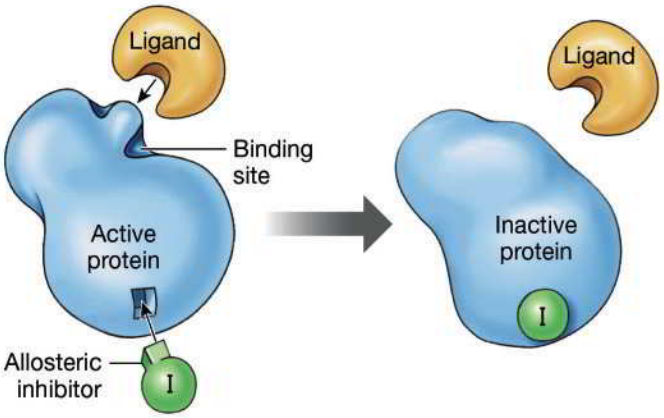


Protein Binding Interactions

Proteins (P) bind to Ligands (L)

$P + L \rightleftharpoons PL$

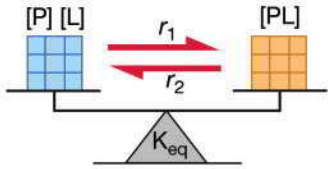




Protein binding demonstrates:

- **Specificity** and **affinity** for ligands
  - **Isoforms** of proteins
- **Competition** for the binding site
  - From **agonists**
  - From **antagonists** (competitive inhibitors)
- **Modulation** Fig. 2.12, 2.13
  - Activate, enhance, or inhibit
  - Reversible or irreversible
  - Noncovalent interaction or covalent bonding
  - At binding site or allosteric
  - Molecular or temperature, pH

Law of Mass Action Fig. 2.11



Rate of reaction in forward direction (r_1) = Rate of reaction in reverse direction (r_2)

At equilibrium

Equilibrium Constant K_{eq}

$$K_{eq} = \frac{[PL]}{[P]\,[L]}$$

Larger K_{eq} means higher affinity of the protein for the ligand.

Links to Resources

[1]DM Stearns *et al*. Chromium(III) picolinate produces chromosome damage in Chinese hamster ovary cells. *FASEB J* 9: 1643–1648, 1995. *https://doi.org/10.1096/fasebj.9.15.8529845*

[2]DM Stearns *et al*. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. *Mutat Res Genet Toxicol Environ Mutagen* 513: 135–142, 2002.*https://doi.org/10.1016/S1383-5718(01)00301-1*

[3]The reciprocal of the equilibrium constant is called the **dissociation constant** (K_d).

$$K_d = \frac{[P][L]}{[PL]}$$

A large K_d indicates low binding affinity of the protein for the ligand, with more P and L remaining in the unbound state. Conversely, a small K_d indicates higher protein affinity for the ligand.

[4]MA Hallmark *et al*. Effects of chromium and resistive training on muscle strength and body composition. *Med Sci Sports Exerc* 28(1):139–144,1996.*https://doi.org/10.1097/00005768-199601000-00025*

[5]National Institutes of Health (NIH) Office of Dietary Supplements (ODS). *Chromium: Fact sheet for health professionals*. 2022. *https://ods.od.nih.gov/factsheets/Chromium-HealthProfessional/*

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. List the four kinds of biomolecules. Give an example of each kind that is relevant to physiology.
2. True or false? All organic molecules are biomolecules.
3. When atoms bind tightly to one another, such as H_2O or O_2, one unit is called a(n) _____.
4. An atom of carbon has four unpaired electrons in an outer shell with space for eight electrons. How many covalent bonds will one carbon atom form with other atoms?
5. Fill in the blanks with the correct bond type.

   In a(n) _____ bond, electrons are shared between atoms. If the electrons are attracted more strongly to one atom than to the other, the molecule is said to be a(n) _____ molecule. If the electrons are evenly shared, the molecule is said to be a(n) _____ molecule.
6. Name two elements whose presence contributes to a molecule becoming a polar molecule.
7. Based on what you know from experience about the tendency of the following substances to dissolve in water, predict whether they are polar or nonpolar molecules: table sugar, vegetable oil.
8. A negatively charged ion is called a(n) _____, and a positively charged ion is called a(n) _____.
9. Define the pH of a solution. If pH is less than 7, the solution is _____; if pH is greater than 7, the solution is _____.
10. A molecule that moderates changes in pH is called a _____.
11. Proteins combined with fats are called _____, and proteins combined with carbohydrates are called _____.
12. A molecule that binds to another molecule is called a(n) _____.
13. Match these definitions with their terms (not all terms are used):

(a) the ability of a protein to bind one molecule but not another	1. irreversible inhibition
(b) the part of a protein molecule that binds the ligand	2. induced fit
(c) the ability of a protein to alter shape as it binds a ligand	3. binding site
	4. specificity
	5. saturation

14. An ion, such as Ca^{2+} or Mg^{2+}, that must be present in order for an enzyme to work is called a(n) _____.
15. A protein whose structure is altered to the point that its activity is destroyed is said to be _____.

Level Two Reviewing Concepts

16. Mapping exercise: Make the list of terms into a map describing solutions.

• concentration	• nonpolar molecule
• equivalent	• polar molecule
• hydrogen bond	• solubility
• hydrophilic	• solute
• hydrophobic	• solvent
• molarity	• water
• mole	

17. A solution in which $[H^+] = 10^{-3}$ M is (acidic/basic), whereas a solution in which $[H^+] = 10^{-10}$ M is (acidic/basic). Give the pH for each of these solutions.
18. Name three nucleotides or nucleic acids, and tell why each one is important.
19. You know that two soluble proteins are isoforms of each other. What can you predict about their structures, functions, and affinities for ligands?

20. You have been asked to design some drugs for the purposes described next. Choose the desirable characteristic(s) for each drug from the numbered list.

(a) Drug A must bind to an enzyme and enhance its activity.	1. antagonist
(b) Drug B should mimic the activity of a normal nervous system signal molecule.	2. competitive inhibitor
(c) Drug C should block the activity of a membrane receptor protein.	3. agonist
	4. allosteric activator
	5. covalent modulator

Level Three Problem Solving

21. You have been summoned to assist with the autopsy of an alien being whose remains have been brought to your lab. The chemical analysis returns with 33% C, 40% O, 4% H, 14% N, and 9% P. From this information, you conclude that the cells contain nucleotides, possibly even DNA or RNA. Your assistant is demanding that you tell him how you knew this. What do you tell him?

22. The harder a cell works, the more CO_2 it produces. CO_2 is carried in the blood according to the following equation:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

What effect does hard work by your muscle cells have on the pH of the blood?

Level Four Quantitative Problems

23. Calculate the amount of NaCl you would weigh out to make one liter of 0.9% NaCl. Explain how you would make a liter of this solution.

24. A 1.0 M NaCl solution contains 58.5 g of salt per liter.

a. How many molecules of NaCl are present in 1 L of this solution?

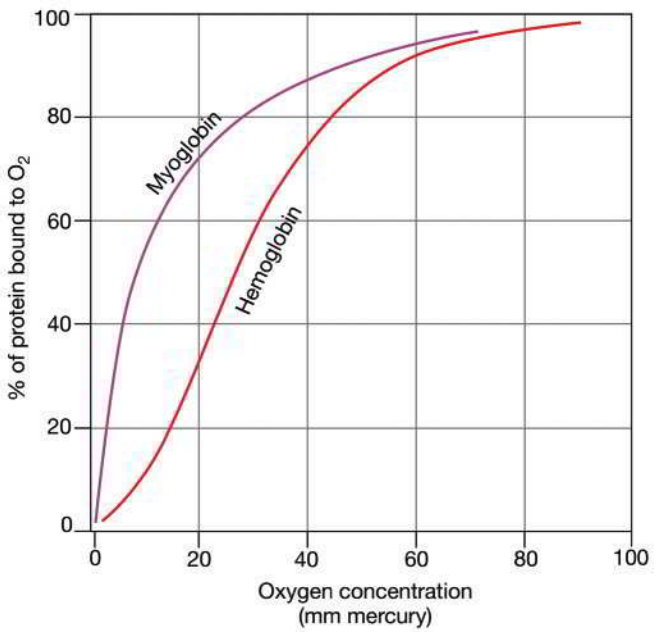
b. How many millimoles of NaCl are present?

c. How many **equivalents** of Na^+ are present?

d. Express 58.5 g of NaCl per liter as a **percent solution**.

25. How would you make 200 mL of a 10% glucose solution? Calculate the molarity of this solution. How many millimoles of glucose are present in 500 mL of this solution? (*Hint:* What is the molecular mass of glucose?)

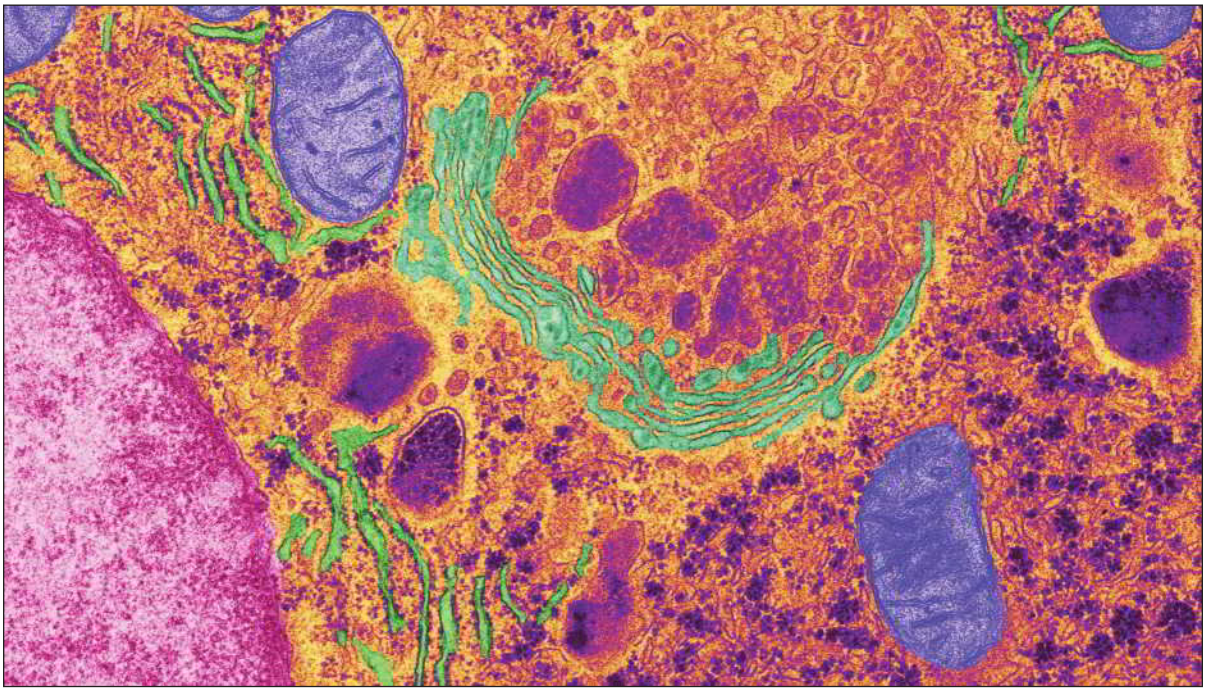
26. The graph shown below represents the binding of oxygen molecules (O_2) to two different proteins, myoglobin and hemoglobin, over a range of oxygen concentrations. Based on the graph, which protein has the higher affinity for oxygen? Explain your reasoning.



Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

3

Compartmentation: Cells and Tissues



Colored electron micrograph of liver organelles

Cells are organisms, and entire animals and plants are aggregates of these organisms.

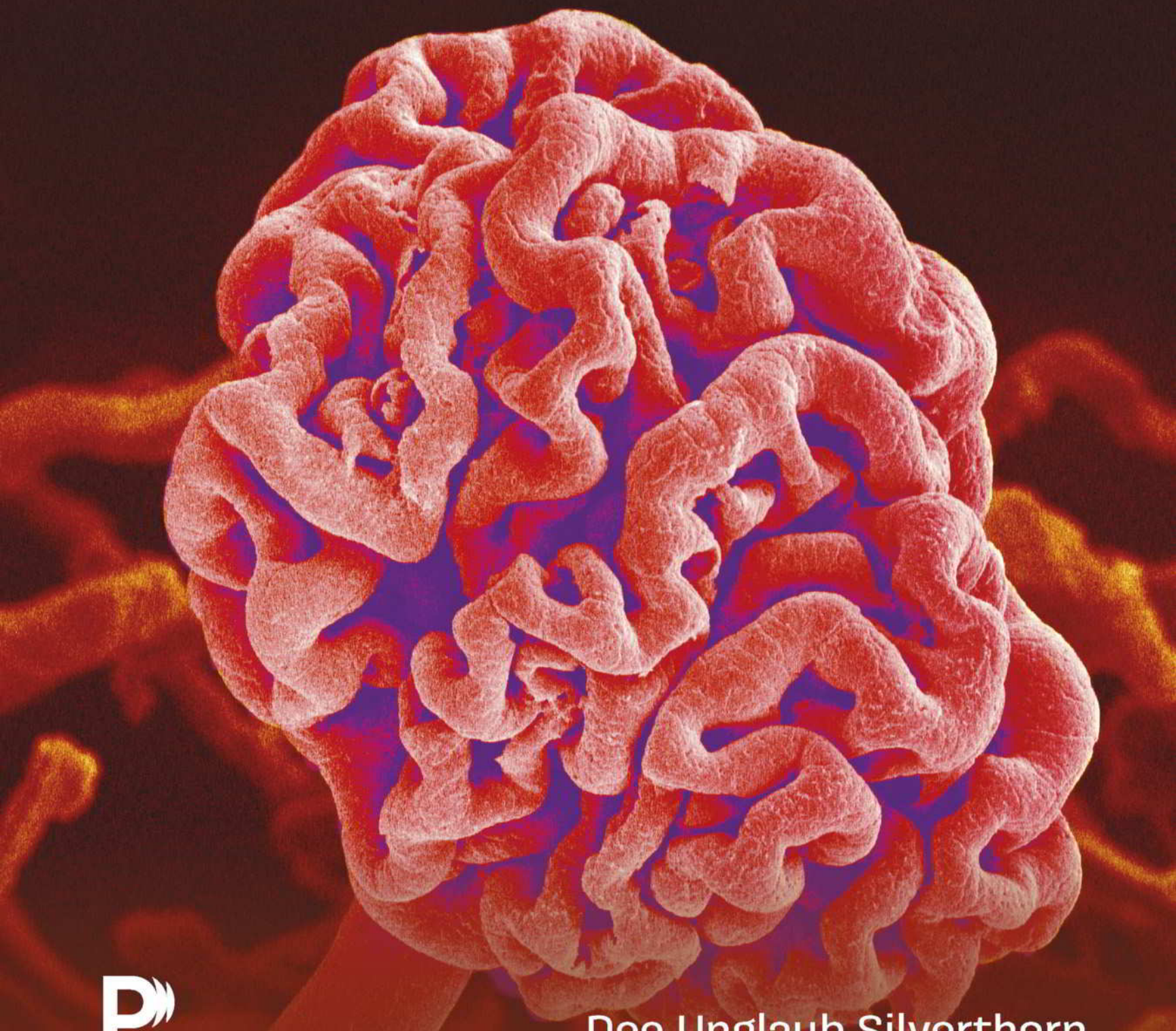
Theodor Schwann, 1839

This chapter focuses on the core concept of compartmentation. The human body has functional compartments at all levels of organization, from the large body cavities like the abdomen to nearly invisible compartments within cells. Compartments serve a vital function by allowing physiological and biochemical processes to be separated in space.

Compartmentation

HUMAN PHYSIOLOGY

AN INTEGRATED APPROACH NINTH EDITION



Dee Unglaub Silverthorn

This page intentionally left blank

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- **Bioflix:** Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- **Bioflix:** Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- **Bioflix:** Electron Transport System
- **Bioflix:** Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- **Physiology in Action:** Osmolarity and Tonicity

Module 5.2

- **A&P Flix:** Membrane Transport

Module 5.7

- **Physiology in Action:** Membrane Potential
- **A&P Flix:** Resting Membrane Potential

Chapter 5 Links to Resources

- **Interactive Physiology Animation:** Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- **Microbiology Animation:** Host Defenses

Module 7.3

- **Microbiology Animation:** Antigen Processing and Presentation: Overview

Module 7.7

- **Microbiology Animation:** Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- **Bioflix:** Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- **BioFlix:** How Synapses Work

Module 9.3

- **Interactive Physiology Animation:** Generation of an Action Potential
- **BioFlix:** Action Potential Conduction

Chapter 9 Links to Resources

- **Interactive Physiology 2.0 Animation:** Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- **Biointeractives:** Circadian Rhythms and the SCN

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

Module 12.2

- **A&P Flix:** The Cross Bridge Cycle

Chapter 13 Muscles

Module 13.1

- **A&P Flix:** The Cross Bridge Cycle
- **Interactive Physiology Animation:** Neuromuscular Junction
- **Interactive Physiology 2.0 Animation:** Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- **Interactive Physiology Animation:** Pathway of Blood through the Heart
- **Interactive Physiology Animation:** Action Potentials in Autorhythmic Cells

Module 15.4

- **Physiology in Action:** Electrocardiogram
- **Interactive Physiology Animation:** Intrinsic Conduction System of the Heart
- **Interactive Physiology Animation:** Cardiac Output

Chapter 15 Links to Resources

- **Interactive Physiology 2.0 Animation:** Electrical Activity of the Heart
- **Interactive Physiology 2.0 Animation:** Cardiac Cycle
- **Interactive Physiology 2.0 Animation:** Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- **Physiology in Action:** Orthostatic Hypotension
- **Interactive Physiology Animation:** Arterial Baroreceptor Reflex

Chapter 16 Links to Resources

- **Interactive Physiology Animation:** Factors Affecting Blood Pressure
- **Interactive Physiology 2.0 Animations:** Factors Affecting Blood Pressure

Chapter 18 Mechanics of Breathing

Module 18.3

- **Physiology in Action:** The Spirometer
- **Physiology in Action:** Subatmospheric Pleural Cavity
- **Physiology in Action:** Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- **BioFlix:** Gas Exchange
- **Physiology in Action:** Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- **Interactive Physiology 2.0 Animation:** Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- **Interactive Physiology Animation:** Glomerular Filtration

Module 20.6

- **Interactive Physiology 2.0 Animation:** Prox tubule Reabsorption & Secretion

Module 20.7

- **Physiology in Action:** Renal Clearance

Chapter 20 Links to Resources

- **Interactive Physiology 2.0 Animation:** Glomerular Filtration
- **Interactive Physiology Animation:** Anatomy Review: Urinary System
- **Interactive Physiology 2.0 Animation:** Tubular Reabsorption & Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- **Interactive Physiology Animation:** Aldosterone and ADH in Salt & Water Processing
- **Interactive Physiology Animation:** Mechanisms for Acid-Base Homeostasis
- **Interactive Physiology Animation:** Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- **Interactive Physiology Animation:** Anatomy Review
- **Interactive Physiology Animation:** Control of Digestion
- **Interactive Physiology Animation:** Digestive System Secretion
- **Interactive Physiology Animation:** Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- **Physiology in Action:** Blood Pressure and Exercise

Strategies for Success

Top Ten Ways to Succeed in Classes that Use Active Learning

By Marilla Svinicki, Ph.D., former Director of the University of Texas Center for Teaching Effectiveness

1. Make the switch from an authority-based conception of learning to a self-regulated conception of learning. Recognize and accept your own responsibility for learning.
2. Be willing to take risks and go beyond what is presented in class or the text.
3. Be able to tolerate ambiguity and frustration in the interest of understanding.
4. See errors as opportunities to learn rather than failures. Be willing to make mistakes in class or in study groups so that you can learn from them.
5. Engage in active listening to what's happening in class.
6. Trust the instructor's experience in designing class activities and participate willingly if not enthusiastically.
7. Be willing to express an opinion or hazard a guess.
8. Accept feedback in the spirit of learning rather than as a reflection of you as a person.
9. Prepare for class physically, mentally, and materially (do the reading, work the problems, etc.).
10. Provide support for your classmate's attempts to learn. The best way to learn something well is to teach it to someone who doesn't understand.

Dr. Dee's Eleventh Rule:
DON'T PANIC! Pushing yourself beyond the comfort zone is scary, but you have to do it in order to improve.

Word Roots for Physiology

Simplify physiology and medicine by learning Latin and Greek word roots. The list below has some of the most common ones.

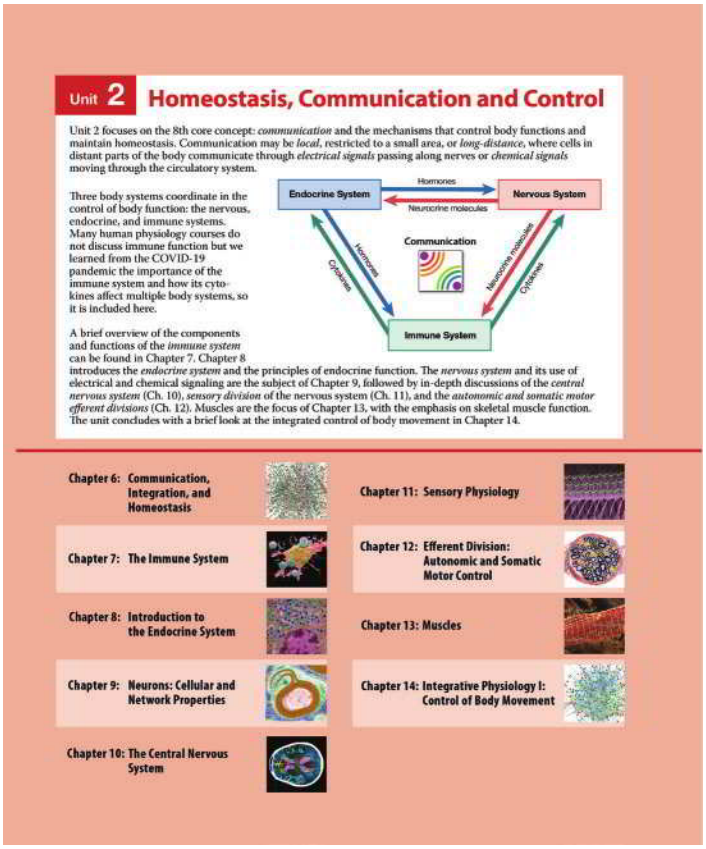
Using the list, can you figure out what *hyperkalemia* means?*

a- or **an-** without, absence
anti- against
-ase signifies an enzyme
auto self
bi- two
brady- slow
cardio- heart
cephalo- head
cerebro- brain
contra- against
-crine a secretion
crypt- hidden
cutan- skin
-cyte or **cyto-** cell
de- without, lacking
di- two
dys- difficult, faulty
-elle small
-emia in the blood
endo- inside or within
epi- over
erythro- red
exo- outside
extra- outside
gastro- stomach
-gen, -genie produce
gluco-, glyco- sugar or sweet
hemi- half
hemo- blood
hepato- liver
homo- same
hydro- water
hyper- above or excess
hypo- beneath or deficient
inter- between
intra- within
-itis inflammation of
kali- potassium
leuko- white
lipo- fat
lumen inside of a hollow tube
-lysis split apart or rupture
macro- large
micro- small
mono- one
multi- many
myo- muscle
oligo- little, few
para- near, close
patho-, -pathy related to disease
peri- around
poly- many
post- after
pre- before
pro- before
pseudo- false
re- again
retro- backward or behind
semi- half
sub- below
super- above, beyond
supra- above, on top of
tachy- rapid
trans- across, through

*Hyper = excess, kali = potassium, -emia = in the blood, or elevated blood potassium

Owner's Manual

Welcome to Human Physiology! As you begin your study of the human body, one of your main tasks will be to construct for yourself a global view of the body, its systems, and the many processes that keep the systems working. This "big picture" is what physiologists call the integration of systems, and it is a key theme in this book. To integrate information, however, you must do more than simply memorize it. You need to truly understand it and be able to use it to solve problems that you have never encountered before. If you are headed for a career in the health professions, you will do this in the clinics. If you plan a career in biology, you will solve problems in the laboratory, field, or classroom. Analyzing, synthesizing, and evaluating information are skills you need to develop while you are in school, and I hope that the features of this book will help you with this goal.



Pattern recognition is important for all healthcare professionals, so you can begin to develop this skill by learning the **core concepts of physiology** that repeat over and over as you study different organ systems. The core concepts are introduced in Unit 1, and each chapter begins with a brief summary of the core concepts in that chapter.

We have also retained the four approaches to learning physiology that proved so popular since this book was first published.

1. **Cellular and Molecular Physiology**
   Most physiological research today is being done at the cellular and molecular level, and there are constantly exciting developments in molecular medicine and physiology. For example, scientists have discovered a new method of cell-to-cell communication: exosomes and ectosomes. We are still learning how these extracellular vesicles play a role in health and disease. Look for similar links between molecular and cellular biology, physiology, and medicine throughout the book.

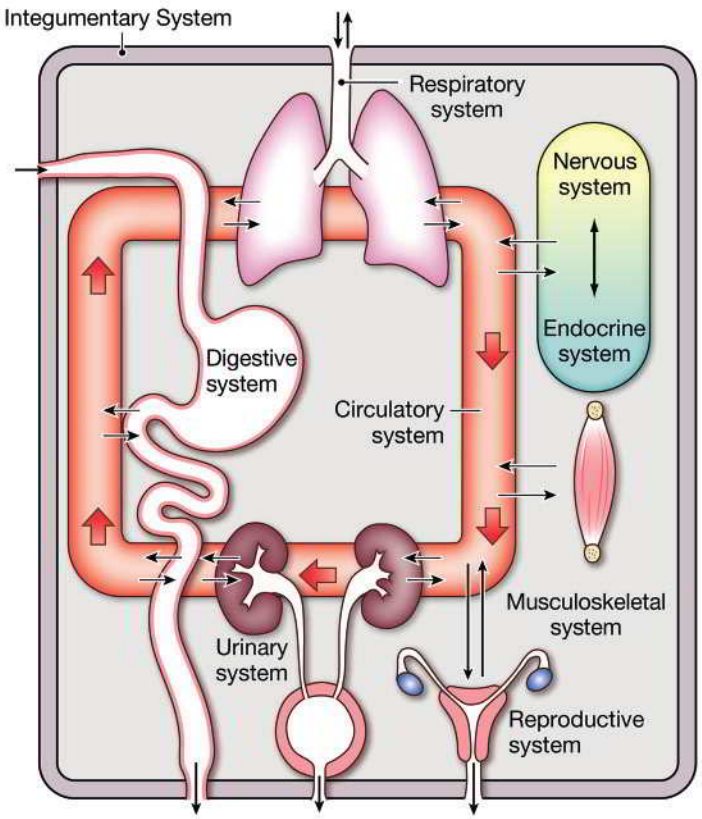
2. **Physiology is a Dynamic Field**
   Physiology is a dynamic discipline, with numerous unanswered questions that merit further investigation and research. Many of the "facts" presented in this text are really only our current theories, so you should be prepared to update your mental models as new information emerges from scientific research.

3. **Physiology is Integrative**
   The organ systems of the body do not work in isolation, although we study them one at a time. To emphasize the integrative nature of physiology, three chapters (Chapters 14, 21, and 25) focus on how the physiological processes of multiple organ systems coordinate with each other, especially when homeostasis is challenged.

4. **A Focus on Problem Solving**
   One of the most valuable life skills all students should acquire is the ability to think critically and use information to solve problems. As you study physiology, you should be prepared to practice these skills. You will find a number of "test yourself" questions designed to challenge your critical thinking and analysis skills.

One of my aims is to provide you not only with information about how the human body functions but also with tips for studying and problem solving. Many of these study aids have been developed with the input of my students, so I think you may find them particularly helpful. The list below is a brief tour of the special features of the book, especially those that you may not have encountered previously in textbooks. Please take a few minutes to read about them so that you can make optimum use of the book as you study.

- **Learning Outcomes** on the chapter opening page list the key questions you should be able to answer by the end of the chapter.
- **Background Basics**, also on the chapter opening page, lists topics you will need to master for understanding the material that follows. The terms include links for review.
- **Anatomy Summaries** provide succinct visual overviews of a physiological system from a macro to micro perspective. Whether you are learning the anatomy for the first time or refreshing your memory, these summaries show you the essential features of each system in a single figure
- **Essentials and Review figures** occur throughout the book. These figures distill the basics about a topic onto one or two pages, much as the Anatomy Summaries do. My students tell me they find them particularly useful for review when there isn't time to go back and read all the text.
- **Reflex Pathways & Concept Maps** organize physiological processes and details into a logical, visual format. These figures use consistent colors and shapes to represent different steps, making it easier to understand complex physiological processes. Chapter 1 includes a special Focus On feature showing you how to do your own concept mapping.
- **Running Problems** in each chapter are clinical scenarios related to the chapter topic. Read the segments as you work through the text and see if you can answer the questions that ask you to apply what you're learning to the problem. Answers are in the summary table at the conclusion of the problem.



- **Figure Questions and Graph Questions** challenge you to apply visual literacy or data interpretation skills as you read an illustration, photo, or graph.
- **Concept Checks** are placed at intervals throughout the chapters, helping to test your understanding before continuing to the next topic. Click the interactive buttons to show the answer or get a hint.
- **Quick Reference to Integrated Media by Chapter** provides an easy reference to key animations and videos.
- The **Appendices** have answers to the end-of-chapter questions, as well as reviews of physics, logarithms, and basic genetics.
- The **Useful Resources** section of the eTextbook includes a periodic table of the elements, diagrams of anatomical positions of the body, tables with unit conversions. and normal values of blood components.

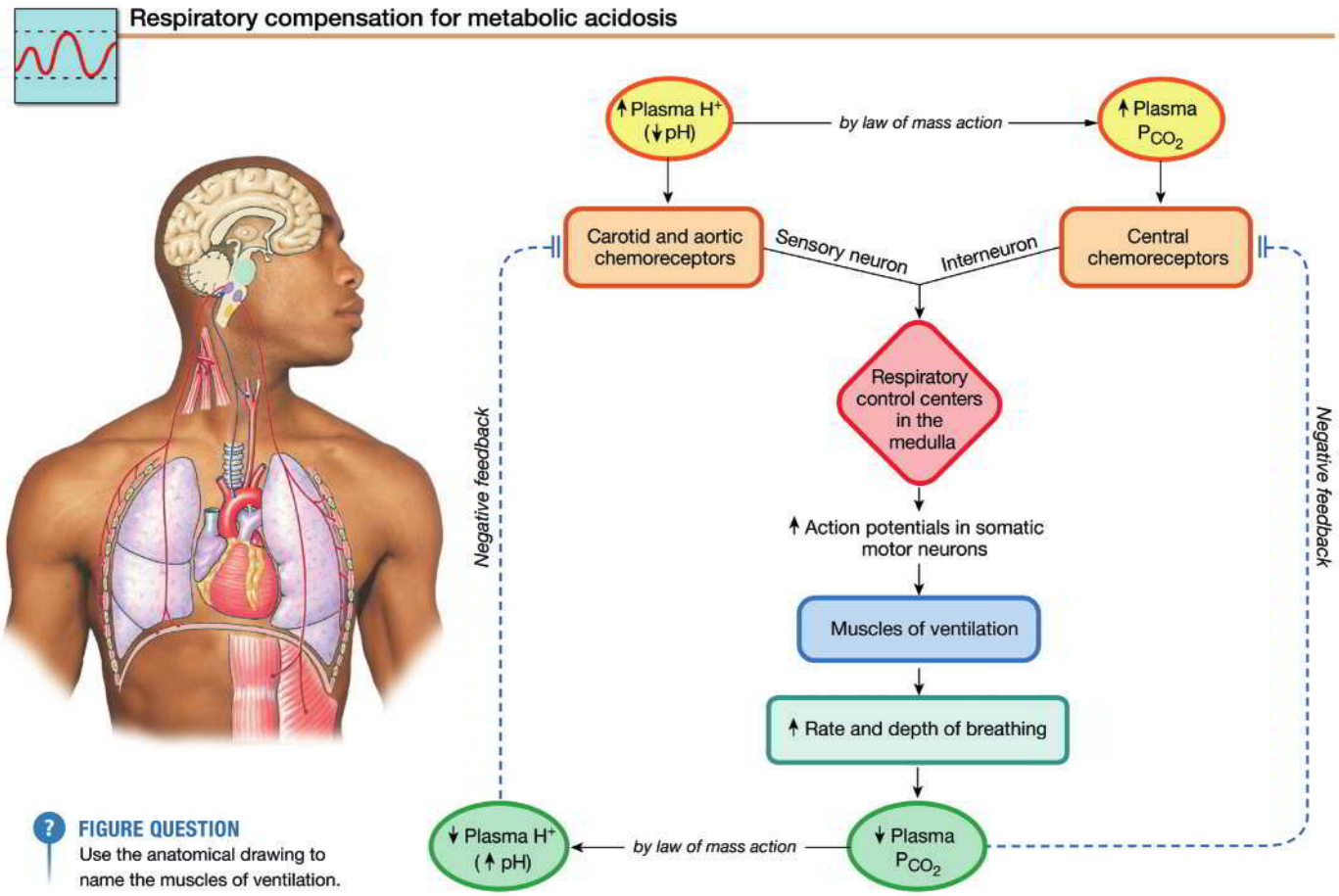
Take a few minutes to look at all these features so that you can make optimum use of them.

It is my hope that by using this book, you will develop an integrated view of physiology that allows you to enter your chosen profession with respect for the complexity of the human body and a clear vision of the potential of physiological and biomedical research. May you find physiology as fun and exciting I do. Good luck with your studies!

Warmest regards,

Dr. Dee (as my students call me)

silverthorn@utexas.edu



Human Physiology

An Integrated Approach

Ninth Edition

Dee Unglaub Silverthorn, Ph.D.
UNIVERSITY OF TEXAS, AUSTIN

with contributions by

Bruce R. Johnson, Ph.D.
CORNELL UNIVERSITY

Michael Chirillo, M.D., Ph.D.
UNIVERSITY OF RHODE ISLAND

and

William C. Ober, M.D.
ILLUSTRATION COORDINATOR

Claire E. Ober, R.N.
ILLUSTRATOR

Anita Impagliazzo
ILLUSTRATOR

Andrew C. Silverthorn, M.D.
CLINICAL CONSULTANT

Pearson

Content and Product Management: Michael Gillespie; Serina Beauparlant; Alexa Frank; Caroline Ayres; Ayushi Khandelwal
Content Production: Katie Foley; Titas Basu; Win Clark; Sharon Cahill; Francesca Monaco; Annamarie Boley, *Straive*; Kerri Tomasso, *Straive*; Rajesh Kumar Rajan, *Straive*; Carrie Keller, *Straive*; Krishnamurthy Muralidharan, *Straive*; Rebecca Marshall, *Lachina*; Molly Montanaro, *Lachina*; Cathryn Gear, *Lachina*; Lalitha Srinivasan, *Continual Engine*; Kani Kapoor, *Integra*
Product Marketing: Courtney Davis, Tim Galligan, Yez Alayan
Rights and Permissions: Ben Ferrini; Matthew Perry, *Straive*; Chenley Calites, *Straive*

Please contact www.AskPearsonSupport.com with any queries on this content.

Pearson puts care into the creation of our products. Our learning materials undergo content reviews to minimize bias and ensure the content is inclusive, accurate, and relevant. Please use this link to report instances of bias and inaccuracies: https://www.pearson.com/report-bias.html

You can learn more about Pearson's commitment to accessibility at https://www.pearson.com/us/accessibility.html

Cover Image by Susumu Nishinaga/Science Source.

Library of Congress Cataloging-in-Publication Data
Library of Congress Control Number: 2025938090

$PrintCode

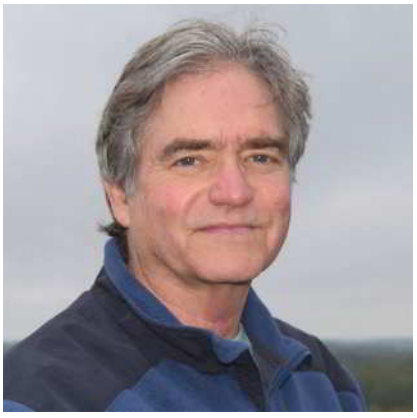
Pearson

ISBN 10: 0-135-31445-3
ISBN 13: 978-0-135-31445-6

About the Author

DEE UNGLAUB SILVERTHORN studied biology as an undergraduate at Newcomb College of Tulane University, where she did research on cockroaches. For graduate school, she switched to studying crabs and received a PhD in marine science from the Belle W. Baruch Institute for Marine and Coastal Sciences at the University of South Carolina. Her research interest is epithelial transport in systems ranging from the crab gill to the chick allantoic membrane. Dr. Dee has taught in a variety of settings, from medical schools (Medical University of South Carolina, Dell Medical School, UT-Austin) to high school. For most of her career, at the University of Texas–Austin, she has taught undergraduate and graduate physiology lectures and labs, and she trains graduate students to develop teaching skills in the life sciences. Dr. Dee has received numerous teaching awards and honors, including a UT System Regents' Outstanding Teaching Award, the American Physiological Society (APS) Arthur C. Guyton Physiology Educator of the Year, and multiple UT–Austin awards, including the Burnt Orange Apple Award. Dr. Dee is past-president of the APS (2022–23) and the Human Anatomy and Physiology Society (2012–2013). She has served as editor-in-chief of *Advances in Physiology Education*, and she is currently an associate editor. Dr. Dee works with members of the International Union of Physiological Sciences to improve physiology education globally, and this book has been translated into seven languages. Her free time is spent creating multimedia fiber art, gardening, and enjoying the Texas hill country with her husband, Andrew, and their dogs.

About the Contributors



Bruce Johnson, PhD is a Senior Lecturer in the Department of Neurobiology and Behavior at Cornell University. He earned biology degrees at Florida State University (BA), Florida Atlantic University (MS), and at the Marine Biological Laboratory in Woods Hole (PhD) through the Boston University Marine Program. He directs Cornell's Principles of Neurophysiology course that he joined in 1988, in which undergraduate and graduate students receive hands-on instruction in principles and methods of neurophysiology. He is a coauthor of *Crawdad: a CD-ROM Lab Manual for Neurophysiology* and the *Laboratory Manual for Physiology*. Bruce has directed and taught in faculty workshops for neuroscience laboratory teaching sponsored by NSF (Crawdad), ADInstruments (CrawFly), the Grass Foundation and the Faculty for Undergraduate Neuroscience (FUN). He has taught in international workshops and neuroscience courses at the Universities of Copenhagen (Denmark), Cologne (Germany), Ibadan (Nigeria), and the Marine Biological Laboratory. Bruce was named a Most Influential Faculty Member by the graduating senior class at Cornell and awarded the John M. and Emily B. Clark Award for Distinguished Teaching at Cornell. His other teaching awards include the FUN Educator of the Year Award, FUN Career Service Award, and he is a co-recipient of the 2016 Award for Education in Neuroscience, sponsored by the Society for Neuroscience. He is currently Senior Editor of the *Journal of Undergraduate Neuroscience Education*. Bruce's research addressed the cellular and synaptic mechanisms of motor network plasticity. His work now focuses on development of open-source neurophysiology and imaging equipment for laboratory teaching and research.

Michael Chirillo, MD, PhD is an assistant teaching professor at the University of Rhode Island in the College of the Environment and Life Sciences. He earned degrees in music performance (BM) at the College-Conservatory of Music at the University of Cincinnati and at the Butler School of Music at UT Austin (MM). He completed concurrent degrees in medicine (MD) at the McGovern Medical School in the Texas Medical Center in Houston and in neuroscience (PhD) at UT Austin. During his time as a doctoral student in Austin, Michael met and worked with Dr. Silverthorn on best teaching practices in the undergraduate physiology classroom. Following his internship in internal medicine-pediatrics at the University of Utah, he was awarded a Fulbright U.S. Scholar Grant to work with colleagues at the University of Belgrade in Serbia, investigating how to best incorporate core concepts of physiology into introductory courses. He frequently travels to southeastern Europe to continue this work.

About the Illustrators

William C. Ober, MD (*art coordinator and illustrator*) received his undergraduate degree from Washington and Lee University and his M.D. from the University of Virginia. He also studied in the Department of Art as Applied to Medicine at Johns Hopkins University. After graduation, Dr. Ober completed a residency in Family Practice and later was on the faculty at the University of Virginia in the Department of Family Medicine and in the Department of Sports Medicine. He also served as Chief of Medicine of Martha Jefferson Hospital in Charlottesville, VA. He most recently taught at Washington & Lee University, where he also led student trips to the Galapagos Islands. He was part of the Core Faculty at Shoals Marine Laboratory, where he taught Biological Illustration for 22 years. The textbooks illustrated by Medical & Scientific Illustration have won numerous design and illustration awards.

Claire E. Ober, RN (*illustrator*) practiced pediatric and obstetric nursing before turning to medical illustration as a full-time career. She returned to school at Mary Baldwin College where she received her degree with distinction in studio art. Following a five-year apprenticeship, she has worked as Dr. Ober's partner in Medical and Scientific Illustration since 1986. She was also on the Core Faculty at Shoals Marine Laboratory and co-taught Biological Illustration at both Shoals Marine Lab and at Washington and Lee University.

Anita Impagliazzo, MA is a medical and scientific illustrator in Howardsville, VA. She studied art and biology at the University of Virginia and obtained her graduate degree in biomedical illustration from University of Texas Southwestern Medical Center at Dallas in 1987. She has contributed to many textbooks, creates exhibits for medical malpractice cases, and illustrates current discoveries for research labs across the US.

About the Clinical Consultant

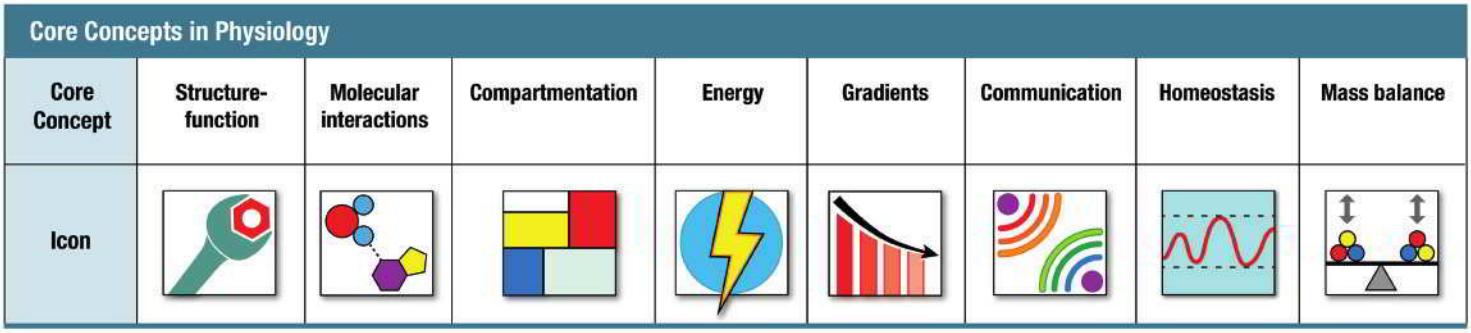
Andrew C. Silverthorn, MD is a graduate of the United States Military Academy (West Point). He served in the infantry in Vietnam, and upon his return entered medical school at the Medical University of South Carolina in Charleston. He was chief resident in family medicine at the University of Texas Medical Branch, Galveston, and is a family physician in solo practice in Austin, Texas. When Andrew is not busy with patients, he may be found on the golf course or playing with his two rescue dogs, Molly and Callie.

Dedication

I would like to dedicate this 9th edition to all the people who have worked out of the spotlight on different aspects of this book as it evolved through the years: physiologists, educators, and publishing professionals alike. A special thanks goes to two of my editors—DKB and AAR—for their vision and support.

New to this Edition

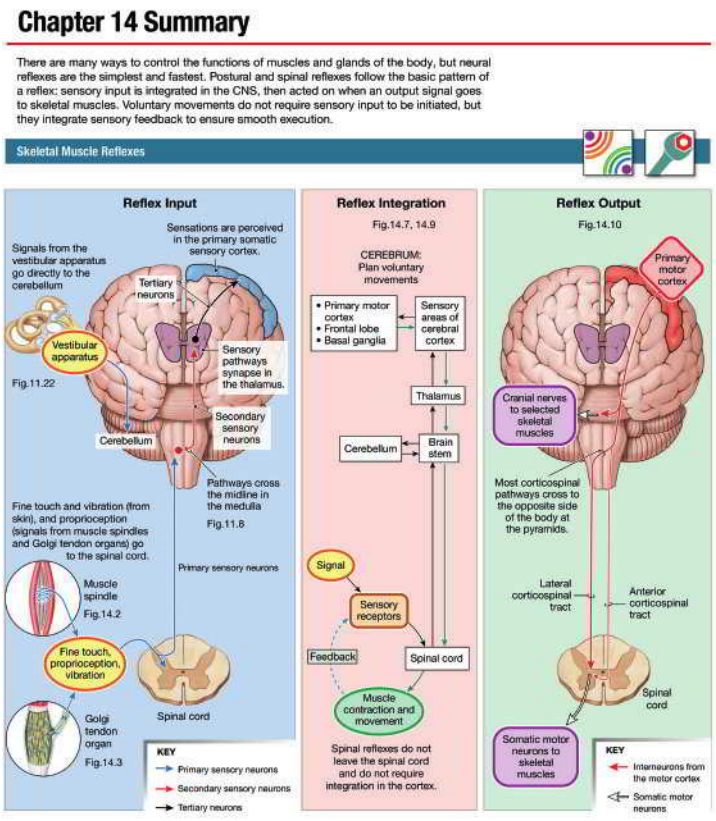
The Ninth Edition of *Human Physiology: An Integrated Approach* builds upon the thorough coverage of integrative and molecular physiology topics that have always been the foundation of this book. It has been nearly eight years since the last revision, and a lot has changed in the world of physiology and medicine, including the global SARS-CoV-2 pandemic. Studying the pathophysiology of COVID-19 made biomedical scientists aware of how the immune system influences body functions in ways we had not previously realized. In recognition of that fact, we have **promoted the immune system from Chapter 24 in the last edition to Chapter 7**, giving it new status as the third control system, coordinating with the nervous and endocrine systems through chemical signals.



The other major change in this edition is a focus throughout the book on the **core concepts of physiology**. The eight selected core concepts are introduced and discussed, along with their icons, in Unit 1, then become a unifying theme throughout the text. The four units in the book—Core Concepts in Physiology; Homeostasis, Communication, and Control; Integration of Function; and Metabolism, Growth, and Reproduction—are now introduced with a visual overview page that previews the unit's chapters. Each chapter begins with a brief introduction to the core concepts featured in that chapter. Core concept icons can be found on many pieces of art, challenging students to see if they can find the core concept represented in the art. Finally, the **text chapter summaries have been replaced with visual summaries**, many featuring new art, that review the key ideas covered in the chapter.

This edition was written to take advantage of the interactive features available only in the eTextbook. Answers to the Concept Checks and Figure and Graph questions are now visible with a click on the SHOW ANSWER button, as are HINTS. Key words have popup definitions, and the links for quick review of topics covered earlier in the book take you to that content. Short animations and the Physiology in Action videos featuring two of my early-career colleagues are embedded right in the eTextbook. Learn more about the other features of Pearson eTextbooks after the Owner's Manual.

Finally, when revising this book, we kept in mind the new **HAPS Physiology Learning Outcomes (PLOs) for Human Physiology**. *https://www.hapsweb.org/haps-learning-outcomes/haps-physiology-learning-outcomes/*. There can be tremendous variability in how introductory physiology is taught, so a **correlation guide** between this ninth edition's learning outcomes and the HAPS PLOs has been provided within the Instructor Resources. In addition, we reviewed the entire text and updated language to be more inclusive, following suggested guidelines from the U.S. National Institutes of Health and various biomedical and clinical societies. All art has been updated to reflect the latest WCAG guidelines to ensure our figures are fully accessible to all learners.



As always, the major focus of the book is to incorporate the latest findings from biomedical research and relate them to the physiology that is the basis for human health and disease. The list that follows highlights the new content in this ninth edition.

Chapter-by-Chapter Changes in the Ninth Edition

Chapter 1 Introduction to Physiology

- Revised themes into eight core concepts. Added gradients as a core concept
- New core concepts figure with icons
- Updated discussion of reflex loops
  - Adds open-loop and closed-loop control systems to address misconception that all reflexes are for homeostasis
  - Difference between regulated and controlled variables
- New table of 10 key regulated physiological variables
- New figure of homeostatic control system model with a regulated variable
- New Running Problem on searching for information about health benefits of probiotics; added artificial intelligence as a search method
- Updated
  - "Omics" box and added *multiomics*
  - Use of the word *normal*

Chapter 2 Molecular Interaction

- Updated research on chromium picolinate (Running Problem)
- Revised Section 2.3 on protein binding interactions
- Added *motor proteins* to protein function list

Chapter 3 Compartmentation: Cells and Tissues

- Added *transcellular compartments* to body compartmentation
- Section 3.3 on Cells updated and revised. New art and table in Fig. 3.4
  - Updated discussion on mitochondrial dynamics
  - Primary cilia moved from Emerging Topics box into the text
  - New topics: biomolecular condensates, proteasomes and ubiquitin
  - Clearly distinguished inclusions from nonmembranous organelles
- Section 3.4 Tissues
  - Clarification of difference between basal lamina and basement membrane
  - Added specialized epithelia as a sixth category
  - Added the ependyma to ciliated epithelia
- Section 3.5: Updated discussion on stem cells includes organoids and regenerative medicine

Chapter 4 Energy and Cellular Metabolism

- New figure on the electron transport system

Chapter 5 Membrane Dynamics

- Updated Section 5.5 on vesicular transport
  - Revised mechanisms: micropinocytosis, clathrin-dependent and -independent endocytosis
  - Extracellular vesicles: exosomes and ectosomes
  - New map of vesicular transport
- Added discussion of ectoenzymes
- Updated information on cystic fibrosis

Chapter 6 Communication, Integration, and Homeostasis

- Added immune system as the third control system
- Updated information on cytokines
- New figure showing neuro-endo-immune interactions
- Added extracellular vesicles to discussion and art

Chapter 7 The Immune System

This chapter was rewritten to focus on the immune system's role as a control system.

- Multiple figures were significantly revised. Added two new figures
- Updated ethnic distributions of blood types table
- Added information on:
  - Lifestyle-associated molecular patterns or LAMPs
  - Toll-like receptors (TLRs)
  - Pro-inflammatory cytokines
  - SARS-CoV-2, COVID-19, coronavirus

Chapter 8 Introduction to the Endocrine System

- Updated information on calcitonin gene-related peptide (CGRP) and migraine
- Updated information on oxytocin and autism

Chapter 9 Neurons: Cellular and Network Properties

- New introduction on undergraduate researchers and cone snail toxins
- Updated discussions and revised figures:
  - Neuron structure and function

- Channel activation and inactivation
- Axonal transport
- mRNA transport and neuronal protein synthesis
- Glial cell functions
- Types of neurotransmitter receptors (Tbl. 9.4)
- Signaling by gaseous signal molecules
- Mechanisms for LTP and LTD, including local protein synthesis in dendrites
- Plasticity

- Updated Try It! box on Venus flytrap action potential mechanism

Chapter 10 The Central Nervous System

- Moved glymphatics from Emerging Concepts box into the text
  - New art for blood-brain barrier
  - Paravascular CSF flow
- Note on changing terminology for CNS directions
- New section on mind-body interactions and psychoneuroimmunology
- Updated information on:
  - Alzheimer's
  - BRAIN initiative progress
  - Emergent properties
  - Evolution of electrical signaling
- Added:
  - Nonmotor functions of the cerebellum
  - Role of pericytes in control of cerebral blood flow
  - Associative learning doesn't require a brain

Chapter 11 Sensory Physiology

- New introduction to Meniere's Running Problem (astronaut Alan Shepard)
- New box on COVID-19 and loss of taste and smell
- Updated model of pain and nociception
  - Gate control theory of pain is no longer the current model
- Updated:
  - Sound transduction
  - Melanopsin and mRCG cells
  - Models for taste cell transduction
- Added:
  - Piezo cation channels and TRPV1 ion channels for somatic senses
  - 2021 Nobel Prize in Physiology or Medicine for sensory receptors
  - Intrinsically photosensitive retinal ganglion cell (ipRGC)
  - Blood-retinal barrier

Chapter 12 Efferent Division: Autonomic and Somatic Motor Control

- Expanded somatic motor disorders
  - Myasthenia gravis
  - Poliomyelitis
  - Lambert-Eaton myasthenic syndrome
- Transcutaneous vagal nerve stimulation in medicine
- Updated information on nicotine addiction to include vaping and recent statistics

Chapter 13 Muscles

- Changed sliding filament theory to sliding filament mechanism
- Updated information about myosin family of proteins
- Updated figure of muscle fiber mitochondrial anatomy
- Introduced new theories:
  - Role of titin in muscle contraction
  - Branching of sarcomeres
  - Myosin activation in sliding filament mechanism

Chapter 14 Integrative Physiology I: Control of Body Movement

- Revised discussion of proprioception
  - Updated functions of spindles, joint receptors, Golgi tendon organs
  - Add Piezo2 ion channels
- Updated information on deep brain stimulation for Parkinson's
- New examples of innate reflexes
- Clinical applications of reflex testing

Chapter 15 Cardiovascular Physiology

- New title for Section 15.2 Core Concept: Gradients and Flow
  - Review gradients from earlier chapters and relate to pressure gradients
- Expanded discussion of cyanosis to reflect signs in people with dark skin
- Introduced sinoatrial and atrioventricular nodes and Purkinje fiber cells as the three autorhythmic tissues of the heart
- New terminology: His-Purkinje system
  - Clarify that all ventricular conducting cells are Purkinje fiber cells

Chapter 16 Blood Flow and the Control of Blood Pressure

- Added focus on core concepts of mass balance and homeostasis

- Corrected model for anatomy of the microcirculation, with new text and new art
- Reorganized discussion on blood pressure, resistance, and flow to tissues
- Added intraosseous infusion into bone marrow sinusoids
- Updated:
  - Vasovagal (neurocardiogenic) syncope
  - Lymphatics, with new art
  - Myogenic autoregulation
  - Cardiovascular disease

Chapter 17 Blood

- Consolidated discussion of iron homeostasis with 2 new figures
  - Ferroportin (FPN)
  - Hepcidin
- Updated:
  - Thrombopoietin and thrombopoietin receptor agonists (TPO-RAs)
  - Gene therapy for sickle cell disease
  - Platelet-rich plasma
  - Schematic of hematopoietic stem cells and hematopoietic cytokines
  - Gene therapy for hemophilia

Chapter 18 Mechanics of Breathing

- New introduction about COVID-19 and the respiratory system
- New discussion, figure, and table of airway epithelial cells
  - Club cells, ionocytes, tuft cells, pulmonary neuroendocrine cells, and basal cells
  - Periciliary mucus layer
- New section on respiratory system defense mechanisms
- Revised:
  - Discussion of gas laws
  - Effect of altitude on gas partial pressures
- Updated type II alveolar cell functions

Chapter 19 Gas Exchange and Transport

- Revised model and new figure on central control of breathing
  - Respiratory central pattern generator (rCPG)
  - Pontine-medullary network
- Updated:
  - Factors that affect pulse oximeter accuracy
  - Blood substitutes
  - Protective reflexes

Chapter 20 The Kidneys

- Added alternate terminology for anatomical structures
- Updated:
  - Mesangial cell functions
  - Gout and uric acid excretion
  - SGLT2 inhibitors and urate excretion
- Moved Glucosuria and Diabetes Try It! activity to Chapter 23

Chapter 21 Integrative Physiology II: Fluid and Electrolyte Balance

- New Clinical Focus box and figure on SARS-CoV-2 and ACE2
- New Try It! box on Osmotic Diuresis with calculations
- Updated:
  - Cell volume regulation
  - Vasopressin pathologies

Chapter 22 The Digestive System

- Reorganized to put function before anatomy
  - Moved hepatic portal system to anatomy section
  - New discussion and figure of gut mucosal cells, including immune cells of the mucosa
    - Lymphoid follicles
    - Paneth cells
    - Enteroendocrine cells (EEC)
- New Section 22.3 on overview of digestive processes
- New Section 22.9 on microbiome and gut-brain communication
- Expanded discussion and new figure on bile salt recycling and enterohepatic circulation
- Updated:
  - Table 22.1 on signal peptides
  - Guanylin and uroguanylin in natriuretic peptide family
  - Role of immune system in digestive diseases
  - Section 22.8 on defense mechanisms
  - Information on colorectal cancer

Chapter 23 Metabolism and Energy Balance

- Reorganized introduction to put energy balance before food intake
- Revised model for control of food intake
  - Set point theory
  - Role of POMC and agouti-related peptide (AgRP)
- Updated discussion of body mass index (BMI)
- Updated:
  - Statistics on obesity and diabetes

  - Table 23.4 on drugs for diabetes
    - Semaglutide
- New information on diagnosis and treatment of diabetes
  - Hemoglobin A1C (HbA1c)
  - New section on how physiology is related to drug development for diabetes
  - Try It! box on glucosuria and insulin

Chapter 24 Endocrine Control of Growth and Metabolism

- Updated information on growth hormone therapy
- Updated information on control of bone remodeling
  - Coupling of bone remodeling
  - Clastokines
- Updated information on calcitonin
  - Calcitonin gene-related peptide (CGRP)

Chapter 25 Integrative Physiology III: Exercise

- Updated model of autonomic control of heart rate increase during exercise
- Discussion of difficulty of doing research on exercise
- Updated chemical signals affecting exercise metabolism
  - Myokines and exerkines

Chapter 26 Reproduction and Development

- Updated discussions on:
  - Biological sex and gender
  - Sex as a biological variable and the importance of sex in health and disease
- Revised discussion of sex determination and differentiation
  - X chromosome inactivation
  - Testis-determining genes: SRY and SOX9 genes
- Revised figure and explanation of gametogenesis
- Introduction of differences of sex development (DSD) and ambiguous genitalia
  - Non-invasive prenatal testing (NIPT)
- Role of exosomes in sperm maturation
- Updated table on contractive methods
- Revised model for endocrine control of initiation of labor

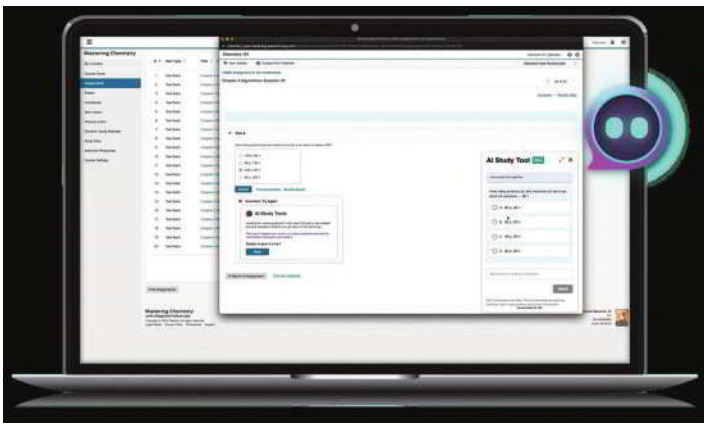
Pearson eTextbook

The Pearson eTextbook is a simple-to-use, mobile-optimized, personalized reading experience. It allows students to easily highlight, take notes, listen to the textbook, and review vocabulary all in one—even when offline. Students using the Pearson eTextbook will reap all the benefits of the new text features, while also benefitting from the following new and existing interactive features, which are integrated directly into the online text:

EXPANDED! Over 50 animations and videos embedded in the Pearson eTextbook bring A&P concepts to life featuring A&P Flix, Interactive Physiology, BioFlix, and more.

NEW! Hot Topics in Physiology bring regularly updated author-written articles to the eTextbook to inform readers of new research and developments in human physiology today. Located in each unit opener, these articles help students relate core content to the world around them.

NEW! AI Study Tool pulls from vetted Pearson content to help students achieve proficiency and master key course concepts. Our generative AI chat tool goes beyond a one-size-fits-all approach to provide individualized support, practice and feedback that meet the unique needs of every learner.

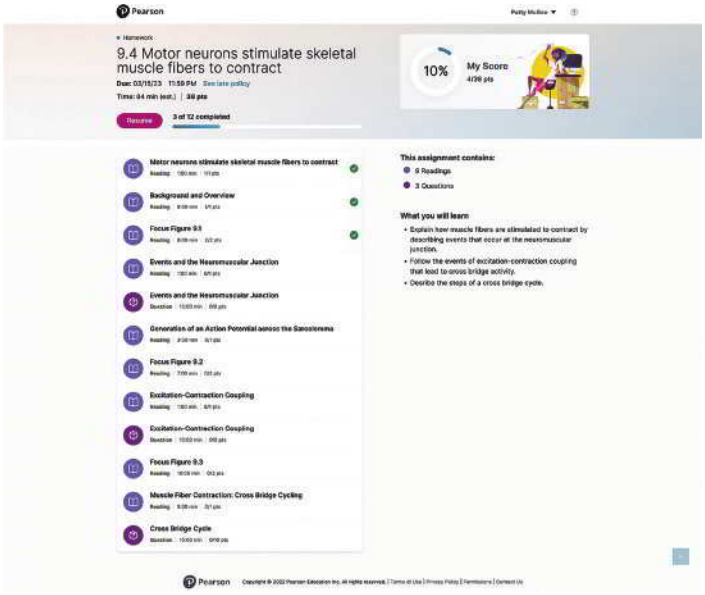


NEW! Quick Reference—Pearson eTextbook Integrated Media by Chapter provides easy reference to key animations and videos available for each chapter in the eTextbook and in Mastering. Media call-outs are also highlighted in the relevant chapter pages.

What's New in Mastering A&P

Mastering A&P is the most widely used online assessment and tutorial program for A&P, providing an extensive library of hundreds of animations, tutorials, and questions that are graded automatically.

NEW: Interactive Reading Assignments let students read, watch and practice in one seamless experience. Instructors can now assign specific sections of the eTextbook plus coaching and drag and drop assignments, and more for auto-grading.



NEW! Interactive Labs for Anatomy and Physiology are a fully customizable and auto-graded wet lab experience for your specific course objectives. Students engage with thought-provoking readings, videos, and realistic simulations aimed at critical thinking and data interpretation. These virtual labs can be assigned as a wet lab replacement, pre-lab preparation, post-lab review, or as a make-up lab. We recommend previewing the pre-built learning path by navigating to the Assignment Manager>Create>Import Pre-Built Assignment. See section below on Assignment Settings, Scoring, and LMS Integration.

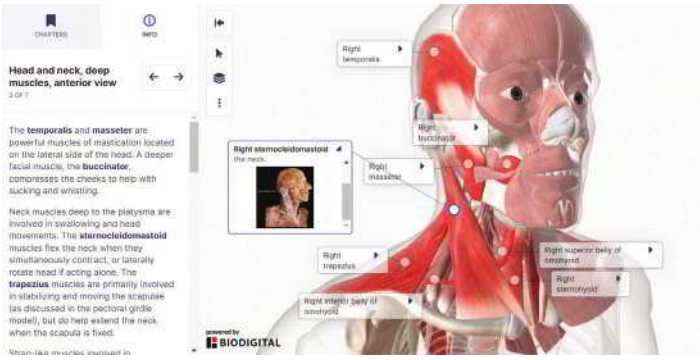
EXPANDED! Interactive Physiology 2.0 helps students advance beyond memorization to a genuine understanding of the toughest topics in A&P. Fully accessible on all mobile devices. I.P. 2.0 tutorials are assignable as coaching activities in Mastering A&P. New topics include Carbon Dioxide Transport and Exchange and Propagation of an Action Potential.

PhysioEx™10.0 Laboratory Simulations in Physiology provide newly formatted exercises in HTML for increased stability, web browser flexibility, and improved accessibility. The 12 Exercises contain 63 easy-to-use laboratory simulation activities that complement or replace wet labs, including those that are expensive or time-consuming to perform in class. PhysioEx allows students to repeat labs as often as they like, perform experiments without harming live animals, and conduct experiments that are difficult to perform in a wet lab environment because of time, cost, or safety concerns.

NEW! Gap Finder: A&P Diagnostic Assessment identifies any student knowledge gaps for material they should know for success in the course. This Diagnostic module contains approximately 130 questions based on these topics: Study Skills, Math Essentials, Chemistry Basics, Cell Biology Basics, and Biology Basics. Instructors can deselect as many questions as they want. There's no minimum number they have to adhere to in order for the program to work.

NEW and UPDATED! Dynamic Study Modules have been updated to reflect new content in the ninth edition. In addition, shadow questions, that change the root of the question, have been created for select questions to help keep students from memorizing questions.

NEW! Practice Anatomy Lab (PAL 4.0) featuring fully interactive 3-D models and custom assignability of your structure list is available in Mastering Assignment Manager and student Study Area.



NEW! Histology Videos include 10 new videos of histology tissues that provide short, focused walk-throughs of commonly covered tissue types in A&P.

NEW! TEAS and HESI exam practice questions help students prep for nursing school entrance exams with 150 TEAS and 300 HESI multiple-choice questions with wrong answer feedback for all questions.

UPDATED! Instructor Resources. This area of Mastering provides one-stop shopping for PowerPoint Lecture Presentations; all figures in JPEG and PPT format; Instructor Guide with Running Problems; Test Bank; animations; videos; Interactive Physiology (including the worksheets); Clinical Case Studies with Teaching Strategies and case study worksheets; PAL 4.0 Resources; PhysioEx

Resources; Interactive Lab Resources; and the new HAPS Learning Outcomes Correlation Guide.

NEW! Teaching Strategies for Active Learning is an invaluable resource for instructors looking for strategies for actively engaging students in the classroom. Edited by Cathy Whiting, this manual includes over 40 hands-on activities on key topics in A&P submitted by thought leaders across the country. Each activity is tied to HAPS Learning Outcomes and includes estimated time for the activity.

Learning Catalytics allows students to use their smartphone, tablet, or laptop to respond to questions in class. For more information, visit learningcatalytics.com.

Study Area features Resources by chapter; Practice Quizzes; TEAS & HESI Exam Practice, Animations and Videos including "Physiology in Action"; Interactive Physiology 2.0; Practice Anatomy Lab 4.0; Physio Ex; Clinical Case Studies, and more.

Acknowledgements

Writing, editing, and publishing a textbook is a group project that requires the talent and expertise of many people. No one scientist has the detailed background needed in all areas to write a book of this scope, and I am indebted to all my colleagues who so generously share their expertise in each edition. I particularly want to acknowledge Bruce Johnson, Cornell University, Department of Neurobiology and Behavior, a superb neurobiologist and educator, who once again ensured that the chapters on neurobiology are accurate and reflect the latest developments in that rapidly changing field. Bruce was joined in this edition by Michael Chirillo, UT-Austin Center for Learning and Memory, a former graduate teaching assistant of mine who has worked with me for over ten years. You can meet Michael if you watch the Physiology in Action videos.

The art team of Bill Ober, MD, and Claire Ober, RN, has worked with me since the first edition, and I am always grateful for their scientifically astute suggestions and revisions. They have been joined by Anita Impagliazzo, who brings a fresh eye and new figure ideas to our illustration program.

As we were developing the new core concepts chapter introductions and visual summaries for this edition, I relied on feedback from several colleagues to tell me if what I was creating would be helpful for their teaching. Thanks go to Jennifer Stokes, Jan M. Machart, Jennifer L. Thompson, and Meg Flemming for their prompt and honest input.

Special thanks go to some of my former students who over the years suggested topics and created storyboards for running problems: Matt Pahnke, Susan E. Johnson, Claire Conroy, and Douglas Shannon.

Instructors and students often contact me directly about the book, and for this edition I would particularly like to thank Collin Ellis, Heidi Engelhardt, and David Poole for comments and suggestions. Thanks also to my students who keep me informed of the typos that creep in no matter how many people look at the manuscript in production.

Many other people devoted their time and energy to making this book a reality, and I would like to thank them all, collectively and individually. I apologize in advance to anyone whose name I have omitted.

Ninth Edition Reviewers

I am particularly grateful to the instructors who reviewed one or more chapters of the last edition. There were many suggestions in their thoughtful reviews that I was unable to include in the text, but and others that I did. I appreciate the time and thought that went into their comments. The reviewers for this edition include:

- Sulekha Anand, *San Jose State University*
- Erwin Bautista, *University of California, Davis*
- Shawn Bearden, *Idaho State University*
- Simone Brito, *Fresno City College*
- George Brusch, *Oklahoma State University*
- Edward Eivers, *California State University, Los Angeles*
- Collin Ellis, *Santa Monica College*
- Heidi Engelhardt, *University of Waterloo*
- Luke Hoekstra, *Oklahoma State University*
- Erin Jacobs, *Mount Saint Mary's University*
- Mary Kinkel, *Appalachian State University*
- Catalina Reyes Gonzalez, *University of California, San Diego*
- Otto Sanchez, *University of Minnesota*

Many other instructors and students took time to write or e-mail queries or suggestions for clarification, for which I thank them. I am always delighted to have input, and I apologize that I do not have room to acknowledge them all individually.

Specialty Reviews

No one can be an expert in every area of physiology, and I am deeply grateful for my friends and colleagues who have reviewed entire chapters or answered specific questions over many editions. Even with their help, there may be errors, for which I take full responsibility.

In this edition, I am indebted to David Poole (Kansas State University) for his input on exercise physiology and for guidance to correct the erroneous figure of pre-capillary sphincters in the microcirculation (Chapter 16) that can be found in most physiology textbooks. Every instructor should read the article by Tatsuo Sakai and Yasue Hosoyamada (*https://link.springer.com/article/10.1007/s12576-013-0274-7*) to learn how we perpetuate errors in our teaching.

Photographs

I would like to thank Kristen Harris, University of Texas, who generously provided micrographs of dendritic spines from her research.

Supplements

Thank you to Meg Flemming, *Austin Community College* and Pat Clark, *Indiana University, Bloomington*, for updating the Test Bank, and to Eric Walsh, *University of Wisconsin-Madison*, for revising the PowerPoints for the ninth edition. Mastering assets for this edition were possible thanks to Catalina Reyes Gonzalez, *University of California, San Diego*, and to Max Adolphs, *University of Florida*, for their contributions to Mastering reading quizzes and chapter tests; as well as to Janet Casagrand, *University of Colorado Boulder*, and Simone Brito, *Fresno City College*, for their collective work on the improved Dynamic Study Modules. Additional thanks to *Pat Clark, Indiana University, Bloomington*, for

creating the prebuilt Interactive Reading Assignments for the ninth edition. Finally, thank you to Dr. Ryan Downey, *American University of the Caribbean School of Medicine; Georgetown University* and Genevieve Wager, *Cornell University* for their contributions to the Instructor Guide.

The Development and Production Team

Writing a manuscript is only a first step in the long and complicated process that results in a published book with all its ancillaries. The team that works with me on book development deserves a lot of credit for the finished product. Carie Keller at Straive designed the ninth edition's striking cover that continues our tradition of images that show science as art.

The team at Pearson Education worked tirelessly to see this edition move from manuscript to eText and bound book. My Editor and Commercial Product Manager, Alexa Frank, has been supportive, encouraging, and fun to work with as we scrambled to catch up on eight years of scientific advances and add the new emphasis on core concepts while staying on schedule. I also want to recognize Serina Beauparlant, Senior Manager of Product Management, who has been the one constant in the ebb and flow of publishing over many years. Serina's approach to the care and feeding of authors, especially during assorted crises, has kept writing and publishing fun.

Behind the scenes, thanks go to Ayushi Khandelwal, Editorial Assistant, who kept track of reviewers and feedback for this revision. Thank you also to our Product Marketer, Courtney Davis, who used her talents to shine a spotlight on this important revision and to Caroline Ayres, Senior Digital Program Director, for her support in the new revision workflow.

Special recognition goes to my team of Content Producers. The revision workflow for this edition completely changed to put creation of the eText before the print text, and it was a major adjustment for the authors and illustrators. The team of Francesca Monaco, Sharon Cahill, and Win Clark guided us through the new process with cheerfulness and infinite patience. Thanks also go to Katie Foley, Managing Producer, and Titas Basu, Assistant Managing Producer. The old production sequence of reviewing page proofs is gone, and I am grateful for the help of Kerri Tomasso, Project Management, in figuring out where we were in the review process. Thanks to Molly Montanaro, Rebecca Marshall, and Cathryn Gear from Lachina Creative who prepared the art for production. I would also like to thank Ben Ferrini, Matthew Perry and Chenley Calites for their many roles contributing to the Rights and Permissions as well as Kani Kapoor, Krishnamurthy Muralidharan, and Rajesh Kumar for sharing their skills and talents to make this edition possible.

Special Thanks

As always, I would like to thank my students and colleagues who looked for errors and areas that needed improvement. I've learned that awarding one point of extra credit for being the first student to report a typo works really well. My graduate teaching assistants over the years have all played a huge role in my teaching, and their input has helped shape how I teach. Many of them are now faculty members themselves. They include:

Ari Berman, PhD; Lawrence Brewer, PhD; Kevin Christmas, PhD; Michael Chirillo, MD, PhD; Lynn Cialdella Kam, MS, MBA, PhD; Sarah Davies Kanke, PhD; Peter English, PhD; Carol C. Linder, PhD; Karina Loyo-Garcia, PhD; Jan M. Machart, PhD; Tonya Thompson, MD; Patti Thorn, PhD; Justin Trombold, PhD; Kurt Venator, PhD; and Kira Wenstrom, PhD.

Finally, special thanks to my colleagues in the American Physiological Society, the Human Anatomy and Physiology Society, and the International Union of Physiological Sciences whose experiences in the classroom have enriched my own understanding of how to teach physiology. I would also like to recognize a special group of friends for their continuing support: Penelope Hansen (Memorial University, St. John's), Mary Anne Rokitka (SUNY Buffalo), Rob Carroll (East Carolina University School of Medicine), Joel Michael (Rush Medical College), Jennifer Stokes (Southwestern University), and Ryan Downey (American University of the Caribbean), as well as Peter English, Jan M. Machart, Ruth Buskirk, and Marilla Svinicki (University of Texas).

As always, I thank my family and friends for their patience, understanding, and support during the chaos that seems inevitable with book revisions. The biggest thank you goes to my husband Andrew, whose love, support, and willingness to forgo home-cooked meals on occasion have helped me meet my deadlines for nine editions.

A Work in Progress

One of the most rewarding aspects of writing a textbook is the opportunity it has given me to meet or communicate with other instructors and students. In the many years since the first edition was published, I have heard from people around the world and have had the pleasure of hearing how the book has been incorporated into their teaching and learning.

Because science textbooks are revised periodically, they are always works in progress. I invite you to contact me or my publisher with any suggestions, corrections, or comments about this edition. I am most reachable through e-mail at silverthorn@utexas.edu.

Dee U. Silverthorn *silverthorn@utexas.edu* University of Texas Austin, Texas.

Quick Reference Pearson eTextbook Integrated Media

Chapter 1 Introduction to Physiology

Module 1.3

- Bioflix: Homeostasis: Regulating Blood Sugar

Chapter 3 Compartmentation: Cells and Tissues

Module 3.3

- Bioflix: Tour of an animal cell

Chapter 4 Energy and Cellular Metabolism

Module 4.4

- Bioflix: Electron Transport System
- Bioflix: Protein Synthesis

Chapter 5 Membrane Dynamics

Module 5.1

- Physiology in Action: Osmolarity and Tonicity

Module 5.7

- Physiology in Action: Membrane Potential
- A&P Flix: Resting Membrane Potential

Chapter 5 Links to Resources

- Interactive Physiology Animation: Introduction to Body Fluids

Chapter 7 The Immune System

Module 7.1

- Microbiology Animation: Host Defenses

Module 7.3

- Microbiology Animation: Antigen Processing and Presentation: Overview

Module 7.7

- Microbiology Animation: Humoral Immunity: Clonal Selection and Expansion

Module 7.8

- Bioflix: Summary of the Adaptive Immune Response

Chapter 9 Neurons: Cellular and Network Properties

Module 9.2

- BioFlix: How Synapses Work

Module 9.3

- Interactive Physiology Animation: Generation of an Action Potential
- BioFlix: Action Potential Conduction

Chapter 9 Links to Resources

- Interactive Physiology 2.0 Animation: Propagation of an Action Potential

Chapter 10 The Central Nervous System

Module 10.6

- Biointeractives: Circadian Rhythms and the SCN

Chapter 13 Muscles

Module 13.1

- A&P Flix: The Cross Bridge Cycle
- Interactive Physiology Animation: Neuromuscular Junction
- Interactive Physiology 2.0 Animation: Cross Bridge Cycle

Chapter 15 Cardiovascular Physiology

Module 15.3

- Interactive Physiology Animation: Pathway of Blood through the Heart
- Interactive Physiology Animation: Action Potentials in Autorhythmic Cells

Module 15.4

- Physiology in Action: Electrocardiogram
- Interactive Physiology Animation: Intrinsic Conduction System of the Heart
- Interactive Physiology Animation: Cardiac Output

Chapter 15 Links to Resources

- Interactive Physiology 2.0 Animation: Electrical Activity of the Heart
- Interactive Physiology 2.0 Animation: Cardiac Cycle
- Interactive Physiology 2.0 Animation: Cardiac Output

Chapter 16 Blood Flow and the Control of Blood Pressure

Module 16.4

- Physiology in Action: Orthostatic Hypotension
- Interactive Physiology Animation: Arterial Baroreceptor Reflex

Chapter 18 Mechanics of Breathing

Module 18.3

- Physiology in Action: The Spirometer
- Physiology in Action: Subatmospheric Pleural Cavity
- Physiology in Action: Effect of Ventilation on Expired CO_2

Chapter 19 Gas Exchange and Transport

Module 19

- BioFlix: Gas Exchange
- Physiology in Action: Hemoglobin/Oxygen Transport

Chapter 19 Links to Resources

- Interactive Physiology 2.0 Animation: Oxygen Transport and Exchange

Chapter 20 The Kidneys

Module 20.4

- Interactive Physiology Animation: Glomerular Filtration

Module 20.6

- Interactive Physiology 2.0 Animation: Proximal Tubule Reabsorption and Secretion

Module 20.7

- Physiology in Action: Renal Clearance

Chapter 20 Links to Resources

- Interactive Physiology 2.0 Animation: Glomerular Filtration
- Interactive Physiology Animation: Anatomy Review: Urinary System
- Interactive Physiology 2.0 Animation: Tubular Reabsorption and Secretion

Chapter 21: Integrative Physiology II: Fluid and Electrolyte Balance

Chapter 21 Links to Resources

- Interactive Physiology Animation: Aldosterone and ADH in Salt and Water Processing
- Interactive Physiology Animation: Mechanisms for Acid-Base Homeostasis
- Interactive Physiology Animation: Acid-Base Disturbances

Chapter 22 The Digestive System

Chapter 22 Links to Resources

- Interactive Physiology Animation: Anatomy Review
- Interactive Physiology Animation: Control of Digestion
- Interactive Physiology Animation: Digestive System Secretion
- Interactive Physiology Animation: Digestion and Absorption

Chapter 25 Integrative Physiology III: Exercise

Module 25.3

- Physiology in Action: Blood Pressure and Exercise

Brief Contents

Contents

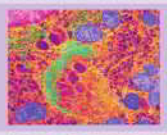
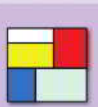
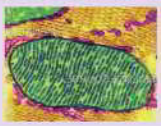
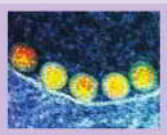
UNIT 1

Basic Cell Processes: Integration and Coordination

Unit 1 Core Concepts in Physiology

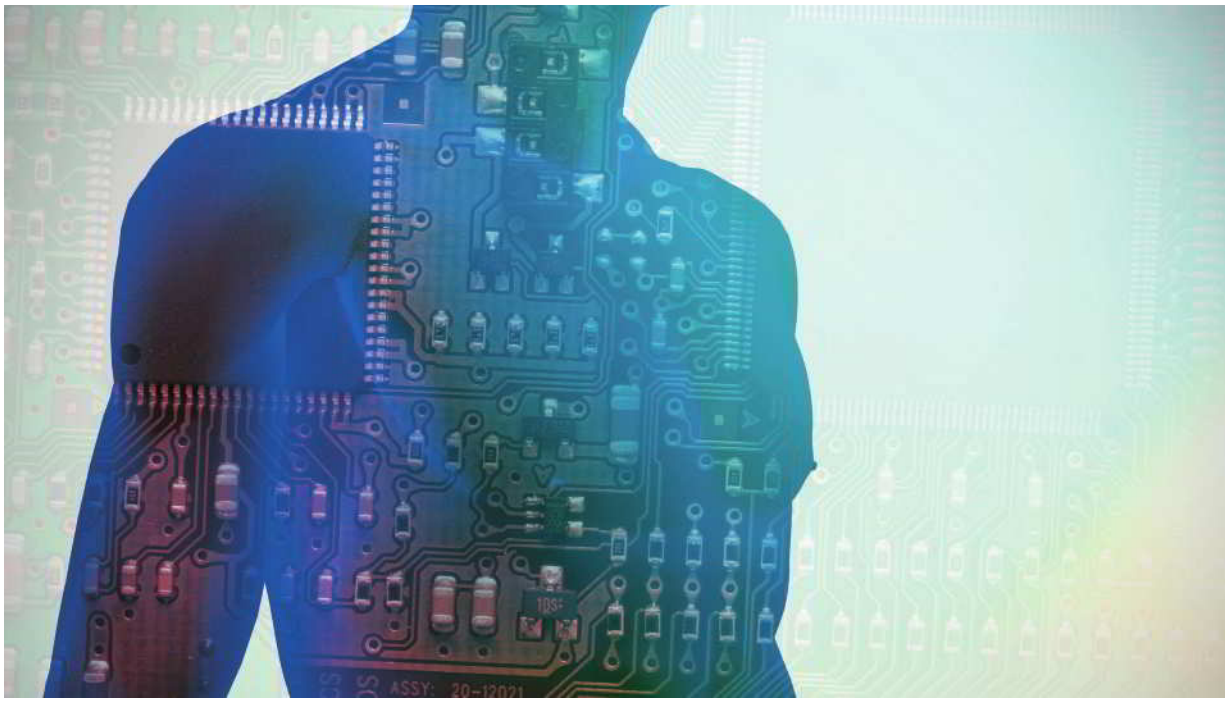
Welcome to the study of human physiology! In the first six chapters of this book you will learn about the core concepts of physiology – the general models or patterns that repeat over and over throughout the different body systems. Being able to recognize these patterns each time you encounter them will simplify learning physiology because you are seeing something familiar in a different context rather than learning a new concept. Pattern recognition is an important skill to acquire in your studies because it is a critical element in developing expertise. Studies have shown that when clinicians make a diagnosis, they are using rapid subconscious pattern recognition to help decide what might be going on.

To simplify learning the eight core concepts in this book, we have created icons that will appear at the start of each chapter to show the important core concepts discussed in that chapter. The icons and their descriptions appear next to the unit chapter titles where they are first discussed. Chapter 6 is the first chapter in Unit 2.

Chapter		Core Concepts	Icon
Chapter 1: Introduction to Physiology		Homeostasis	
		Mass Balance	
		Structure-Function Relationships	
		Communication	
Chapter 2: Molecular Interactions		Molecular Interactions	
Chapter 3: Compartmentation: Cells and Tissues		Compartmentation	
Chapter 4: Energy and Cellular Metabolism		Energy	
Chapter 5: Membrane Dynamics		Gradients	

1

Introduction to Physiology



The current tendency of physiological thought is clearly toward an increasing emphasis upon the unity of operation of the Human Body.

Ernest G. Martin, preface to The Human Body *10th edition, 1917*

Welcome to the study of human physiology! In this chapter you will be introduced to the core concepts of physiology—the general models or patterns that repeat over and over throughout the body systems of living organisms. Here are the core concepts featured in Chapter 1.

Homeostasis

A healthy body stays in homeostasis. Loss of homeostasis can result in illness.

Communication

The organ systems of the body must communicate with each other.

Mass Balance

Body stability requires that what comes in and what goes out remain balanced.

Structure-Function

The structure and function of body parts are closely related, from the tiniest subcellular fibers to the most complex organs.

Compartmentation

Compartments at all levels of organization separate functions.

Learning Outcomes

1.1 Physiology Is an Integrative Science
- **LO 1.1.1** Define physiology.
- **LO 1.1.2** List the levels of organization from atoms to the biosphere.
- **LO 1.1.3** Name the 10 physiological organ systems of the body and give their functions.

1.2 Function and Mechanism
- **LO 1.2.1** Distinguish between mechanistic explanations and teleological explanations.

1.3 Core Concepts in Physiology
- **LO 1.3.1** List and give examples of eight core concepts in physiology.

1.4 Homeostasis
- **LO 1.4.1** Define homeostasis. What happens when homeostasis fails?
- **LO 1.4.2** Name and describe the two major compartments of the human body.
- **LO 1.4.3** Explain the law of mass balance and how it applies to the body's load of a substance.
- **LO 1.4.4** Define mass flow using mathematical units and explain how it relates to mass balance.
- **LO 1.4.5** Define clearance and give an example.
- **LO 1.4.6** Distinguish between equilibrium and steady state.

1.5 Control Systems and Homeostasis
- **LO 1.5.1** List the three components of a control system and give an example.
- **LO 1.5.2** Explain the relationship between a regulated variable and its setpoint.
- **LO 1.5.3** Compare local control, long-distance control, and reflex control.
- **LO 1.5.4** Explain the relationship between a response loop and a feedback loop.
- **LO 1.5.5** Compare negative feedback, positive feedback, and feedforward control. Give an example of each.
- **LO 1.5.6** Explain what happens to setpoints in biological rhythms and give some examples.

1.6 The Science of Physiology
- **LO 1.6.1** Explain and give examples of the following components of scientific research: independent and dependent variables, experimental control, data, replication, variability.
- **LO 1.6.2** Compare and contrast the following types of experimental study designs: blind study, double-blind study, crossover study, prospective and retrospective studies, cross-sectional study, longitudinal study, meta-analysis.
- **LO 1.6.3** Define placebo and nocebo effects and explain how they may influence the outcome of experimental studies.

Welcome to the fascinating study of the human body! For most of recorded history, humans have been interested in how their bodies work. Early Egyptian, Indian, and Chinese writings describe attempts by physicians to treat various diseases and to restore health. Although some ancient remedies, such as camel dung and powdered sheep horn, may seem bizarre, we are still using others, such as blood-sucking leeches and chemicals derived from medicinal plants. The way we use these treatments has changed through the centuries as we have learned more about the human body.

There has never been a more exciting time in human physiology. **Physiology** is the study of the typical functioning of a living organism and its component parts, including all its chemical and physical processes. The term *physiology* literally means "knowledge of nature." Aristotle (384–322 BCE) used the word in this broad sense to describe the functioning of all living organisms, not just of the human body. However, Hippocrates (ca. 460–377 BCE), considered the father of medicine, used the word *physiology* to mean "the healing power of nature," and thereafter the field became closely associated with medicine. By the sixteenth century in Europe, physiology had been formalized as the study of the vital functions of the human body. Currently the term is again used to refer to the study of all living organisms.

Today, we benefit from centuries of work by physiologists who constructed a foundation of knowledge about how the human body functions. Since the 1970s, rapid advances in the fields of cellular and molecular biology have supplemented this work. A few decades ago, we thought that we would find the key to the secret of life by sequencing the human *genome*, which is the collective term for all the genetic information contained in the DNA of a species. However, this deconstructionist view of biology has proved to have its limitations, because living organisms are much more than the simple sum of their parts.

1.1 Physiology Is an Integrative Science

Many complex systems—including those of the human body—possess **emergent properties,** which are properties that cannot be predicted to exist based only on knowledge of the system's individual components. An emergent property is not a property of any single component of the system, and it is greater than the simple sum of the system's individual parts. Emergent properties result from complex, nonlinear interactions of the different components.

For example, suppose someone broke down a car into its nuts and bolts and pieces and laid them out on a floor. Could you predict that, properly assembled, these bits of metal and plastic would become a vehicle capable of converting the energy in gasoline into movement? Who could predict that the right combination of elements into molecules and assemblages of molecules would result in a living organism? Among the most complex emergent properties in humans are emotion, intelligence, and other aspects of brain function. None of these properties can be predicted from knowing the individual properties of nerve cells.

When the Human Genome Project began in 1990, scientists thought that by identifying and sequencing all the genes in human DNA, they would understand how the body worked. However, as research advanced, scientists had to revise their original idea that a given segment of DNA contained one gene that coded for one protein. It became clear that one DNA sequence could code for many proteins. The Human Genome Project ended in 2003, but before then researchers had moved beyond genomics to *proteomics*, the study of proteins in living organisms.

Now scientists have realized that knowing that a protein is made by a particular cell does not always tell us the significance of that protein to the cell, the tissue, or the functioning organism. The exciting new areas in biological research are using a *multiomics approach* that applies data from many fields of study to explain the integrated function of the human body.

Emerging Concepts

The Changing World of Omes

Contemporary research is now in an era of "omes" and "omics." What is an "ome"? The term apparently derives from the Latin word for a mass or tumor and refers to a collection of items that make up a whole, such as a genome. One of the earliest uses of the "ome" suffix in biology is the term *biome*, meaning all organisms living in a major ecological region, such as the marine biome. A *genome* is all the genetic material of an organism. Its *physiome* describes the organism's coordinated molecular, cellular, and physiological functioning. The related adjective "omics" describes the research related to studying an "ome."

New "omes" emerge every year. The human connectome project sponsored by the U.S. National Institutes of Health is a collaborative effort to map all the neural connections of the human brain. The human microbiome project is studying the influence of microbes that normally live on or in the human body. Long ignored for many years, these microbes have now been shown to have an influence on both health and disease.

1.2 Function and Mechanism

We define physiology as the typical functioning of the body, but physiologists are careful to distinguish between *function* and *mechanism*. The **function** of a physiological system or event is the "why" of the system or event: Why does a certain response help an animal survive in a particular situation? In other words, what is the *adaptive significance* of this event for this animal?

For example, humans are large, mobile, terrestrial animals, and our bodies maintain relatively constant water content despite living in a dry, highly variable external environment. Dehydration is a constant threat to our well-being. What processes have evolved in our anatomy and physiology that allow us to survive in this hostile environment? One is the production of highly concentrated urine by the kidney, which allows the body to conserve water. This statement tells us *why* we produce concentrated urine but does not tell us *how* the kidney accomplishes that task.

Thinking about a physiological event in terms of its adaptive significance is the **teleological approach** to science. For example, the teleological answer to the question of why red blood cells transport oxygen is "because cells need oxygen and red blood cells bring it to them." This answer explains *why* red blood cells transport oxygen—their function—but says nothing about *how* the cells transport oxygen.

In contrast, most physiologists study physiological processes, or **mechanisms**—the "how" of a system. The **mechanistic approach** to physiology examines process. The mechanistic answer to the question "How do red blood cells transport oxygen?" is "Oxygen binds to hemoglobin molecules in the red blood cells." This very concrete answer explains exactly how oxygen transport occurs but says nothing about the significance of oxygen transport to the animal.

Students often confuse these two approaches to thinking about physiology. Studies have shown that even medical students tend to answer questions with teleological explanations when the more appropriate response would be a mechanistic explanation.[1] Often they do so because instructors ask why a physiological event occurs when they really want to know how it occurs. Staying aware of the two approaches will help prevent confusion.

Although function and mechanism seem to be two sides of the same coin, it is possible to study mechanisms, particularly at the cellular and subcellular level, without understanding their function in the life of the organism. As biological knowledge becomes more complex, scientists sometimes become so involved in studying complex processes that they fail to step back and look at the adaptive significance of those processes to cells, organ systems, or the animal. Conversely, it is possible to use teleological thinking incorrectly by saying, "Oh, in this situation the body needs to do this." *This* may be a good solution, but if a mechanism for doing *this* doesn't exist, the situation cannot be corrected.

Applying the concept of integrated functions and mechanisms is the underlying principle in **translational research,** an approach sometimes described as "bench to bedside." Translational research uses the insights and results gained from basic biomedical research on mechanisms to develop treatments and strategies for preventing human diseases. For example, researchers working on rats found that a chemical from the pancreas named *amylin* reduced the rats' food intake. These findings led directly to a translational research study in which human volunteers injected a synthetic form of amylin and recorded their subsequent food intake, but without intentionally modifying their lifestyle.[2] The drug suppressed food intake in humans, and was later approved by the Food and Drug Administration for treatment of diabetes mellitus.

At the systems level, we know about most of the mechanics of body function from centuries of research. The unanswered questions today mostly involve integration and control of these mechanisms, particularly at the cellular and molecular levels. Nevertheless, explaining what happens in test tubes or isolated cells can only partially answer questions about function. For this reason, animal and human trials are essential steps in the process of applying basic research to treating or curing diseases.

Running Problem 1.1: What to Believe?

Hiro had just left his first physiology class when he saw a friend's social media link to a video claiming that everyone should take probiotics for gut health. He watched some of the video but he wasn't sure exactly what probiotics were and whether the information in the video was accurate. "I wonder if there is any scientific evidence supporting this claim," Hiro thought. "Let's see what I can find out."

1.3 Core Concepts in Physiology

"Physiology is not a science or a profession but a point of view."[3] Physiologists pride themselves on relating the mechanisms they study to the functioning of the organism as a whole. For students, being able to think about how multiple body systems integrate their function is one of the more difficult aspects of learning physiology. To develop expertise in physiology, you must do more than simply memorize facts and learn new terminology. Researchers have found that the ability to solve problems requires a conceptual framework, or "big picture," of the field.

This book will help you build a conceptual framework for physiology by explicitly emphasizing the basic biological themes, or **core concepts** that are common to all living organisms. These concepts form patterns that repeat over and over, and you will begin to recognize them when you encounter them in specific contexts. Pattern recognition is an important skill in healthcare professions, and it will also simplify learning physiology.

In the recent years, multiple organizations issued reports to encourage the teaching of biology using these fundamental concepts.[4] Although the descriptions vary from report to report, five major ideas emerge:

1. structure and function across all levels of organization
2. energy transfer, storage, and use
3. information flow, storage, and use within single organisms and within a species of organism
4. homeostasis and the control systems that maintain it
5. evolution

In addition, these reports emphasize the importance of understanding how science is done and of the quantitative nature of biology.

FIGURE 1.1 lists the eight core concepts we will focus on in this book. The major core concepts most related to physiology are structure-function relationships (anatomy and levels of organization, molecular interactions, compartmentation), biological energy use, gradients and flow, communication, and homeostasis, which includes mass balance. The first six chapters introduce the fundamentals of these core concepts, which you may already be familiar with from earlier biology or chemistry classes. The core concepts, with variations, then re-appear over and over in subsequent chapters of this book. Look for their icons throughout the chapters and in the summary material at the end of each chapter.

Core Concept 1: Structure and Function Are Closely Related

This overarching core concept subdivides into three major ideas: anatomy and levels of organization, molecular interactions, and compartmentation.

Anatomy and Levels of Organization

Anatomy is the study of body structures, and in all living organisms, structure and function are closely linked. The **integration of function** across many **levels of organization,** from the molecular level to the intact body, is a special focus of physiology. (To *integrate* means to bring varied elements together to create a unified whole.)

FIGURE 1.2 illustrates levels of organization ranging from the molecular level all the way up to populations of different species living together in *ecosystems* and in the *biosphere*. The levels of organization are shown along with the various subdisciplines of chemistry and biology related to the study of each organizational level. There is considerable overlap between the different fields of study, and these artificial divisions vary according to who is defining them. Notice, however, that physiology includes multiple levels, from molecular and cellular biology to the ecological physiology of populations.

Fig. 1.1 Core concepts and their icons

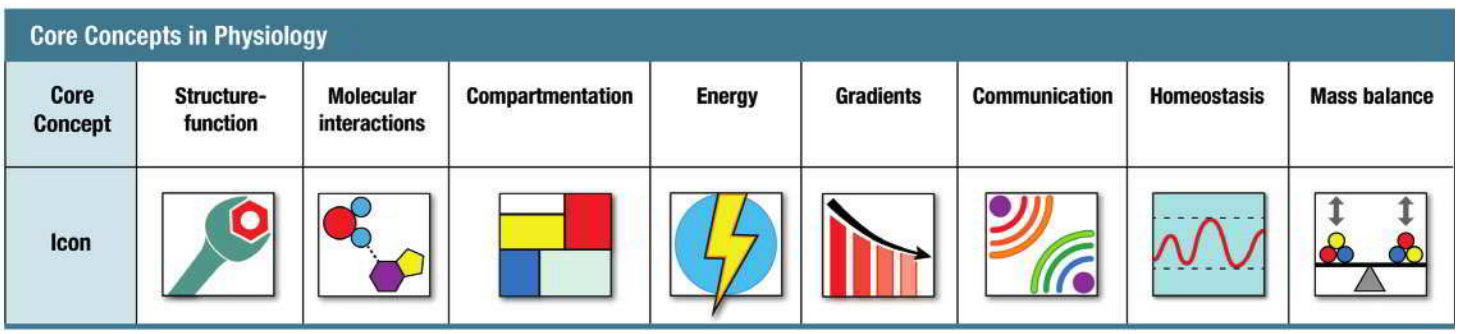
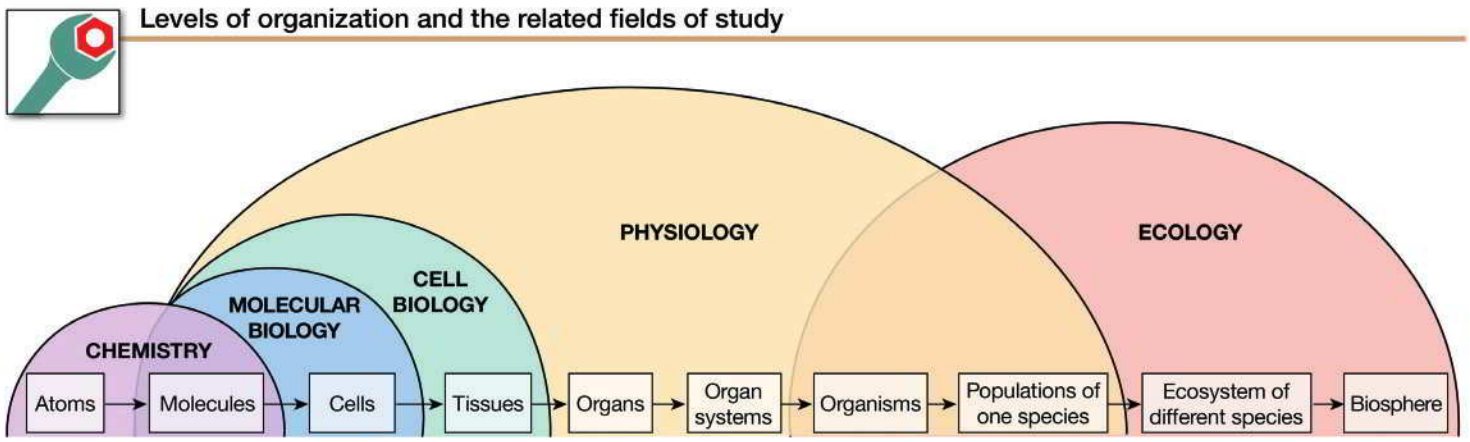


Fig. 1.2 Levels of organization



At the most basic level of organization shown in Figure 1.2, atoms of elements link together to form molecules. Collections of molecules in living organisms form **cells,** the smallest unit of structure capable of carrying out all life processes. A lipid and protein barrier called the **cell membrane** (also called the *plasma membrane*) separates cells from their external environment. Simple organisms are composed of only one cell, but complex organisms have many cells with different structural and functional specializations.

Collections of cells that carry out related functions are called **tissues** {*texere*, to weave}. Tissues form structural and functional units known as **organs** {*organon*, tool}, and groups of organs integrate their functions to create **organ systems**. Chapter 3 reviews the anatomy of cells, tissues, and organs.

The structure of a cell, tissue, or organ must provide an efficient physical base for its function. For this reason, it is nearly impossible to study the physiology of the body without understanding the underlying anatomy. Because of the interrelationship of anatomy and physiology, you will find Anatomy Summaries throughout the book. These special review features illustrate the basic anatomy of the physiological systems at different levels of organization.

Running Problem 1.2

When Hiro got back to his room, he sat down at his computer and googled *probiotics*. Almost instantly, he got back more than 244 million results. The first results were sponsored links from *seed.com*, *amazon.com*, and *ritual.com*. These were followed by pages from *mayoclinic.org*, *www.nccih.nih.gov*, *webmd.com*, *healthline.com*, *health.harvard.edu*, *en.wikipedia.org*, and *www.ods.od.nih.gov*. Hiro thought to himself, "Wow, there is a lot of information out there. What should I look at first?"

Q1: *Rank these 10 results from most to least likely to have good information and explain how you chose your rankings.*

The 10 physiological organ systems in the human body are illustrated in **FIGURE 1.3**. Several of the systems have alternate names, given in parentheses, that are based on the organs of the system rather than the function of the system. The **integumentary system** {*integumentum*, covering}, composed of the skin, forms a protective boundary that separates the body's internal environment from the external environment (the outside world). The **musculoskeletal system** provides support and body movement.

Four systems move material into and out of the body. The **respiratory system (pulmonary)** exchanges gases; the **digestive system (gastrointestinal)** takes up nutrients and water and eliminates wastes; the **urinary system (renal)** removes excess water and waste material; and the **reproductive system** produces eggs or sperm.

The remaining four systems extend throughout the body. The **circulatory system (cardiovascular)** distributes materials by pumping blood through vessels. The **nervous system** and **endocrine system** coordinate body functions. Note that the figure shows them as a continuum rather than as two distinct systems. Why? Because the lines between these two systems have blurred as we have learned more about the integrative nature of physiological function.

The one system not illustrated in Figure 1.3 is the diffuse **immune system,** which includes but is not limited to the anatomical structures known as the **lymphatic system**. The specialized cells of the immune system are scattered throughout the body. They protect the internal environment from foreign substances by intercepting material that enters through the intestines and lungs or through a break in the skin. In addition, immune tissues are closely associated with the circulatory system. Cells of the immune system secrete chemical messengers that communicate and coordinate with the nervous and endocrine systems.

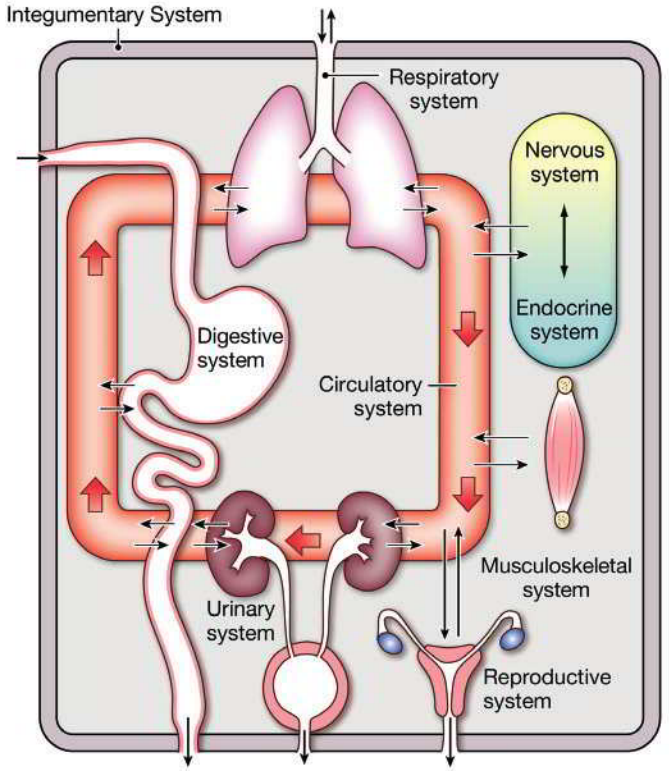
Traditionally, physiology courses and books are organized by organ system. Students study cardiovascular physiology and regulation of blood pressure in one chapter, and then study the kidneys and control of body fluid volume in a different chapter. In the functioning human, however, the cardiovascular and renal systems communicate with each other, so that a change in one is

Fig. 1.3 Organ systems of the human body and their integration

ESSENTIALS Organ Systems of the Human Body

System Name	Includes	Representative Functions
Circulatory	Heart, blood vessels, blood	Transport of materials between all cells of the body
Digestive	Stomach, intestine, liver, pancreas	Conversion of food into particles that can be transported into the body; elimination of some wastes
Endocrine	Thyroid gland, adrenal gland	Coordination of body function through synthesis and release of regulatory molecules
Immune	Thymus, spleen, lymph nodes	Defense against foreign invaders
Integumentary	Skin	Protection from external environment
Musculoskeletal	Skeletal muscles, bone	Support and movement
Nervous	Brain, spinal cord	Coordination of body function through electrical signals and release of regulatory molecules
Reproductive	Ovaries and uterus, testes	Perpetuation of the species
Respiratory	Lungs, airways	Exchange of oxygen and carbon dioxide between the internal and external environments
Urinary	Kidneys, bladder	Maintenance of water and solutes in the internal environment; waste removal

The Integration between Systems of the Body



This schematic figure indicates relationships between systems of the human body. The interiors of some hollow organs (shown in white) are part of the external environment.

likely to cause a reaction in the other. For example, body fluid volume influences blood pressure, while changes in blood pressure alter kidney function because the kidneys regulate fluid volume. In this book, each of the four units ends with an integrative physiology chapter that highlights the coordination of function across multiple organ systems.

Understanding how different organ systems work together is just as important as memorizing facts, but the complexity of interactions can be challenging. One way physiologists simplify and integrate information is by using visual representations of physiological processes called maps. The Focus on Mapping feature in this chapter will help you learn how to make maps. The first type of map, shown in **FIGURE 1.4**, is a schematic representation of structure or function. The second type of map diagrams a physiological process as it proceeds through time. These process maps are also called *flow charts*, and they are frequently used in health care. You will be able to practice creating maps with special end-of-chapter questions throughout the book. You will also find maps in the visual summary at the end of each chapter.

Molecular Interactions

The ability of individual molecules to bind to or react with other molecules is essential for biological function. A molecule's function depends on its structure and shape, and even a small change to the structure or shape may have significant effects on the function. The classic example of this phenomenon is the change in one amino acid of the hemoglobin protein. (Hemoglobin is the oxygen-carrying pigment of the blood.) This one small change in the protein converts normal hemoglobin to the form associated with sickle cell disease.

Many physiologically significant molecular interactions that you will learn about in this book involve the class of biological molecules called *proteins*. Functional groups of proteins include *enzymes* that speed up chemical reactions, *signal molecules* and the *receptor proteins* that bind signal molecules, and specialized proteins that function as biological pumps, filters, motors, or transporters. Chapter 2 describes molecular interactions involving proteins in more detail.

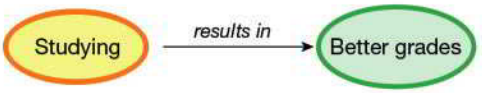
Fig. 1.4 Focus on . . . Mapping

Focus on . . . Mapping

Why use maps to study physiology? The answer is simple: maps will help you organize information you are learning in a way that makes sense to you and they will make that information easier to recall on a test. Creating a map requires higher-level thinking about the relationships among items on the map.

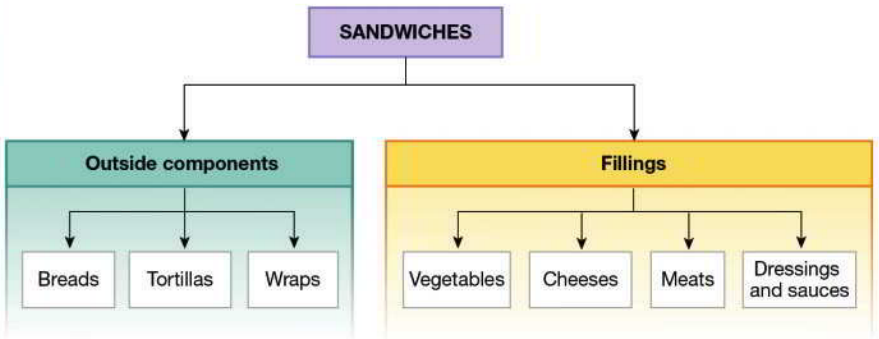
Mapping is not just a study technique. Scientists map out the steps in their experiments. Healthcare professionals create maps to guide them while diagnosing and treating patients. You can use mapping for almost every subject you study.

What is a map? Mapping is a nonlinear way of organizing material. A map can take a variety of forms but usually consists of terms (words or short phrases) linked by arrows to indicate associations. You can label the connecting arrows to describe the type of linkage between the terms (structure/function, cause/effect) or with explanatory phrases.

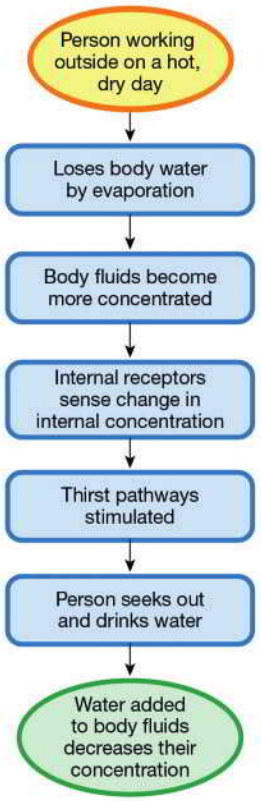


Here are two typical maps used in physiology.

Structure/function maps focus on the relationships between anatomical structures and their functions.



Process maps or **flow charts** follow normal homeostatic control pathways or the body's responses to abnormal (pathophysiological) events as they unfold over time.



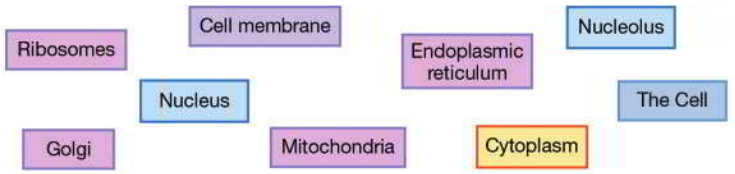
Practice making maps. Many maps appear in this textbook, and they can serve as the starting point for your own maps. However, the real benefit of mapping comes from preparing maps yourself rather than memorizing someone else's maps. Your instructor can help you get started.

HINTS

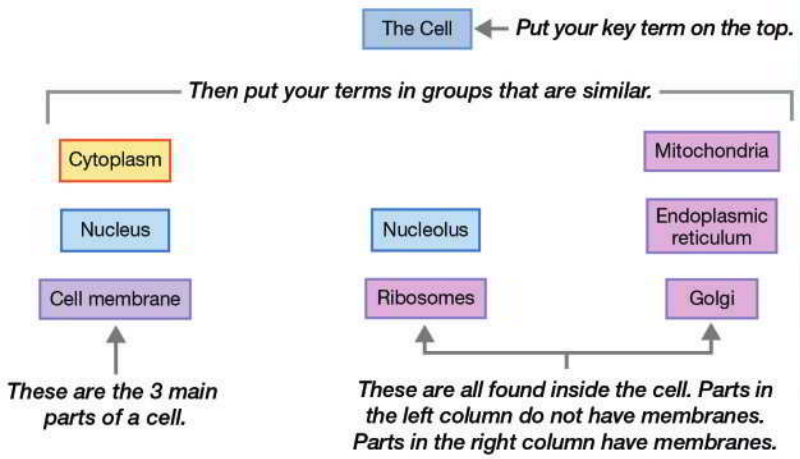
- To help you get started, the end-of-chapter questions in this book include at least one list of terms to map for each chapter.
- Write your terms on individual slips of paper or small sticky notes so that you can rearrange the map more easily.
- Some terms may seem to belong to more than one group. Do not duplicate the item but make a note of it, as this term will probably have several arrows pointing to it or leading away from it.
- If arrows crisscross, try rearranging the terms on the map.
- Use color to indicate similar items.
- Add pictures and graphs that are associated with specific terms in your map.

Electronic mapping. Some people do not like the messiness of hand-drawn maps. There are several electronic ways of making maps, including PowerPoint or free and commercial software programs. Free concept mapping software is available from IHMC CmapTools at https://cmap.ihmc.us.

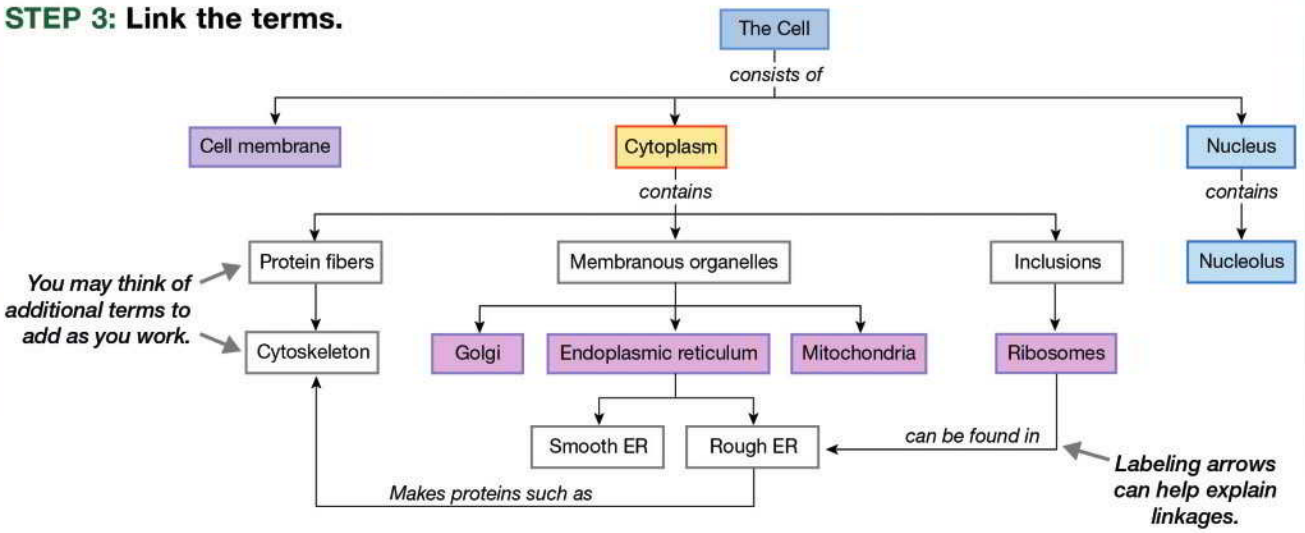
STEP 1: Write out the terms to map.
If you need help generating ideas for topics to map, the end-of-chapter mapping questions in each chapter have lists of terms to help you get started.



STEP 2: Organize the terms.



STEP 3: Link the terms.



Once you have created your map, sit back and think about it. Are all the items in the right place? You may want to move them around once you see the big picture. Add new concepts or correct wrong links. Review by recalling the main concept and then moving to the more specific details. Ask yourself questions like, What is the cause and what is the effect? What parts are involved? What are the main characteristics?

Science is a collaborative field. A useful way to study with a map is to **trade maps with a classmate** and try to understand each other's maps. Your maps will almost certainly not look the same! It's OK if they are different. Remember that your map reflects the way you think about the subject, which may be different from the way someone else thinks about it. Did one of you put in something the other forgot? Did one of you have an incorrect link between two items?

Interactions between proteins, water, and other molecules influence cell structure and the mechanical properties of cells and tissues. Mechanical properties you will encounter in your study of physiology include *compliance* (ability to stretch), *elastance* (stiffness or the ability to return to the unstretched state), strength, flexibility, and fluidity (*viscosity*).

Compartmentation

Compartmentation is the division of space into separate compartments, with or without obvious dividing walls. Compartments allow a cell, a tissue, or an organ to specialize and isolate functions. Each level of organization is associated with different types of compartments. At the macroscopic level, the tissues and organs of the body form discrete functional compartments, such as body cavities or the insides of hollow organs. At the microscopic level, cell membranes separate cells from the fluid surrounding them and also create tiny compartments within the cell called organelles. Compartmentation is the theme of Chapter 3.

Running Problem 1.3

Hiro looked at the results on the first page. He had heard of the NIH, and knew it was the U.S. National Institutes of Health, run by the federal government, so he clicked on *www.nccih.nih.gov*. This link went to a page for the NIH-Sponsored National Center for Complementary and Integrative Health (NCCIH). Hiro decided to learn more about NCCIH by using the ABOUT link. He used the SEARCH box to see what NCCIH said about probiotics.

Q2: *Go to www.nccih.nih.gov. What is the mission of NCCIH?*

Q3: *What does NCCIH say about whether probiotics are helpful and whether they are safe?*

Core Concept 2: Living Organisms Need Energy

Growth, reproduction, movement, homeostasis—these and all other processes that take place in an organism require the continuous input of energy. Where does this energy come from, and how is it stored? We will answer those questions and describe some of the ways that energy in the body is used for building and breaking down molecules in Chapter 4. In subsequent chapters, you will learn how energy is used to transport molecules across cell membranes and to create movement.

Core Concept 3: Gradients and Flow

A **gradient** {*gradiens*, to walk} is a gradual change in the value or magnitude of a function over distance or over time. In physiology, most of the gradients you will encounter represent a change in magnitude from one location to another, such as from the beginning to the end of a tube or between the inside and outside of a cell. The gradients icon (Fig. 1.1) shows two gradients moving from left to right: a decrease in size and a decrease in color intensity. Three types of gradients are particularly important in physiology: concentration (chemical) gradients, pressure gradients, and electrical gradients. You may also encounter other gradients, such as temperature gradients. Gradients are a form of stored (*potential*) energy, and substances will move or flow down a gradient unless there is a barrier blocking their movement.

Core Concept 4: Communication Coordinates Body Functions

Communication is the transmission of information within or between organisms. Information flow in living systems ranges from the transfer of information stored in DNA from generation to generation (genetics) to the flow of information within the body of a single organism. At the organismal level, information flow includes translation of DNA's genetic code into proteins responsible for cell structure and function as well as the communication signals between cells that coordinate function.

Cell-to-cell communication uses chemical signals, electrical signals, or a combination of both. Information may go from one cell to its neighbors (local communication) or from one part of the body to another (long-distance communication). Chapter 5 looks at the electrical gradients responsible for electrical signaling, while Chapter 6 discusses chemical communication in the body.

When chemical signals reach their target cells, they must get their information into the cell. Some molecules are able to pass through the barrier of the cell membrane, but signal molecules that cannot enter the cell must transfer their message across the cell membrane. How molecules cross biological membranes is the topic of Chapter 5, Chapter 6 looks at how chemical signals pass their information across the cell membrane.

Core Concept 5: Homeostasis Maintains Internal Stability

Organisms that survive in challenging habitats cope with external variability by keeping their internal environment relatively stable, an ability known as **homeostasis** {*homeo-*, similar + *-stasis*, condition}. Homeostasis and regulation of the internal environment are key principles of physiology and form an underlying core concept in each chapter of this book. The next section looks in detail at the key elements of this important core concept.

1.4 Homeostasis

The concept of a relatively stable internal environment is attributed to the French physician Claude Bernard in the mid-1800s. During his studies of experimental medicine, Bernard noted the stability of various physiological functions, such as body temperature, heart rate, and blood pressure. As the chair of physiology at the University of Paris, he wrote "La fixité du milieu intérieur est la condition de la vie libre, indépendante." (The constancy of the

internal environment is the condition for a free and independent life.)[5] This idea was applied to many of the experimental observations of his day, and it became the subject of discussion among physiologists and physicians.

In 1929, an American physiologist named **Walter B. Cannon** wrote a review for the American Physiological Society.[6] Using observations made by numerous physiologists and physicians during the nineteenth and early twentieth centuries, Cannon proposed a list of variables that are under homeostatic control. We now know that his list was both accurate and complete. Cannon divided his variables into what he described as environmental factors that affect cells (osmolarity, temperature, and pH) and "materials for cell needs" (nutrients, water, sodium, calcium, other inorganic ions, oxygen, as well as "internal secretions having general and continuous effects"). Cannon's "internal secretions" are the hormones and other chemicals that our cells use to communicate with one another.

In his essay, Cannon created the word *homeostasis* to describe the regulation of the body's internal environment. He explained that he selected the prefix *homeo-* (meaning *like* or *similar*) rather than the prefix *homo-* (meaning *same*) because the internal environment is maintained within a range of values rather than at an exact fixed value. He also pointed out that the suffix *-stasis* in this instance means a *condition*, not a state that is static and unchanging. Cannon's homeostasis, therefore, is a state of maintaining "a similar condition," similar to Claude Bernard's relatively constant internal environment.

Some physiologists contend that a literal interpretation of *stasis* {a state of standing} in the word *homeostasis* implies a static, unchanging state. They argue that we should use the word *homeodynamics* instead, to reflect the small changes constantly taking place in our internal environment {*dynamikos*, force or power}. Whether the process is called homeostasis or homeodynamics, the important concept to remember is that the body monitors its internal state and takes action to correct disruptions that threaten its normal function. Physiologists today generally recognize 10 variables (**TABLE 1.1**) that the body monitors and regulates to maintain homeostasis.

If the body fails to maintain homeostasis of the critical variables listed by Walter Cannon, then healthy function is disrupted and a disease state, or **pathological** condition {*pathos*, suffering}, may result. Diseases fall into two general groups according to their origin: those in which the problem arises from internal failure of some normal physiological process, and those that originate from some outside source. Internal causes of disease include the abnormal growth of cells, which may cause cancer or benign tumors; the production of antibodies by the body against its own tissues (autoimmune diseases); and the premature death of cells or the failure of cell processes. Inherited disorders are also considered to have internal causes. External causes of disease include toxic chemicals, physical trauma, and foreign invaders such as viruses and bacteria.

In both internally and externally caused diseases, when homeostasis is disturbed, the body attempts to compensate (**FIG. 1.5**). If the compensation is successful, homeostasis is restored. If compensation fails, illness or disease may result. The study of body functions in a disease state is known as **pathophysiology.** You will encounter many examples of pathophysiology as we study the various systems of the body.

One very common pathological condition in the United States is **diabetes mellitus,** a metabolic disorder characterized by abnormally high blood glucose concentrations. Although we speak of diabetes as if it were a single disease, it is actually a whole family of diseases with various causes and manifestations. You will learn more about diabetes in the focus boxes scattered throughout the chapters of this book. The influence of this one disorder on many systems of the body makes it an excellent example of the integrative nature of physiology.

What Is the Body's Internal Environment?

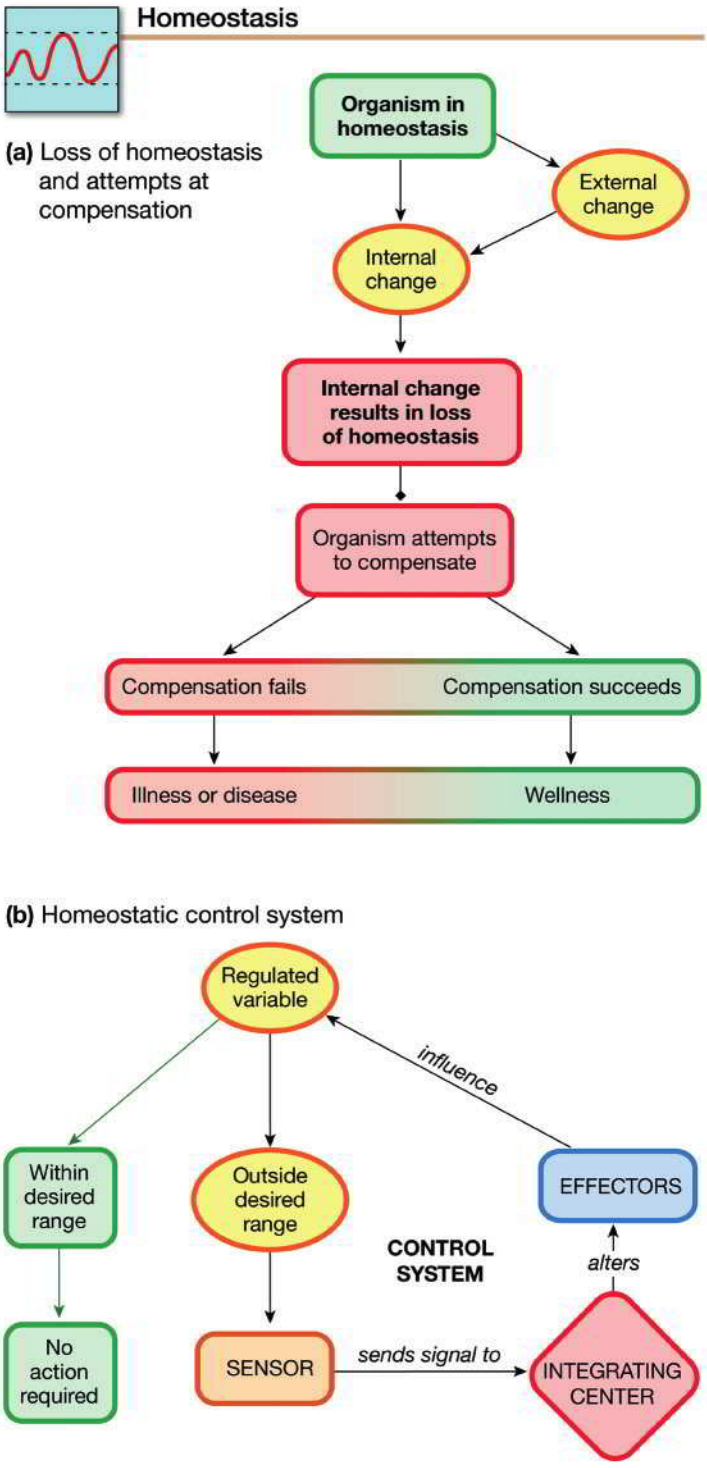
Claude Bernard wrote of the "constancy of the internal environment," but why is constancy so essential? As it turns out, most cells in our bodies are not very tolerant of changes in their surroundings. In this way they are similar to early organisms that lived in tropical seas, a stable environment where salinity, oxygen content, and pH vary little and where light and temperature cycle in predictable ways. The internal composition of these ancient creatures was almost identical to that of seawater. If environmental conditions changed, conditions inside the primitive organisms changed as well. Even today, marine invertebrates cannot tolerate significant changes in salinity and pH, as you know if you have ever maintained a saltwater aquarium.

In both ancient and modern times, many marine organisms relied on the constancy of their external environment to keep their internal environment in balance. In contrast, as organisms evolved and migrated from the ancient seas into estuaries, then into freshwater environments and onto the land, they encountered highly variable external environments. Rains dilute the salty water of estuaries, and organisms that live there must cope with the influx of water into their body fluids. Terrestrial organisms, including humans, face the challenge of dehydration—constantly losing internal water to the dry air around them. Keeping the internal environment stable means balancing water loss with appropriate water intake.

Table 1.1 Regulated Physiological Variables

Blood gases	Blood solutes	
• Oxygen • Carbon dioxide	• Potassium K^+ • Calcium Ca^{2+} • Hydrogen H^+ (pH) • Glucose	• Arterial blood pressure • Blood volume • Blood osmolarity • Body temperature (core)

Fig. 1.5 Homeostasis



But what exactly is the internal environment of the body? For multicellular animals, it is the watery internal environment that surrounds the cells, a "sea within" the body called the **extracellular fluid (ECF)** {*extra-*, outside of} (**FIG. 1.6**). Extracellular fluid serves as the transition between an organism's external environment and the **intracellular fluid (ICF)** inside cells {*intra-*, within}. Because extracellular fluid is a buffer zone between cells and the outside world, elaborate physiological processes have evolved to keep its composition relatively stable.

When the extracellular fluid composition varies outside its acceptable range of values, compensatory mechanisms are activated in an attempt to return the fluid to its usual state. For example, when you drink a large volume of water, the dilution of your extracellular fluid triggers a mechanism that causes your kidneys to remove excess water and protect your cells from swelling. Most cells of multicellular animals do not tolerate much change. They depend on the constancy of extracellular fluid to maintain their function.

Homeostasis Depends on Mass Balance

In the 1960s, a group of conspiracy theorists obtained a lock of Napoleon Bonaparte's hair and sent it for chemical analysis in an attempt to show that he died from arsenic poisoning. Today, a group of students sharing a pizza joke about the garlic odor on their breath. At first glance these two scenarios appear to have little in common, but in fact Napoleon's hair and "garlic breath" both demonstrate how the human body works to maintain the balance that we call *homeostasis*.

The human body is an open system that exchanges heat and materials with the outside environment. To maintain homeostasis, the body must maintain mass balance. We will consider mass balance to be another of our core concepts in physiology (Fig. 1.1).

The **law of mass balance** says that if the amount of a substance in the body is to remain constant, any gain must be offset by an equal loss (**FIG. 1.7a**). The amount of a substance in the body is also called the body's **load,** as in "sodium load."

For example, water loss to the external environment (output) in sweat and urine must be balanced by water intake from the external environment plus metabolic water production (input). The concentrations of other substances, such as oxygen and carbon dioxide, salts, and hydrogen ions (pH), are also maintained through mass balance. The following equation summarizes the law of mass balance:

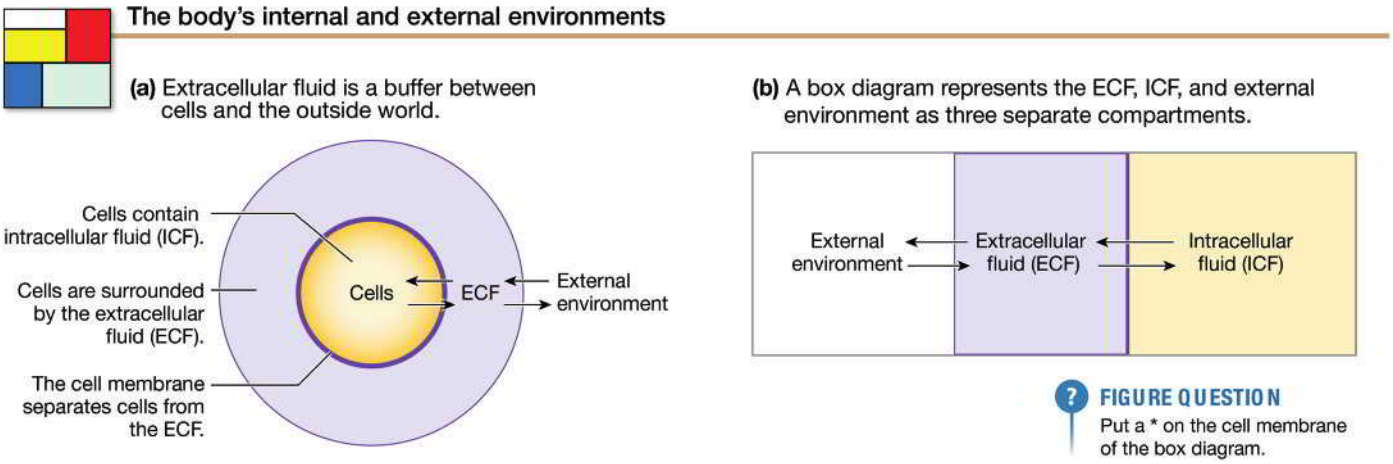
$$\text{Total amount of substance } x \text{ in the body} = \text{intake} + \text{production} - \text{excretion} - \text{metabolism}$$

Most substances enter the body from the outside environment, but some (such as carbon dioxide) are produced internally through metabolism (Fig. 1.7b). In general, water and nutrients enter the body as food and drink absorbed through the intestine. Oxygen and other gases and volatile molecules enter through the lungs. A few lipid-soluble chemicals make their way to the internal environment by penetrating the barrier of the skin.

To maintain mass balance, the body has two options for output. The simplest option is simply to excrete the material. **Excretion** is defined as the elimination of material from the body, usually through the urine, feces, lungs, or skin. For example, carbon dioxide (CO_2) produced during metabolism is excreted by the lungs. Many foreign substances that enter the body, such as drugs or artificial food additives, are excreted by the liver and kidneys. (Any foreign substance in the body is called a *xenobiotic*, from the Greek word *xenos*, a stranger.)

A second output option for maintaining mass balance is to convert the substance to a different substance through metabolism. Nutrients that enter the body become the starting point for

Fig. 1.6 Internal and external environments



metabolic pathways that convert the original nutrient to a different molecule. However, converting the original nutrient to something different then creates a new mass balance disturbance by adding more of the new substance, or *metabolite*, to the body. (*Metabolite* is the general term for any product created in a metabolic pathway.)

Mass Flow

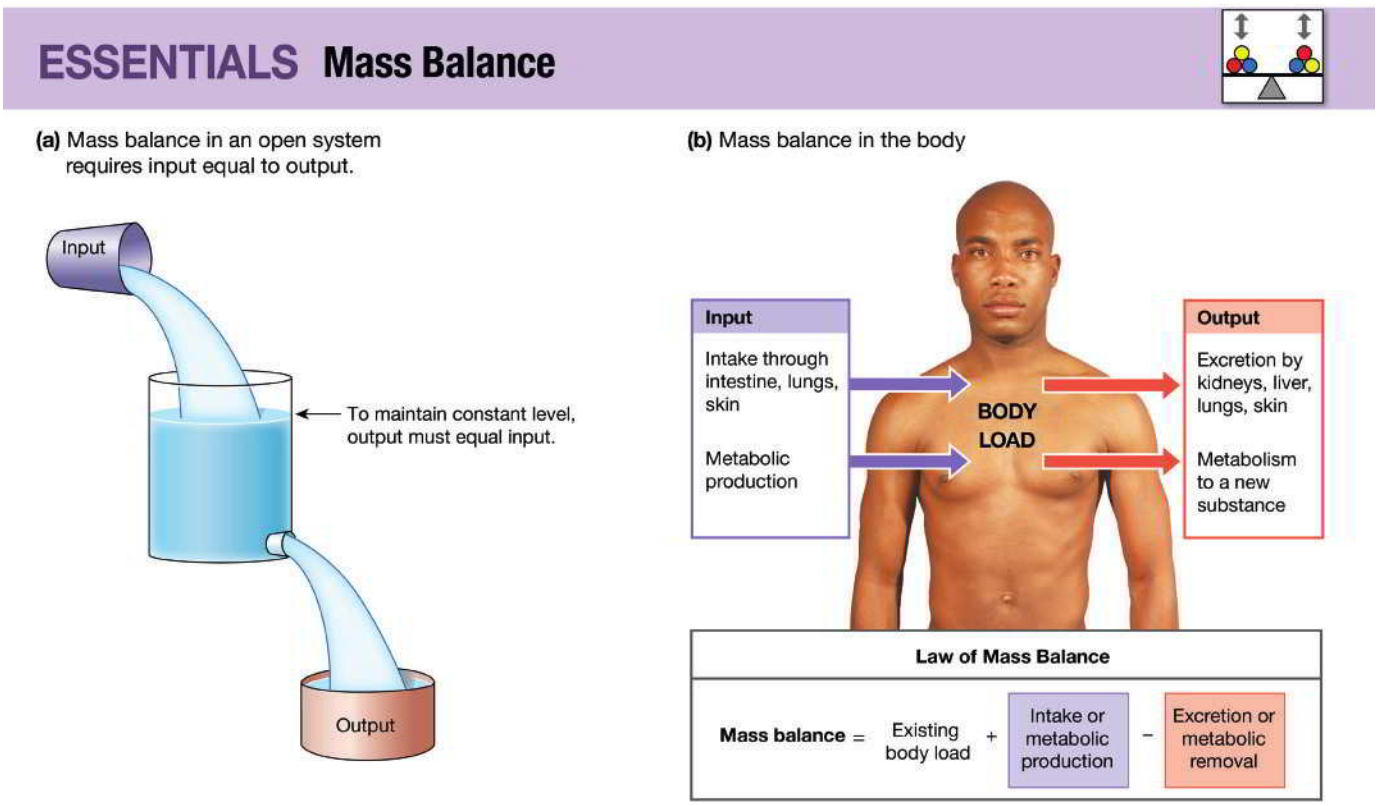
Scientists use **mass flow** to follow material throughout the body. Mass flow describes the rate of transport of a substance x as it moves through body fluids or into and out of the body. The equation for mass flow is

$$\text{Mass flow (amount } x/\text{min)} = \text{concentration of } x \text{ (amount } x/\text{vol)} \times \text{volume flow (vol/min)}$$

where volume flow describes the flow rate of a volume of blood, air, urine, and the like.

For example, suppose a person is given an intravenous (IV) infusion of glucose solution that has a concentration of 50 grams of glucose per liter of solution. If the infusion is given

Fig. 1.7 Mass balance



at a rate of 2 milliliters per minute, the mass flow of glucose into the body is:

$$\frac{50 \text{ g glucose}}{1000 \text{ mL solution}} \times 2 \text{ mL solution/min} = 0.1 \text{ g glucose/min}$$

The rate of glucose input into the body is 0.1 g glucose/min.

Mass flow applies not only to the entry, production, and removal of substances but also to the movement of substances from one compartment in the body to another. When materials enter the body, they first become part of the extracellular fluid. Where a substance goes after that depends on whether or not it can cross the barrier of the cell membrane and enter the cells.

Running Problem 1.4

Hiro wondered if there was another option for finding more information about probiotics, so he asked Jennifer, a friend who had just started graduate school in Public Health, how she would search. "I usually start with Google Scholar (scholar.google.com) rather than just googling. Google Scholar only shows you scholarly literature, so you won't get all the websites that are trying to sell you something. Or if you want to search the way scientists and healthcare professionals do, then try PubMed (www.pubmed.gov), the free database published by the U.S. National Library of Medicine." Hiro entered *probiotics* into Google Scholar and then repeated the same search in PubMed. "This is still way too much information," Hiro thought. "Surely there are ways to narrow this down."

Q4: *Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from the simple Google search.*

Q5: *One way to get fewer results is to limit the results to only recent papers. Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*

Excretion and Metabolism Clear Substances from the Body

It is relatively easy to monitor how much of a substance enters the body from the outside world, but it is more difficult to track molecules inside the body to monitor their excretion or metabolism. Instead of directly measuring the substance, we can follow the rate at which the substance disappears from the blood, a concept called **clearance.** Clearance is usually expressed as a volume of blood *cleared* of substance x per unit of time. For this reason, clearance is only an indirect measure of how substance x is handled by the body.

Clearance cannot tell you if the substance is disappearing by excretion or metabolism or by both. For example, urea is a normal metabolite produced from protein metabolism. A typical value for urea clearance is 70 mL plasma cleared of urea per minute, written as $urea\ clearance = 70\ mL\ plasma/min$. Knowing the rate at which urea disappears does not tell us anything about where urea is going. (It is being excreted by the kidneys.)

The kidney and the liver are the two primary organs that clear solutes from the body. *Hepatocytes* {*hepaticus*, pertaining to the liver + *cyte*, cell}, or liver cells, metabolize many different types of molecules, especially xenobiotics such as drugs. The resulting metabolites may be secreted into the intestine for excretion in the feces or released into the blood for removal by the kidneys. Pharmaceutical companies testing chemicals for their potential use as therapeutic drugs must know the clearance of the chemical before they can develop the proper dosing schedule.

Clearance also takes place in tissues other than the liver and kidneys. Saliva, sweat, breast milk, and hair all contain substances that have been cleared from the body. Salivary secretion of the hormone *cortisol* provides a simple noninvasive source of hormone for monitoring chronic stress.

An everyday example of clearance is "garlic breath," which occurs when volatile lipid-soluble garlic compounds in the blood pass into the airways and are exhaled. The lungs also clear ethanol in the blood: exhaled alcohol is the basis of the "breathalyzer" test used by law enforcement agencies. Drugs and alcohol secreted into breast milk are potentially dangerous because a breastfeeding infant will ingest these substances.

The 1960s analysis of Napoleon Bonaparte's hair tested it for arsenic because hair follicles help clear some compounds from the body. The test results showed significant concentrations of the poison in his hair, but the question remains whether Napoleon was murdered, poisoned accidentally, or died from stomach cancer.

Concept Check

1. If a person eats 12 milligrams (mg) of salt in a day and excretes 11 mg of it in the urine, what happened to the remaining 1 mg?
2. Glucose is metabolized to CO_2 and water. Explain the effect of glucose metabolism on mass balance in the body.

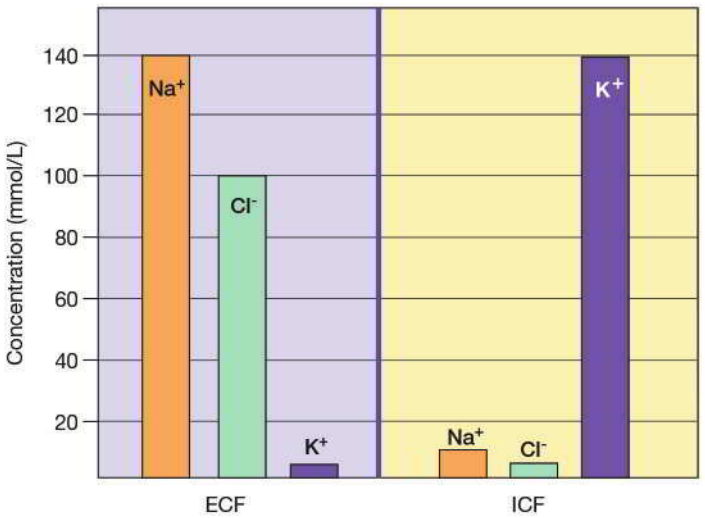
Homeostasis Does Not Mean Equilibrium

When physiologists talk about homeostasis, they are speaking of the stability of the body's **internal environment**—in other words, the stability of the extracellular fluid compartment (ECF). One reason for focusing on extracellular fluid homeostasis is that it is relatively easy to monitor by taking a blood sample. When you centrifuge blood, it separates into two parts: **plasma,** the fluid component, plus the heavier blood cells. Plasma is part of the extracellular fluid compartment, and its composition can be easily analyzed. It is much more difficult to follow what is taking place in the intracellular fluid compartment (ICF), although cells do maintain *cellular homeostasis*.

Fig. 1.8 Steady-state disequilibrium

Steady-state disequilibrium

The body compartments are in a dynamic steady state but are not at equilibrium. Ion concentrations are very different in the extracellular fluid compartment (ECF) and the intracellular fluid compartment (ICF).



In a state of homeostasis, the composition of both body compartments is relatively stable. This condition is a dynamic **steady state.** The modifier *dynamic* indicates that materials are constantly moving back and forth between the two compartments. In a steady state, there is no *net* movement of materials between the compartments.

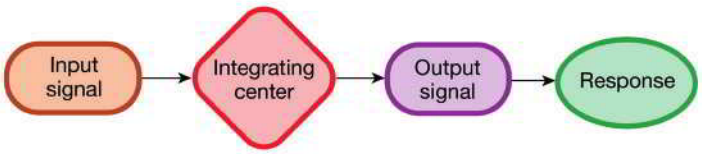
Steady state is not the same as **equilibrium** {*aequus*, equal + *libra*, balance}, however. Equilibrium implies that the composition of the body compartments is identical. If we examine the composition of the ECF and ICF, we find that the concentrations of many substances are different in the two compartments (**FIG. 1.8**). For example, sodium (Na^+) and chloride (Cl^-) are far more concentrated in the ECF than in the ICF, while potassium (K^+) is most concentrated in the ICF. Because of these concentration differences, the two fluid compartments are not at equilibrium. Instead the ECF and ICF exist in a state of relatively stable **disequilibrium** {*dis-* is a negative prefix indicating the opposite of the base noun}. For living organisms, the goal of homeostasis is to maintain the dynamic steady states of the body's compartments, not to make the compartments the same.

1.5 Control Systems and Homeostasis

In their simplest form, all **control systems** have three components (**FIG. 1.9**): (1) an input signal; (2) a controller, or **integrating center** {*integrare*, to restore}, that integrates incoming information and initiates an appropriate response; and (3) an output signal that creates a response. Long-distance reflex control systems are more complex than this simple model, however, as they may include input from multiple sources and have output that acts on multiple targets.

Fig. 1.9 A simple control system

A simple control system



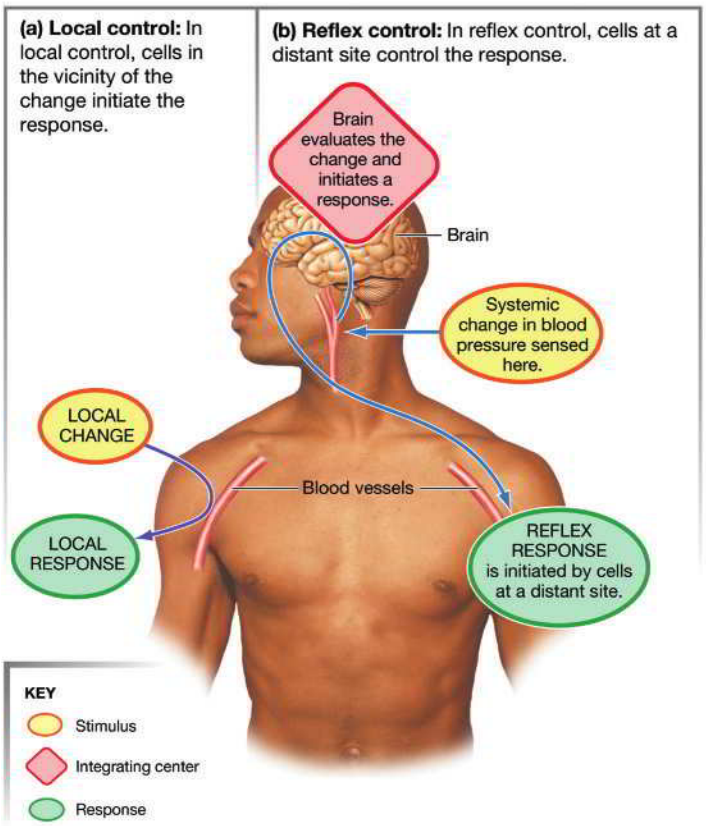
Local Control Is Restricted to a Tissue

The simplest form of control is **local control,** which is restricted to the tissue or cell involved (**FIG. 1.10**). In local control, a relatively isolated change occurs in a tissue. A nearby cell or group of cells senses the change in their immediate vicinity and responds, usually by releasing a chemical. The response is restricted to the region where the change took place—hence the term *local control*.

One example of local control can be observed when oxygen concentration in a tissue decreases. Cells lining the small blood vessels that bring blood to the area sense the lower oxygen concentration and respond by secreting a chemical signal. The signal molecule diffuses to nearby muscles in the blood vessel

Fig. 1.10 Local control and reflex control

A comparison of local control and reflex control



wall, bringing them a message to relax. Relaxation of the muscles widens (*dilates*) the blood vessel, which increases blood flow into the tissue and brings more oxygen to the area.

Reflex Control Uses Long-Distance Signaling

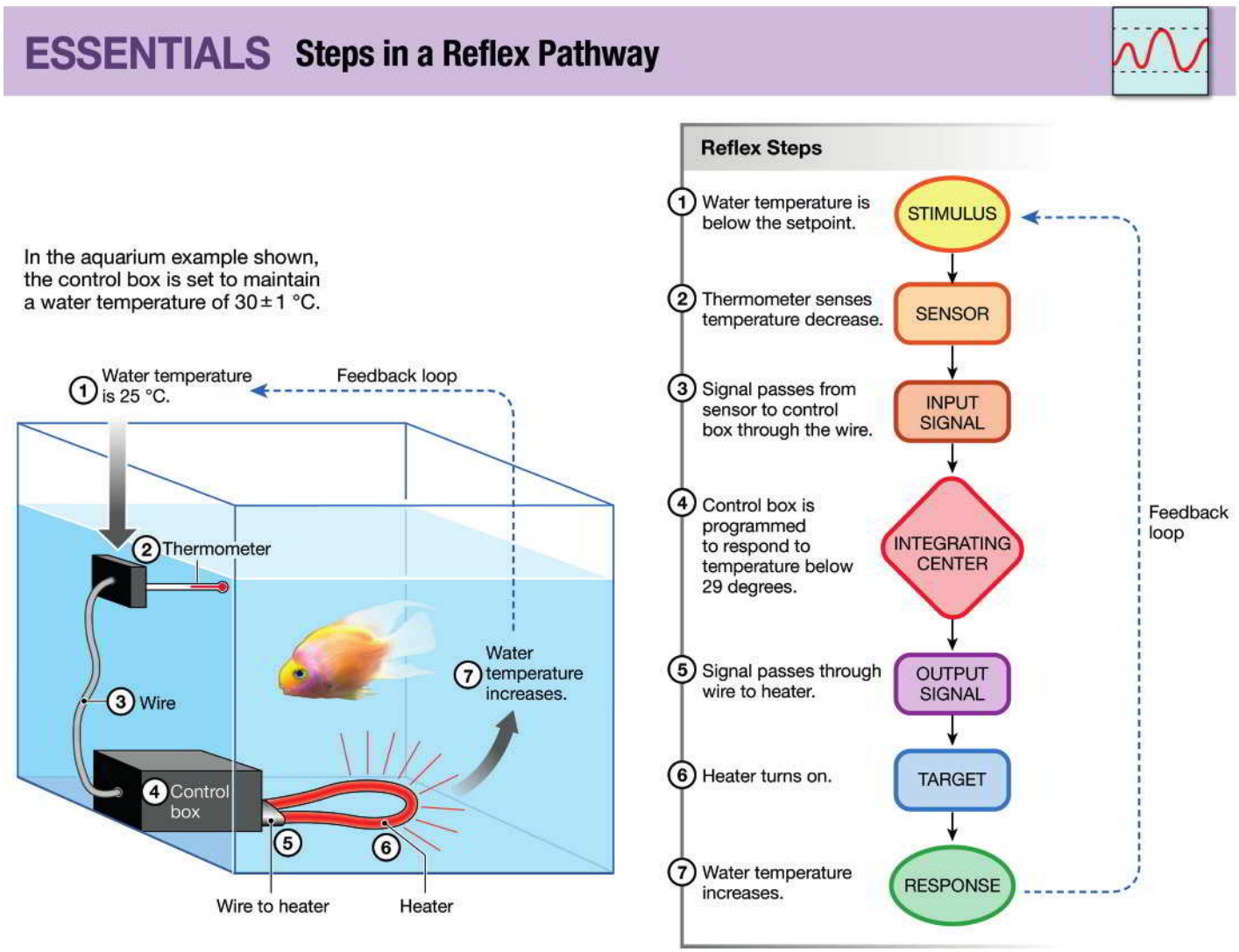
Changes that are widespread throughout the body, or *systemic* in nature, require more complex control systems. For example, maintaining blood pressure to drive blood flow throughout the body is a systemic issue rather than a local one. Because blood pressure is body-wide, maintaining it requires long-distance communication and coordination. We will use the term **reflex control** to mean any long-distance pathway that uses the nervous system, endocrine system, or both. Chapter 6 discusses different reflex pathways in more detail. It is important to note that not all reflexes are homeostatic! For example, the knee jerk reflex (patellar tendon reflex), where your lower leg kicks out after a tap just below the kneecap, is a reflex but it has nothing to do with homeostasis.

Physiological reflexes can be represented by response loops (**FIG. 1.11**). As with the simple control system just described, a **response loop** has three primary components: an *input signal*, an *integrating center* to integrate the signal, and an *output signal*. These three components can be expanded into the following sequence of seven steps to form a pattern that is found with slight variations in all reflex pathways:

Stimulus → sensor → input signal → integrating center → output signal → target → response

The input side of the response loop starts with a *stimulus*—the change that occurs when the regulated variable moves out of its desirable range. A specialized **sensor** monitors the variable. If the sensor is activated by the stimulus, it sends an input signal to the integrating center. The integrating center evaluates the information coming from the sensor and initiates an output signal. The output signal directs a target to carry out a response.

Fig. 1.11 The steps in a reflex pathway



In mammals, integrating centers are usually part of the nervous system or endocrine system. Output signals may be chemical signals, electrical signals, or a combination of both. The targets activated by output signals can be any cell of the body. If the reflex ends with the response, such as the knee-jerk reflex, the reflex is considered an **open-loop control system**. Open response loops are not homeostatic. A *closed-loop control system* has **feedback**, where the pathway's response "feeds back" to inform the sensor that a change has occurred. You will encounter both open and closed response loops as you study physiology, but homeostasis requires closed response loops with negative feedback.

Homeostasis Requires Monitored Variables

To maintain homeostasis, the human body monitors certain key functions, such as blood pressure and blood glucose concentration, that must stay within a particular operating range if the body is to remain healthy (Tbl. 1.1). These important **regulated variables** (monitored variables) are kept within their acceptable (normal) range by long-distance reflex control mechanisms that kick in if the variable ever strays too far from its **setpoint**, or preferred value.

To illustrate closed response loops and homeostasis, let's apply the concept to a simple nonbiological example. Think about an aquarium whose heater is programmed to maintain the water temperature (the regulated variable) at 30 °C (Fig. 1.11). The room temperature is 25 °C. The desired water temperature (30 °C) is the *setpoint* for the regulated variable.

Assume that initially the aquarium water is at room temperature, 25 °C. When you turn the control box on, you set the response loop in motion. The thermometer (sensor) registers a temperature of 25 °C. It sends this information through a wire (input signal) to the control box (integrating center). The control box is programmed to evaluate the incoming temperature signal, compare it with the setpoint for the system (30 °C), and "decide" whether a response is needed to bring the water temperature up to the setpoint. The control box sends a signal through another wire (output signal) to the heater (the target), which turns on and starts heating the water (response). This sequence—from stimulus to response—is the response loop.

This aquarium example involves a variable (temperature) controlled by a single control system (the heater). We can also describe a system that is under dual control. For example, think of a house that has both heating and air conditioning. The owner would like the house to remain at 70 °F (about 21 °C). On chilly autumn mornings, when the temperature in the house falls, the heater turns on to warm the house. Then, as the day warms up, the heater is no longer needed and turns off. When the sun heats the house above the setpoint, the air conditioner turns on to cool the house back to 70 °F. The heater and air conditioner have *antagonistic control* over house temperature because they work in opposition to each other. Similar situations occur in the human body when two branches of the nervous system or two different hormones have opposing effects on a single target.

Concept Check

3. What is the drawback of having only a single control system (a heater) for maintaining aquarium water temperature in some desired range?

Feedback Loops Modulate the Response Loop

The response loop is only the first part of many reflexes. For example, in the aquarium just described, the sensor sends temperature information to the control box, which recognizes that the water is too cold. The control box responds by turning on the heater to warm the water. Once the response starts, what keeps the heater from sending the temperature up to, say, 50 °C?

The answer is a **feedback loop,** where the response "feeds back" to influence the input portion of the pathway. In the aquarium example, turning on the heater increases the temperature of the water. The sensor continuously monitors the temperature and sends that information to the control box. When the control box gets feedback that the temperature has warmed up to the maximum acceptable value, it shuts off the heater, ending the reflex response.

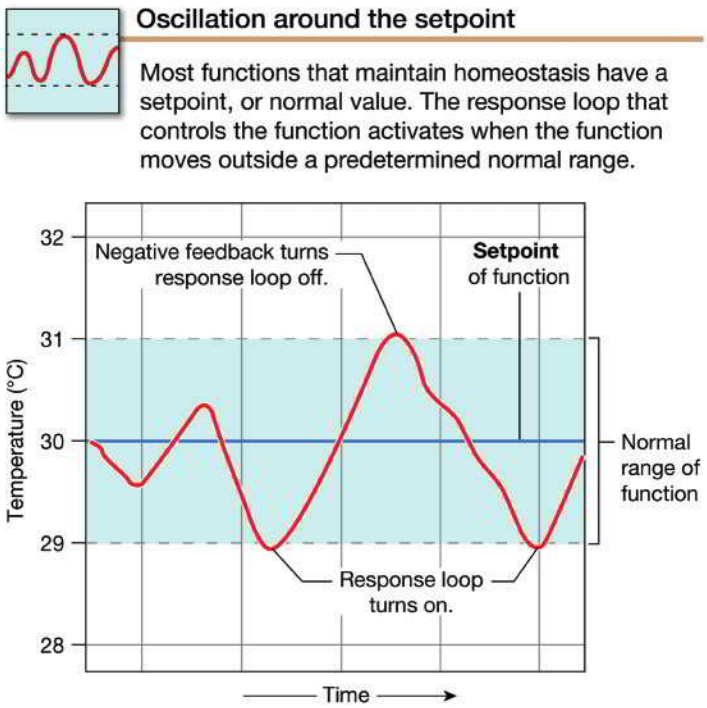
Negative Feedback Loops Are Homeostatic

For most reflexes, feedback loops are homeostatic—that is, designed to keep the system at or near a setpoint so that the regulated variable is relatively stable. How well an integrating center succeeds in maintaining stability depends on the *sensitivity* of the system. In the case of our aquarium, the control box is programmed to have a sensitivity of ±1 °C. If the water temperature drops from 30 °C to 29.5 °C, it is still within the acceptable range, and no response occurs. If the water temperature drops below 29 °C (30 − 1), the control box turns the heater on (**FIG. 1.12**). As the water heats up, the control box constantly receives information about the water temperature from the sensor. When the water reaches 31 °C (30 ± 1), the upper limit for the acceptable range, the feedback loop causes the control box to turn the heater off. The water then gradually cools off until the cycle starts all over again. The end result is a regulated variable that *oscillates* {*oscillare*, to swing} around the setpoint.

In physiological systems, some sensors are more sensitive than others. For example, the sensors that trigger reflexes to conserve water activate when blood concentration increases only 3% above the acceptable range, but the sensors for low oxygen in the blood will not respond until oxygen has decreased by 40%.

A pathway in which the response opposes or removes the signal is known as **negative feedback** (**FIG. 1.13a**). Negative feedback loops *stabilize* the regulated variable and thus aid the system in maintaining homeostasis. In the aquarium example, the heater warms the water (the response) and removes the

Fig. 1.12 Oscillation around the setpoint



stimulus (low water temperature). With loss of the stimulus for the pathway, the response loop shuts off. *Negative feedback loops can restore the usual state but cannot prevent the initial disturbance.*

Positive Feedback Loops Are Not Homeostatic

A few reflex pathways are not homeostatic. In a **positive feedback loop,** the response *reinforces* the stimulus rather than decreasing or removing it. In positive feedback, the response sends the regulated variable even farther from its usual value. This initiates a vicious cycle of ever-increasing response and sends the system temporarily out of control (Fig. 1.13b). Because positive feedback escalates the response, this type of feedback requires some intervention or event outside the loop to stop the response.

One example of a positive feedback loop involves the hormonal control of uterine contractions during childbirth (**FIG. 1.14**). When the baby is ready to be delivered, it drops lower in the uterus and begins to put pressure on the *cervix,* the opening of the uterus. Sensory signals from the cervix to the brain cause release of the hormone *oxytocin,* which causes the uterus to contract and push the baby's head even harder against the cervix, further stretching it. The increased stretch causes more oxytocin release, which causes more contractions that push the baby harder against the cervix. This cycle continues until finally the baby is delivered, releasing the stretch on the cervix and stopping the positive feedback loop.

Concept Check

4. Does the aquarium heating system in Figure 1.11 operate using positive feedback or negative feedback?

Feedforward Control Allows the Body to Anticipate Change

Negative feedback loops can stabilize a function and maintain it within an acceptable range but are unable to prevent the change that triggered the reflex in the first place. A few reflexes have evolved that enable the body to predict that a change is about to occur and start the response loop in anticipation of the change. These anticipatory responses are called **feedforward control.**

Fig. 1.13 Negative and positive feedback

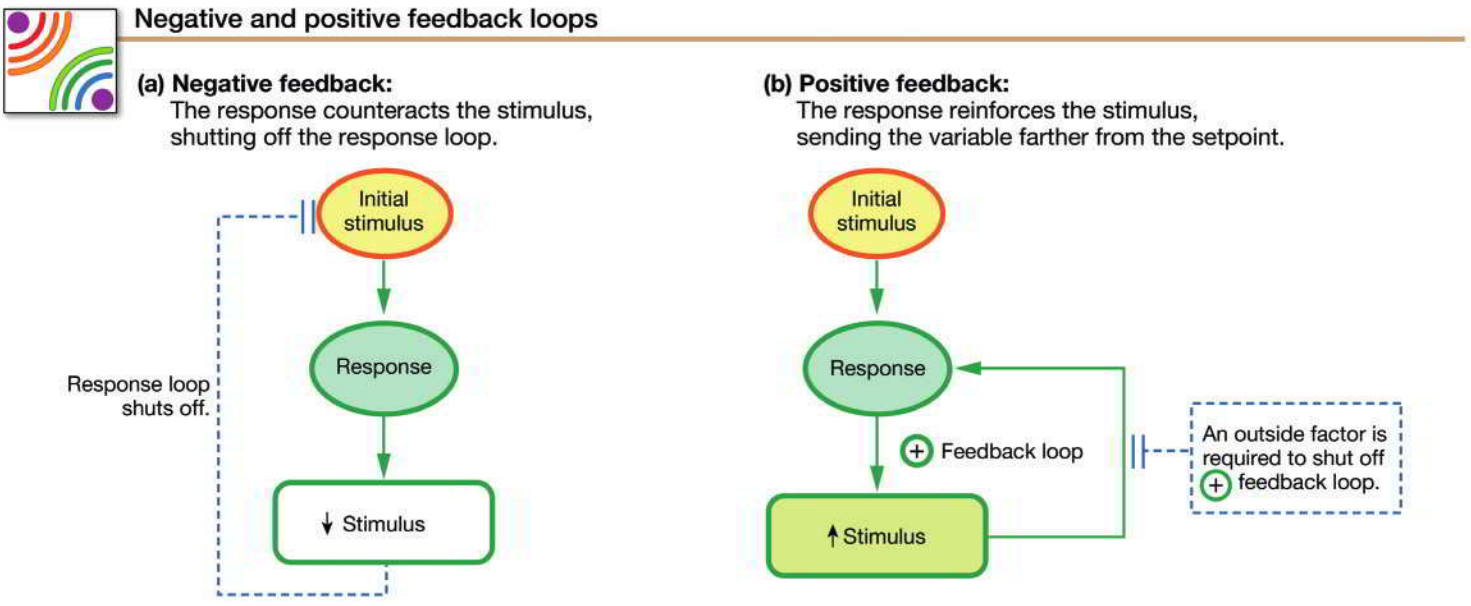
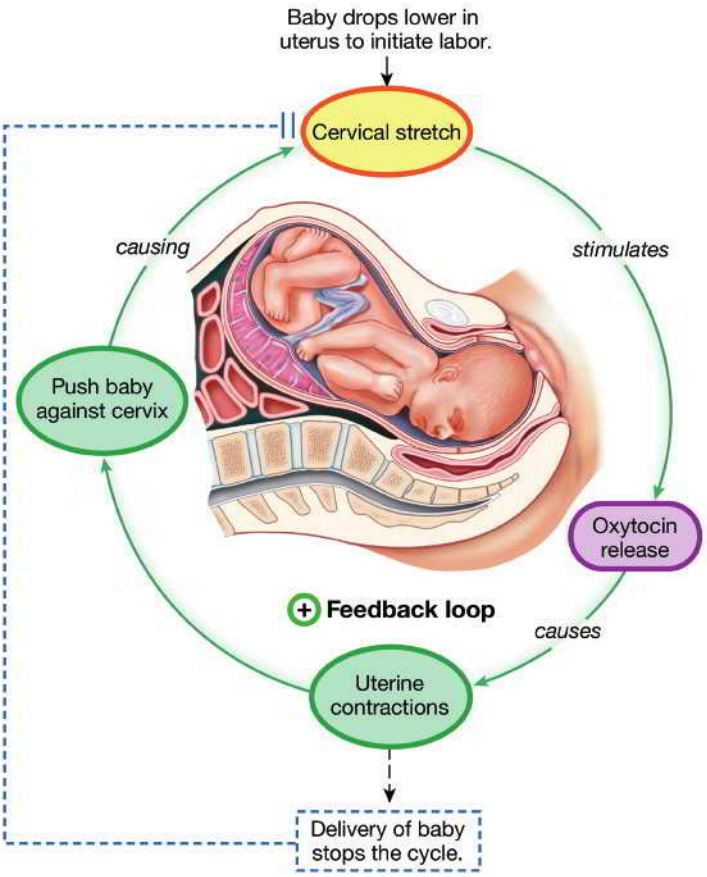


Fig. 1.14 A positive feedback loop



An easily understood physiological example of feedforward control is the salivation reflex. The sight, smell, or even the thought of food is enough to start our mouths watering in expectation of eating the food. This reflex extends even further, because the same stimuli can start the secretion of hydrochloric acid as the stomach anticipates food on the way. One of the most complex feedforward reflexes appears to be the body's response to exercise discussed in Chapter 25.

Biological Rhythms Result from Changes in a Setpoint

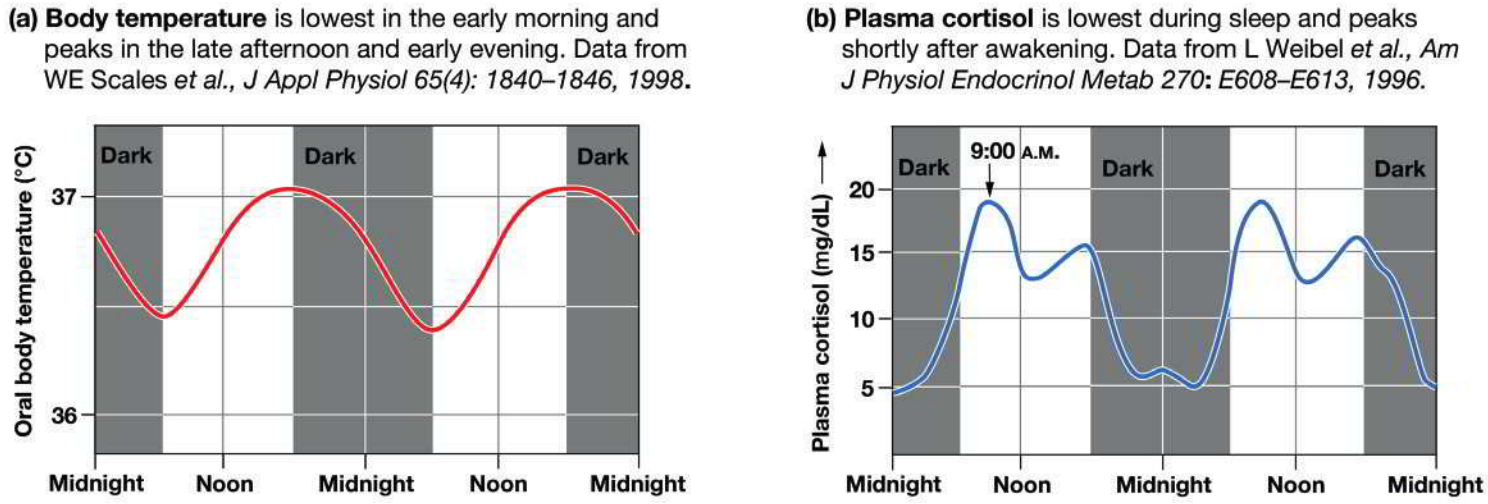
As discussed earlier, each regulated variable has an acceptable range within which it can vary without triggering a correction. In physiological systems, the setpoints for many regulated variables are different from person to person, or may change for the same individual over a period of time. Factors that influence an individual's setpoint for a given variable include normal biological rhythms, inheritance, and the conditions to which the person has become accustomed.

Regulated variables that change predictably and create repeating patterns or cycles of change are called **biological rhythms**, or *biorhythms*. The timing of many biorhythms coincides with a predictable environmental change, such as daily light–dark cycles or the seasons. Biological rhythms reflect changes in the setpoint of the regulated variable.

For example, all animals exhibit some form of daily biological rhythm, called a **circadian rhythm** {*circa*, about + *dies*, day}. Humans have circadian rhythms for many body functions, including blood pressure, body temperature, and metabolic processes. For example, body temperature peaks in the late afternoon and declines dramatically in the early hours of the morning (**FIG. 1.15a**). Have you ever been studying late at night and noticed that you feel cold? This is not because of a drop in environmental temperature but because your thermoregulatory reflex has turned down your internal thermostat.

One of the interesting correlations between circadian rhythms and behavior involves body temperature. Researchers found that self-described "morning people" have temperature rhythms that cause body temperature to climb before they wake

Fig. 1.15 Circadian rhythms in humans



up in the morning, so that they get out of bed prepared to face the world. On the other hand, "night people" may be forced by school and work schedules to get out of bed while their body temperature is still at its lowest point, before their bodies are prepared for activity. These night people are still going strong and working productively in the early hours of the morning, when the morning people's body temperatures are dropping and they are fast asleep.

Many hormones in humans have blood concentrations that fluctuate predictably in a 24-hour cycle. Cortisol, growth hormone, and the sex hormones are among the most noted examples. A cortisol concentration in a 9:00 AM sample might be nearly twice as high as one taken in the early afternoon (Fig. 1.15b).

If a patient has a suspected abnormality in hormone secretion, it is therefore important to know when hormone levels are measured. A concentration that is normal at 9:00 AM is high at 2:00 PM. One strategy for avoiding errors due to circadian fluctuations is to collect information for a full day and calculate an average value over 24 hours. For example, cortisol secretion is estimated indirectly by measuring all urinary cortisol metabolites excreted in 24 hours.

What is the adaptive significance of functions that vary with a circadian rhythm? Our best answer is that biological rhythms create an anticipatory response to a predictable environmental variable. There are seasonal rhythms of reproduction in many organisms. These rhythms are timed so that the offspring have food and other favorable conditions to maximize survival.

Circadian rhythms cued by the light–dark cycle may correspond to rest-activity cycles. These rhythms allow our bodies to anticipate behavior and coordinate body processes accordingly. You may hear people who are accustomed to eating dinner at 6:00 PM say that they cannot digest their food if they wait until 10:00 PM to eat because their digestive system has "shut down" in anticipation of going to bed.

Some variability in setpoints is associated with changing environmental conditions rather than biological rhythms. The adaptation of physiological processes to a given set of environmental conditions is known as **acclimatization** when it occurs naturally. If the process takes place artificially in a laboratory setting, it is called **acclimation**. Each winter, people in the upper latitudes of the northern hemisphere go south in February, hoping to escape the bitter subzero temperatures and snows of the northern climate. As the northerners walk around in 40 °F (about 4 °C) weather in short-sleeve shirts, the southerners, all bundled up in coats and gloves, cannot understand why: the weather is cold! The difference in behavior is due to different temperature acclimatization, a difference in the setpoint for body temperature regulation that is a result of prior conditioning.

Biorhythms and acclimatization are complex processes that scientists still do not completely understand. Some rhythms arise from special groups of cells in the brain and are reinforced by information about the light–dark cycle that comes in through the eyes. Some organs outside the nervous system generate their own rhythms of protein synthesis and breakdown. Research in simpler animals such as flies is helping explain the molecular basis for biological rhythms. We discuss the cellular and molecular basis for circadian rhythms in Chapter 10.

Running Problem 1.5

Most of the articles Hiro found in PubMed and Google Scholar seemed to be focused on detailed descriptions of experiments. "Is there any way to find papers that are not so complicated?" he asked Jennifer.

"Well, when I'm trying to learn about a new topic, I look for review articles, which are summaries of recent research. Both Google Scholar and PubMed have options that let you limit your results to show only review articles." Hiro went back to PubMed and Google Scholar to see if this would help him find the information he was looking for.

Jennifer had also mentioned using artificial intelligence to answer the question. "But you need to be cautious and always verify what an AI program tells you." Hiro went to ChatGPT (chat.openai.com) and typed "What does research say about taking probiotics?"

Q6: *On the Google Scholar and PubMed pages with results from the last 5 years, select the option for review articles. Now how many results are there?*

Q7: *Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*

1.6 The Science of Physiology

How do we know what we know about the physiology of the human body? The first descriptions of physiology came from simple observations. But physiology is an experimental science, one in which researchers generate **hypotheses** {*hypotithenai*, to assume; singular *hypothesis*}, or logical guesses, about how events take place. They test their hypotheses by designing experiments to collect evidence that supports or disproves their hypotheses, and they publish the results of their experiments in the scientific literature. Healthcare providers look in the scientific literature for evidence from these experiments to help guide their clinical decision-making. Critically evaluating the scientific evidence in this manner is a practice known as *evidence-based medicine*. Observation and experimentation are the key elements of **scientific inquiry.**

Good Scientific Experiments Must Be Carefully Designed

A common type of biological experiment either removes or alters some variable that the investigator thinks is an essential part of an observed phenomenon. That altered variable is the **independent variable.** For example, a biologist notices that birds at a feeder seem to eat more in the winter than in the summer. She generates a hypothesis that cold temperatures cause birds to increase their food intake. To test her hypothesis, she designs an experiment in

which she keeps birds at different temperatures and monitors how much food they eat. In her experiment, temperature, the manipulated element, is the independent variable. Food intake, which is hypothesized to be dependent on temperature, becomes the **dependent variable.**

Concept Check

5. Students in the laboratory run an experiment in which they drink different volumes of water and measure their urine output in the hour following drinking. What are the independent and dependent variables in this experiment?

An essential feature of any experiment is an experimental **control.** A control group is usually a duplicate of the experimental group in every respect except that the independent variable is not changed from its initial value. Ideally, all other conditions are kept identical in the control and experimental groups, and those factors are considered **controlled variables**. For example, in the bird-feeding experiment, the control group would be a set of birds maintained at a warm summer temperature but otherwise treated exactly like the birds held at cold temperatures. The purpose of the control group is to ensure that any observed changes are due to the manipulated variable and not to changes in some other variable. For example, suppose that in the bird-feeding experiment food intake increased after the investigator changed to a different food. Unless she had a control group that was also fed the new food, the investigator could not determine whether the increased food intake was due to temperature or to the fact that the new food was more palatable. The type of food fed to the birds would be a controlled variable.

During an experiment, the investigator carefully collects information, or **data** {plural; singular *datum*, a thing given}, about the effect that the manipulated (independent) variable has on the observed (dependent) variable. Once the investigator feels that she has sufficient information to draw a conclusion, she begins to analyze the data. Analysis can take many forms and usually includes statistical analysis to determine if apparent differences are statistically significant. A common format for presenting data is a graph (**FIG. 1.16**).

If one experiment supports the hypothesis that cold causes birds to eat more, then the experiment should be repeated to ensure that the results were not an unusual one-time event. This step is called **replication.** When the data support a hypothesis in multiple experiments, the hypothesis may become a working **model.** A model with substantial evidence from multiple investigators supporting it may become a **scientific theory.**

Most information presented in textbooks like this one is based on models that scientists have developed from the best available experimental evidence. On occasion, investigators publish new experimental evidence that does not support a current model. In that case, the model must be revised to fit the available evidence. For this reason, you may learn a physiological "fact" while using this textbook, but in 10 years that "fact" may be inaccurate because of what scientists have discovered in the interval.

For example, in 1970, students learned that the cell membrane was a "butter sandwich," a structure composed of a layer of fats sandwiched between two layers of proteins. In 1972, however, scientists presented a very different model of the membrane, in which globules of proteins float within a double layer of fats. As a result, students who had learned the butter sandwich model had to revise their mental model of the membrane.

Where do our scientific models for human physiology come from? We have learned much of what we know from experiments on animals ranging from fruit flies and squid to rats. In many instances, the physiological processes in such animals are either identical to those taking place in humans or else similar enough that we can extrapolate from the animal model to humans. It is important to use nonhuman models because experiments using human subjects can be difficult to perform.

However, not all studies done on animals can be applied to humans. For example, an antidepressant drug that Europeans had used safely for years was undergoing stringent testing required by the U.S. Food and Drug Administration before it could be sold in this country. When beagle dogs were given the drug for a period of months, the dogs started dying from heart problems. Scientists were alarmed until further research showed that beagles have a unique genetic makeup that causes them to break down the drug into a more toxic substance. The drug was perfectly safe in other breeds of dogs and in humans, and it was subsequently approved for human use.

The Results of Human Experiments Can Be Difficult to Interpret

Many reasons make it difficult to carry out physiological experiments in humans, including variability, psychological factors, and ethical considerations.

Variability

Human populations have tremendous genetic and environmental **variability.** It has been traditional in medicine to talk about "normal values" for body functions, but what is "normal" for one person may not be "normal" for someone else. When possible, it is better to use the word *typical* or *healthy* although you will still encounter *normal* in tables and discussions of variables that can be quantified, such as blood glucose concentrations. Physiology books usually present *average* values for many physiological variables, such as blood pressure, but these average values simply represent a number that falls somewhere near the middle of a wide range of values.

The variability found in human populations can make it difficult to show significant differences between experimental and control groups in a human experiment. Ideally, an investigator would have to include a large number of identical subjects in a study. However, getting two groups of people who are *identical* in every respect is impossible. Instead, the researcher must attempt to recruit subjects who are *similar* in as many aspects as possible. You may have seen newspaper advertisements requesting research volunteers: "Healthy males between 18 and 25,

Fig. 1.16 Focus on . . . Graphing

Focus on . . . Graphing

Graphs are pictorial representations of the relationship between two (or more) variables, plotted in a rectangular region. Graphs present a large amount of numerical data in a small space, emphasize comparisons between variables, or show trends over time.

A viewer can extract information much more rapidly from a graph than from a table of numbers or from a written description. A well-constructed graph should contain (in very abbreviated form) everything the reader needs to know about the data, including the purpose of the experiment, how the experiment was conducted, and the results.

All scientific graphs have common features.

The horizontal axis is called the **x-axis**.

The vertical axis is called the **y-axis**.

The intersection of the two axes is called the **origin**. The origin usually, but not always, has a value of zero for both axes.

The simplest way to know what most graphs mean is the substitute the labels on the X and Y axes into the following sentence:

The effect of [X] on [Y]

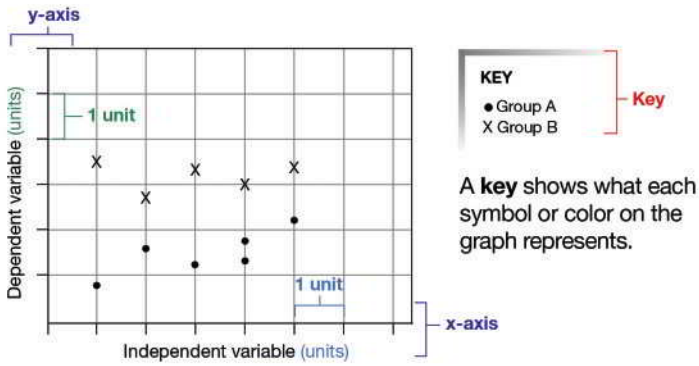
The x-axis shows values of the variable manipulated by the experimenter. This is called the **independent variable**.

The y-axis shows the variable measured by the experimenter. It is called the **dependent variable**.

If the experimental design is valid and the hypothesis is correct, changes in the independent variable (x-axis) will cause changes in the dependent variable (y-axis).

In other words, y is a function of x, or mathematically, y = f(x).

A graph should have a **title** (usually put above the graph) or **legend** below the graph. These describe what the graph represents.



A **key** shows what each symbol or color on the graph represents.

Each axis of a graph is divided into units represented by evenly spaced tick marks on the axis.

Each axis has a label that tells

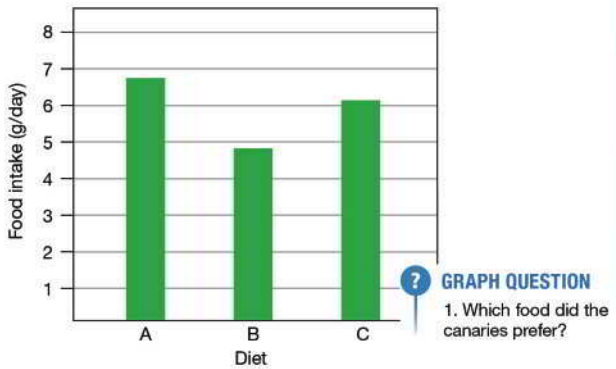
- what variable the axis represents (time, temperature, amount of food consumed)
- the units of the axis (days, degrees Celsius, grams per day).

Most graphs you will encounter in physiology display data either as bars (bar graphs or histograms), as lines (line graphs), or as dots (scatter plots). Some typical types of graphs are shown here.

Here's one approach to reading graphs:

1. Read the title and legend. These are a capsule summary of the graph's contents.
2. Read the axis labels and put them into the sentence
   The effect of [X] on [Y].
3. Look for trends in the graph. Are lines horizontal or do they have a slope? Are bars the same height or different heights?

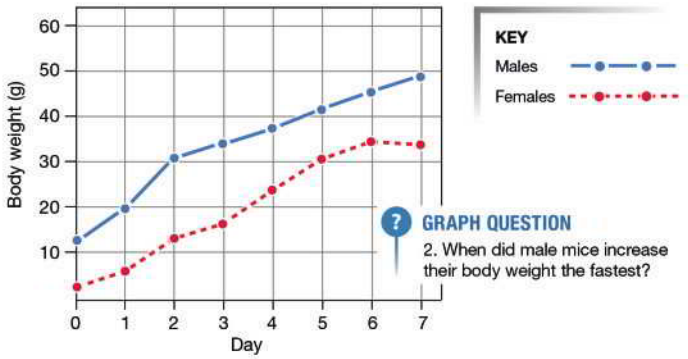
Bar graphs are used when the independent variables are distinct entities. Each bar represents a different variable. The bars are lined up side by side so that they can easily be compared with one another. Scientific bar graphs traditionally have vertical bars.



Canaries were fed one of three diets and their food intake was monitored for three weeks.

Line graphs are used when the independent variable on the x-axis is a continuous phenomenon, such as time, temperature, or weight.

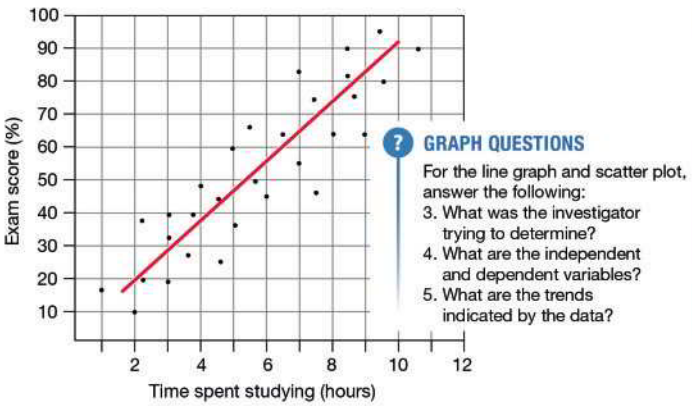
- Each point on the graph represents the average of a set of observations.
- Because the independent variable is a continuous function, the points can be connected with a line (point-to-point connections or a mathematically calculated "best fit" line or curve).
- The slope of the line between two points represents the rate at which the variable changed.
- Connecting the points with lines allows the reader to **interpolate**, or estimate values between the measured values.



Male and female mice were fed a standard diet and weighed daily.

Scatter plots show the relationship between two variables, such as time spent studying for an exam and performance on that exam.

- Usually each point on the plot represents one member of a test population.
- Individual points on a scatter plot are never connected by a line, but a "best fit" line or curve may indicate a trend in the data.



Student scores were directly related to the amount of time they spent studying.

Try It!

Graphing

Students in a physiology laboratory collected heart rate data on one another. In each case, heart rate was measured first for the subject at rest and again after the subject had exercised for 5 minutes using a step test.

Data from the experiment are shown in the table.

Subject	Sex	Age	Resting heart rate (beats/min)	Post exercise heart rate (beats/min)
1	M	20	58	90
2	M	21	62	110
3	F	19	70	111
4	M	20	64	95
5	F	20	85	120
6	F	19	72	98
7	F	21	73	101

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Describe two observations you can make from the data.

(c) Draw one graph that illustrates both findings you described in (b). Label each axis with the correct variable.

(*Hint:* Excel is a simple way to make graphs from data in tables. Excel calls graphs "charts.")

nonsmokers, within 10% of ideal body weight, to participate in a study. . . .” Researchers must take into account the variability inherent in even a select group of humans when doing experiments with human subjects. This variability may affect the researcher’s ability to interpret the significance of data collected on that group.

One way to reduce variability within a test population, whether human or animal, is to do a **crossover study.** In a crossover study, each individual acts both as experimental subject and as control. Thus, the individual’s responses to the treatment can be compared to the same subject's control value. This method is particularly effective when there is wide variability within a population.

For example, in a test of blood pressure medication, investigators might divide subjects into two groups. Group A takes an inactive substance called a **placebo** (from the Latin for “I shall be pleasing”) for the first half of the experiment, then changes to the experimental drug for the second half. Group B starts with the experimental drug, and then changes to the placebo. This scheme enables the researcher to assess the effect of the drug on each individual. In other words, subjects act as their own control. Statistically, the data analysis can use methods that look at the changes within each individual rather than at changes in the collective group data.

Psychological Factors

Another significant variable in human studies is the psychological aspect of administering a treatment. If you give someone a pill and tell the person that it will help alleviate some problem, there is a strong possibility that the pill will have exactly that effect, even if it contains only sugar or an inert substance. This well-documented phenomenon is called the **placebo effect.** Similarly, if you warn people that a drug they are taking may have specific adverse side effects, those people will report a higher incidence of the side effects than a similar group of people who were not warned. This phenomenon is called the **nocebo effect,** from the Latin *nocere,* to do harm. The placebo and nocebo effects show the ability of our minds to alter the physiological functioning of our bodies.

In setting up an experiment with human subjects, we must try to control for the placebo and nocebo effects. The simplest way to do this is with a **blind study,** in which the subjects do not know whether they are receiving the treatment or the placebo. Even this precaution can fail, however, if the researchers assessing the subjects know which type of treatment each subject is receiving. The researchers’ expectations of what the treatment will or will not do may color their measurements or interpretations.

To avoid this outcome, researchers often use **double-blind studies.** A third party, not involved in the experiment, is the only one who knows which group is receiving the experimental treatment and which group is receiving the control treatment. The most sophisticated experimental design for minimizing psychological effects is the **double-blind crossover study.** In this type of study, the control group in the first half of the experiment becomes the experimental group in the second half, and vice versa, but no one involved knows who is taking the active treatment.

Ethical Considerations

Ethical questions arise when humans are used as experimental subjects, particularly when the subjects are people suffering from a disease or other illness. Is it ethical to withhold a new and promising treatment from the control group? A noteworthy example occurred some years ago when researchers were testing the efficacy of a treatment for dissolving blood clots in heart attack victims. The survival rate among the treated patients was so much higher that testing was halted so that members of the control group could also be given the experimental drug.

In contrast, tests on some anticancer agents have shown that the experimental treatments were less effective in stopping the spread of cancer than were the standard treatments used by the controls. Was it ethical to undertreat patients in the experimental group by depriving them of the more effective current medical practice? Most studies now are evaluated continually over the course of the study to minimize the possibility that subjects will be harmed by their participation.

In 2002, a trial on hormone replacement therapy in postmenopausal women was halted early when investigators realized that women taking a pill containing two hormones were developing cardiovascular disease and breast cancer at a higher rate than women on placebo pills. On the other hand, the women receiving hormones also had *lower* rates of colon cancer and bone fractures. The investigators performed a *risk-benefit analysis* and decided that the risks associated with taking the hormones exceeded the potential benefits, so they stopped the study. To learn more about this clinical trial and the pros and cons of hormone replacement therapy, visit MedlinePlus, a website of the U.S. National Library of Medicine.

Human Studies Can Take Many Forms

Almost daily, the newspapers carry articles about clinical trials studying the efficacy of drugs or other medical treatments. Many different aspects of experimental design can affect the validity and applicability of the results of these trials. For example, some trials are carried out for only a limited time on a limited number of people, such as studies conducted for the U.S. Food and Drug Administration’s drug-approval process. In several instances in recent years, drugs approved as a result of such studies have later been withdrawn from the market when extended use of the drug by larger populations uncovered adverse side effects, including deaths.

Longitudinal studies are designed to be carried out for a long period of time. One of the most famous longitudinal studies is the Framingham Heart Study, started in 1948 and still ongoing. Framingham is a **prospective study** {*prospectus*, outlook, looking forward} that recruited healthy people and has been following them for years to identify factors that contribute to the development of cardiovascular disease. This study has already made important contributions to healthcare, and it continues today with the adult children and grandchildren of the original participants.

Additional study designs you may encounter in the literature include cross-sectional and retrospective studies. **Cross-sectional studies** survey a population for the prevalence of a disease or condition. Data from cross-sectional studies identify trends to be

investigated further, such as whether age group or socioeconomic status is associated with a higher risk of developing the condition being surveyed. **Retrospective studies** {*retro*, backward + *spectare*, to look} match groups of people who all have a particular disease to a similar but healthy control group. The goal of these studies is to determine whether development of the disease can be associated with a particular variable.

Often, the results of one or more published studies do not agree with the conclusions of other published studies. In some cases, the reason for the disagreement turns out to be a limitation of the experimental design, such as a small number of subjects who may not be representative of larger populations. In other cases, the disagreement may be due to small but potentially significant differences in the experimental designs of the different studies.

One way scientists attempt to resolve contradictory results is to perform a **meta-analysis** of the data {*meta-*, at a higher level}. A meta-analysis combines all the data from a group of similar studies and uses sophisticated statistical techniques to extract significant trends or findings from the combined data. For example, multiple studies have been done to assess whether glucosamine and chondroitin, two dietary supplements, can improve degenerative joint disease. However, the individual studies had small numbers of subjects (<50) and used different dosing regimens. A meta-analysis using statistical methods is one way to compare the results from these studies.[7]

The difficulty of using human subjects in experiments is one of the reasons scientists use animals to develop many of our scientific models. Since the 1970s, physiological research has increasingly augmented animal experimentation with techniques developed by cellular biologists and molecular geneticists. As we have come to understand the fundamentals of chemical signaling and communication in the body, we have unlocked the mysteries of many processes. In doing so, we also have come closer to being able to treat many diseases by correcting their cause rather than simply treating their symptoms.

More and more, medicine is turning to therapies based on interventions at the molecular level. A classic example is the treatment of cystic fibrosis (CF), an inherited disease in which the mucus of the lungs and digestive tract is unusually thick. For many years, patients with this condition had few treatment options, and most died at a young age. However, basic research into the mechanisms by which salt and water move across cell membranes provided clues to the underlying cause of cystic fibrosis: a defective protein in the membrane of certain cells. The newest treatments for CF now improve the function of the defective protein, and life expectancy of people with CF is close to that of the general population. Without the basic research into how cells and tissues carry out their usual tasks, however, this treatment would never have been developed. Some of the most exciting therapies coming to medicine are interventions targeting gene mutations that result in disease. In late 2023, the U.S. Food and Drug Administration approved two new treatments correcting the gene mutation that causes the abnormal hemoglobin associated with sickle cell disease.

As you read this book and learn what we know about how the human body works, keep in mind that many of the ideas presented are not hard facts – they simply describe models that represent our current understanding and therefore are subject to change. As we learned during the COVID-19 pandemic, scientific knowledge is constantly and rapidly changing. There are still many questions in physiology waiting for investigators to find the answers.

Running Problem 1.6 Conclusion: What to Believe?

After reading a few of the review articles Hiro found while searching, he called Jennifer back. “Hey! Those were great suggestions, but I just need something simple. Is there some place that a nonmedical person should go to learn about probiotics?”

“I send my friends to MedlinePlus (www.medlineplus.gov) when they need basic information,” Jennifer answered. Hiro repeated his search once more in MedlinePlus and found himself back where he had started, with links to the probiotics articles on the NCCIH website. “All these sites are saying we don’t have enough information yet to know whether probiotics are helpful,” Hiro decided.

Most people today begin their quest for information by searching the internet. Be cautious! Anyone can make a website or video and publish it on the web. There is no screening process comparable to peer review in scientific journals, and the reader of a website must decide how valid the information on the site is. Websites published by recognized universities and nonprofit organizations are likely to have good information, but you should view an article about probiotics on a health food store web page with a skeptical eye unless the article cites published peer-reviewed research.

The best websites for health information are sponsored by organizations that are part of the scientific and healthcare communities, such as the National Institutes of Health (NIH), nonprofit groups dedicated to supporting research on a particular disease (e.g., The American Diabetes Association, diabetes.org), or clinics and universities where scientists and physicians are actively investigating causes and treatments for diseases. Treat commercial websites that end in **.com* with extra caution.

Check your answers to the questions against the information in the table below.

Question		Answer and Commentary
Q1:	*Rank these 10 results from most to likely to have good information, and explain how you chose your rankings.*	1. Best: The NIH websites that are written by scientists. *www.nccih.nih.gov, www.ods.od.nih.gov* 2. *mayoclinic.org* and *health.harvard.edu* are vetted by health professionals at medical schools 3. *webmd.com* and *healthline.com* are commercial sites with the potential for bias in favor of advertisers. 4. *en.wikipedia.org*: Wikipedia is a crowd-sourced website and sometimes contains information that is not accurate. 5. *seed.com, amazon.com,* and *ritual.com* are all commercial websites whose goal is to sell products.
Q2:	*What is the mission of NCCIH?*	The ABOUT page says the mission of NCCIH is to provide authoritative, science-based information on the use, safety, and efficacy of products used in complementary and integrative healthcare practices.
Q3:	*What does NCCIH say about whether probiotics are helpful and about whether they are safe?*	The "What you need to know" factsheet[8] on probiotics includes a warning about the risks of giving probiotics to premature infants. The section on effectiveness of probiotics says that although a lot is known, there are still unanswered questions about how probiotics work and when they might be unsafe.
Q4:	*Repeat Hiro's searches in Google Scholar and PubMed. Compare the number of results from these searches to the 244 million results from his simple Google search.*	The Google Scholar search returns over 860,000 results and the PubMed search yields more than 46,000 results.
Q5:	*Use the options in the left sidebar of the Google Scholar and PubMed pages and limit the search to the last 5 years. Now how many results are there?*	For the last 5 years, the Google Scholar search returns more than 32,000 results and the PubMed search has more than 23,000 results.
Q6:	*On the Google Scholar and PubMed pages with results from the last 5 years, select the option for reviews. Now how many results are there?*	For reviews in the last 5 years, the Google Scholar search has more than 21,000 results and the PubMed search has about 5,000 results.
Q7:	*Replicate Hiro's search in ChatGPT or another AI program. What does AI say about taking probiotics?*	The responses of an AI program might differ slightly each time a question is asked, but in January 2024, ChatGPT returned the following answer: *As of my last knowledge update in January 2022, research on probiotics was ongoing, and findings were mixed regarding their overall benefits.* The answer continued to point out that the topic is complex and that there might be more recent information based on better evidence.

Citing Resources

Whenever you use someone else's material, even if it is just for a class project, you should cite your source. If you put a photo from the web into a PowerPoint slide, be sure to include the URL. If you paraphrase something written, acknowledge where you learned the information. Copying or paraphrasing material from another source without acknowledging that source is academic dishonesty.

There are many different citation format styles. PubMed allows you to choose between AMA (American Medical Association), APA (American Psychological Association), MLA (Modern Language Association), and NLM (National Library of Medicine) styles when downloading references. Two useful websites for learning about citation styles are *Scientific Style and Format*[9], published by the Council of Science Editors, and Purdue University's Online Writing Lab, Purdue OWL (owl.purdue.edu).

Citing Web Sources

Unlike formally published resources like scientific journals, web pages are not permanent and frequently disappear or move. Here is one suggested format for citing information from a website:

Author/Editor (if known). Revision or copyright date (if available). Title of web page [Publication medium]. Publisher of webpage. *URL* [Date accessed].

Example:

Patton G (editor). 2005. Biological Journals and Abbreviations. [Online]. National Cancer Institute. *http://home.ncifcrf.gov/research/bja* [accessed April 10, 2005].

Citing Publications

Citation formats for papers in research journals vary but will usually include the following elements (with the punctuation shown):

Author(s). Article title. *Journal Name* volume (issue): inclusive pages, year of publication. DOI.

Example:

Echevarria M, Ilundain AA. Aquaporins. *J Physiol Biochem* 54(2): 107–118, 1998.

Many articles now have a unique DOI (digital object identifier) number. These are alphanumeric codes that provide a permanent link to the article on the Internet, so that even if a website changes names, you will still be able to find the article.

Helpful Hints

- If you access a published journal on the web, you should give the print citation and DOI, not the URL of the website.

- Journal names are abbreviated using standard abbreviations that you can look up online[10]. One-word titles, such as *Science,* are never abbreviated. For example, the *American Journal of Physiology* is abbreviated as *Am J Physiol*.
- Journals group their publications into volumes that correspond to a certain period of time (a year, six months, etc.). The first publication of a given volume is designated issue 1, the second is issue 2, and so on. In the citation *J Physiol Biochem* 54(2): 107–118, 1998, you know that this was volume 54, issue 2.
- Word-for-word quotations placed within quotation marks are rarely used in scientific writing.
- When paraphrasing in written work, acknowledge the source this way:

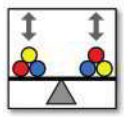
Some rare forms of epilepsy are known to be caused by mutations in ion channels (Mulley *et al*., 2003).

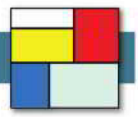
When a paper has three or more authors, we usually use the abbreviation *et al*.—from the Latin *et alii*, meaning "and others"—to save space in the body of the text. All authors' names are given in the full citation, which is usually included within a References section at the end of the paper.

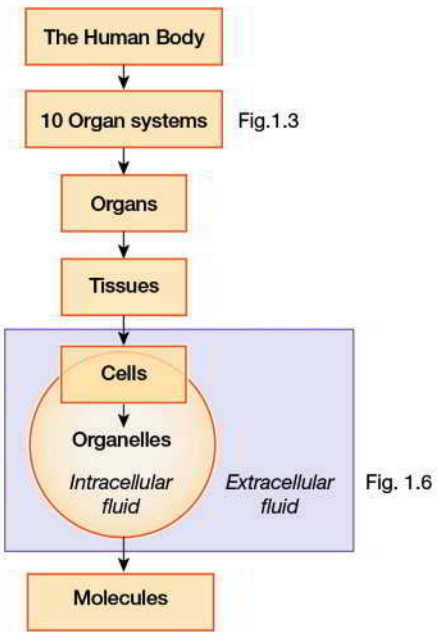
Chapter Summary

Chapter 1 has introduced you to the physiology you will be learning about as you continue through this book. The eight core concepts discussed here and in the other chapters in Unit 1 will provide you with a solid foundation for your studies.

Core Concepts in Physiology

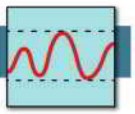
Core Concept	Structure-function	Molecular interactions	Compartmentation	Energy	Gradients	Communication	Homeostasis	Mass balance
Icon								

Levels of Organization 



Homeostasis

Fig. 1.5

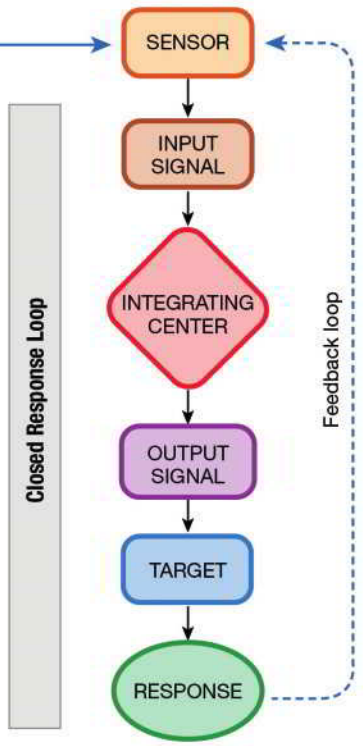


Maintenance of a relatively stable internal environment depends on

Table 1.1

10 Regulated Variables

- Some reflexes are not for homeostasis. Fig. 1.14
- Setpoints that initiate a response loop can vary. Fig. 1.15
- Negative feedback loops help maintain homeostasis. Fig. 1.11
- Positive feedback is not homeostatic. Fig. 1.13
- Feedforward reflexes anticipate a change.



Mass Balance

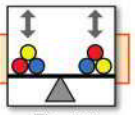
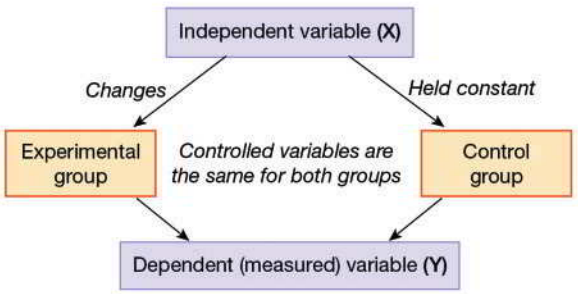


Fig. 1.7

- To maintain a steady state, input must equal output.
- Steady state is not the same as equilibrium.
- A disequilibrium can exist in a steady state. Fig. 1.8

The Science of Physiology

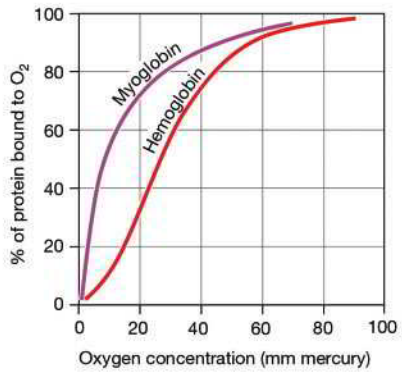
Scientific Experiments



Graphical display of data

Fig. 1.16

The effect of **X** on **Y**



Human Experiments

Complex because of

- Variability among individuals
  - What is "normal"?
- Psychological factors
  - Placebo and nocebo effects
- Ethical considerations
  - Risk-benefit analysis
  - Side effects
  - Undertreating

Types of Studies

- Blind and double-blind
- Crossover studies
- Prospective and retrospective
- Cross-sectional

Links to Resources

[1]DR Richardson. A survey of students' notions of body function as teleologic or mechanistic. *Advan Physiol Educ* 258: 8–10, Jun 1990. https://doi.org/10.1152/advances.1990.258.6.S8

[2]SR Smith et al. Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: a 6-wk translational research study. *Am J Physiol Endocrinol Metab* 293: E620–E627, 2007. https://doi.org/10.1152/ajpendo.00217.2007

[3]*Scientific Foundations for Future Physicians*. Howard Hughes Medical Institute (HHMI) and the Association of American Medical Colleges (AAMC), 2009. https://store.aamc.org/scientific-foundations-for-future-physicians-pdf.html

[4]*Vision and Change: A Call to Action*. National Science Foundation (NSF) and American Association for the Advancement of Science (AAAS). 2011.

[5]C Bernard. *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* (Vol. 1, p. 113), Paris: J.-B. Baillière, 1885. https://www.biodiversitylibrary.org/item/97313#page/151/mode/1up

[6]WB Cannon. Organization for physiological homeostasis. *Physiol Rev* 9: 399–443, 1929. nvc https://doi.org/10.1152/physrev.1929.9.3.399

[7]S Wandel et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *Br Med J* 341: c4675–c4676, 2010. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941572/

[8]*What you need to know* factsheet https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know#

[9]Scientific Style and Format https://www.scientificstyleandformat.org/Welcome.html

[10]https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/

[11]JB Moseley et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *The N Engl J Med* 347: 81–88, 2002. https://doi.org/10.1056/NEJMoa013259

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. Define physiology. Describe the relationship between physiology and anatomy.
2. Name the different levels of organization in the biosphere.
3. Name the 10 systems of the body and give their major function(s).
4. What does "Physiology is an integrative science" mean?
5. Define homeostasis. Name some regulated variables that are maintained through homeostasis.
6. Name eight core concepts in physiology.
7. Put the following parts of a reflex in the correct order for a physiological response loop: input signal, integrating center, output signal, response, sensor, stimulus, target.
8. The name for daily fluctuations of body functions such as blood pressure, temperature, and metabolic processes is a(n) _____.

Level Two Reviewing Concepts

9. **Mapping exercise:** Make a large map showing the organization of the human body. Show all levels of organization in the body (see Fig. 1.2) and all 10 organ systems. Try to include functions of all components on the map and remember that some structures may share functions. (*Hint:* Start with the human body as the most important term. You may also draw the outline of a body and make your map using it as the basis.)
10. Distinguish between the items in each group of terms.
    (a) tissues and organs
    (b) x-axis and y-axis on a graph
    (c) dependent and independent variables
    (d) teleological and mechanistic approaches
    (e) the internal and external environments for a human
    (f) blind, double-blind, and crossover studies
    (g) the target and the sensor in a control system
11. Name as many organs or body structures that connect directly with the external environment as you can.
12. Which organ systems are responsible for coordinating body function? For protecting the body from outside invaders? Which systems exchange material with the external environment, and what do they exchange?
13. Explain the differences among positive feedback, negative feedback, and feedforward mechanisms. Under what circumstances would each be advantageous?

Level Three Problem Solving

14. A group of biology majors went to a mall and asked passersby, "Why does blood flow?" These are some of the answers they received. Which answers are teleological and

which are mechanistic? (Not all answers are correct, but they can still be classified.)

(a) Because of gravity

(b) To bring oxygen and food to the cells

(c) Because if it didn't flow, we would die

(d) Because of the pumping action of the heart

15. Although dehydration is one of the most serious physiological obstacles that land animals must overcome, there are others. Think of as many as you can, and think of various strategies that different terrestrial animals have to overcome these obstacles. (*Hint:* Think of humans, insects, and amphibians; also think of as many different terrestrial habitats as you can.)

Level Four Quantitative Problems

16. A group of students wanted to see what effect a diet deficient in vitamin D would have on the growth of baby guppies. They fed the guppies a diet low in vitamin D and measured fish body length every third day for three weeks. Their data looked like this:

Day	0	3	6	9	12	15	18	21
Average body length (mm)	6	7	9	12	14	16	18	21

(a) What was the dependent variable and what was the independent variable in this experiment?

(b) What was the control in this experiment?

(c) Make a fully labeled graph with a legend, using the data in the table.

(d) During what time period was growth slowest? Most rapid? (Use your graph to answer this question.)

17. You performed an experiment in which you measured the volumes of nine slices of potato, then soaked the slices in solutions of different salinities for 30 minutes. At the end of 30 minutes, you again measured the volumes of the nine slices. The changes you found were:

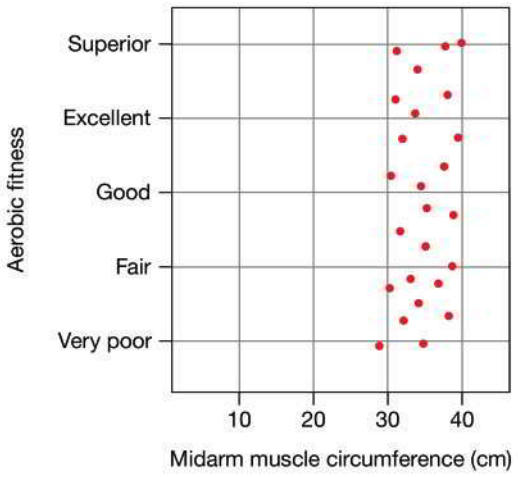
Percent Change in Volume after 30 Minutes			
Solution	**Sample 1**	**Sample 2**	**Sample 3**
Distilled water	10%	8%	11%
1% salt (NaCl)	0%	−0.5%	1%
9% salt (NaCl)	−8%	−12%	−11%

(a) What was the independent variable in this experiment? What was the dependent variable?

(b) Can you tell from the information given whether or not there was a control in this experiment? If there was a control, what was it?

(c) Graph the results of the experiment using the most appropriate type of graph.

18. At the end of the semester, researchers measured an intermediate-level class of 25 male weight lifters for aerobic fitness and midarm muscle circumference. The relationship between those two variables is graphed here.



(a) What kind of graph is this?

(b) What question were the investigators asking?

(c) In one sentence, summarize the relationship between the two variables plotted on the graph.

19. Answer the questions after the following article summary.

A study[11] was carried out on human volunteers to see whether two procedures performed during arthroscopic surgery {*arthro-*, joint + *scopium*, to look at} are effective in relieving knee pain associated with osteoarthritis, or degenerative joint disease {*osteon*, bone + *arthro* −, joint + *−itis*, inflammation}. The volunteers were up to 75 years old and were recruited from a Veterans Affairs Medical Center. They were 93% male and 60% white. One-third of the subjects had placebo operations—that is, they were given anesthesia and their knees were cut open, but the remainder of the treatment procedure was not done. The other two-thirds of the subjects had one of the two treatment procedures performed. Subjects were followed for two years. They answered questions about their knee pain and function and were given an objective walking and stair-climbing test. At the end of the study, the results showed no significant difference in knee function or perception of pain between subjects getting one of the standard treatments and those getting the placebo operation.

(a) Do you think it is ethical to perform placebo surgeries on humans who are suffering from a painful condition, even if the subjects are informed that they might receive the placebo operation and not the standard treatment?

(b) Give two possible explanations for the decreased pain reported by the placebo operation subjects.

(c) Analyze and critique the experimental design of this study. Are the results of this study applicable to everyone with knee pain?

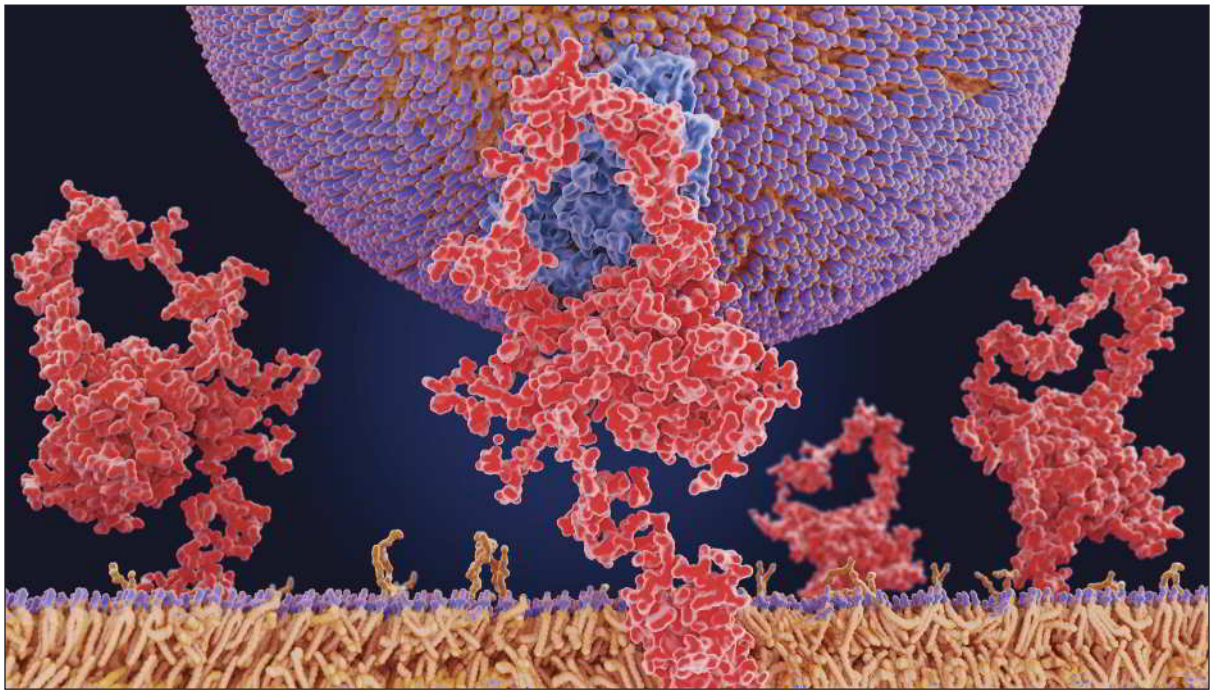
(d) Was this study a blind, double-blind, or double-blind crossover design?

(e) Why do you think the investigators felt it was necessary to include a placebo operation in this study?

Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

2

Molecular Interactions



LDL particle binding to the LDL receptor

Science regards man as an aggregation of atoms temporarily united by a mysterious force called the life-principle.

H. P. Blavatsky, 1877. In Isis Unveiled: A Master-Key to the Mysteries of Ancient and Modern Science and Theology, *Vol. I: Science*

Chapter 2 focuses on the core concept of Molecular Interactions, going from subatomic particles up to complex macromolecules that are responsible for many aspects of physiological function.

The first two sections of the chapter may be a review, depending on your background. Use the REVIEW figures to check your understanding of chemistry and biochemistry.

Section 2.3 focuses on protein binding, one of the key molecular interactions that govern physiological processes. The principles of protein binding apply to membrane transporters and signal receptors as well as to enzymes, so learning the basic patterns here is important.

Molecular Interactions

Learning Outcomes

2.1 Molecules and Bonds

- **LO 2.1.1** Compare and contrast the composition, structure, and functions of the four major groups of biomolecules.
- **LO 2.1.2** Describe four important biological roles of electrons.
- **LO 2.1.3** Describe and compare the different types of covalent and noncovalent bonds.

2.2 Noncovalent Interactions

- **LO 2.2.1** Contrast the structure and solubility of polar and nonpolar molecules.
- **LO 2.2.2** Describe the covalent and noncovalent interactions that contribute to molecular shape, and explain how molecular shape is related to molecular function.
- **LO 2.2.3** Define pH in words and mathematically, and explain the differences between acids, bases, and buffers.

2.3 Protein Interactions

- **LO 2.3.1** List nine important functions of proteins in the body.
- **LO 2.3.2** Explain the meanings of affinity, specificity, saturation, and competition in protein-ligand binding.
- **LO 2.3.3** Explain the different methods by which modulators alter protein binding or protein activity.

Nearly 100 years ago two scientists, Aleksander Oparin in Russia and John Haldane in England, speculated on how life might have arisen on a primitive Earth whose atmosphere consisted mainly of hydrogen, water, ammonia, and methane. Their theories were put to the test in 1953, when a 23-year-old scientist named Stanley Miller combined these molecules in a closed flask and boiled them for a week while periodically discharging flashes of electricity through them, simulating lightning. At the end of his test, Miller found amino acids had formed in the flask. With this simple experiment, he had shown that it was possible to create organic molecules, usually associated with living creatures, from nonliving inorganic precursors.

Miller's experiments were an early attempt to solve one of the biggest mysteries of biology: How did a collection of chemicals first acquire the complex properties that we associate with living creatures? We still do not have an answer to this question. Numerous scientific theories have been proposed, ranging from life arriving by meteor from outer space to molecules forming in deep ocean hydrothermal vents. No matter what their origin, the molecules associated with living organisms have the ability to organize themselves into compartments, replicate themselves, and act as *catalysts* to speed up reactions that would otherwise proceed too slowly to be useful.

The human body is far removed from the earliest life forms, but we are still a collection of chemicals—dilute solutions of dissolved and suspended molecules enclosed in compartments with lipid-protein walls. Strong links between atoms, known as **chemical bonds**, store and transfer energy to support life functions. Weaker interactions between and within molecules create distinctive molecular shapes and allow biological molecules to interact reversibly with each other.

This chapter introduces some of the fundamental principles of molecular interactions that you will encounter repeatedly in your study of physiology. The human body is more than 50% water, and because most of its molecules are dissolved in this water, we will review the properties of aqueous solutions. If you would like to refresh your understanding of the key features of **atoms**, chemical bonds, and biomolecules, you will find a series of one- and two-page review features that encapsulate biochemistry as it pertains to physiology. You can test your knowledge of basic chemistry and biochemistry with a special review quiz at the end of the chapter.

Running Problem 2.1: Chromium Supplements

"Lose weight while gaining muscle," the ads promise. "Prevent heart disease." "Stabilize blood sugar." What is this miracle substance? It's chromium picolinate, a nutritional supplement being marketed to consumers looking for a quick fix. Does it work, though, and is it safe? Some athletes, like Malik—the star running back on the college football team—swear by it. Malik takes 500 micrograms of chromium picolinate daily. Many researchers, however, are skeptical and feel that the necessity for and safety of chromium supplements have not been established.

2.1 Molecules and Bonds

There are more than 100 known elements on Earth, but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are considered *major* **essential elements**. Some additional *minor essential elements* (trace elements) are required in minute amounts, but there is no universal agreement on which trace elements are essential for cell function in humans. The **periodic table** shows the major and commonly accepted minor essential elements.

Most Biomolecules Contain Carbon, Hydrogen, and Oxygen

Molecules that contain carbon are known as **organic molecules,** because it was once thought that they all existed in or were derived from plants and animals. Organic molecules associated with living organisms are also called **biomolecules.** There are four major groups of biomolecules: carbohydrates, lipids, proteins, and nucleotides.

The body uses carbohydrates, lipids, and proteins for energy and as the building blocks of cellular components. The fourth group, the **nucleotides**, includes DNA, **RNA**, ATP, and cyclic AMP. DNA and RNA are the structural components of genetic

material. **ATP** (adenosine triphosphate) and related molecules carry energy, while **cyclic AMP** (adenosine monophosphate; cAMP) and related compounds regulate metabolism.

Each group of biomolecules has a characteristic composition and molecular structure. **Lipids** are mostly carbon and hydrogen (**FIG. 2.1**). **Carbohydrates** are primarily carbon, hydrogen, and oxygen, in the ratio CH_2O (**FIG. 2.2**). **Proteins** and nucleotides contain nitrogen in addition to carbon, hydrogen, and oxygen (**FIGS. 2.3** and **2.4**). Two **amino acids**, the building blocks of proteins, also contain sulfur.

Fig. 2.1 REVIEW Biochemistry of Lipids

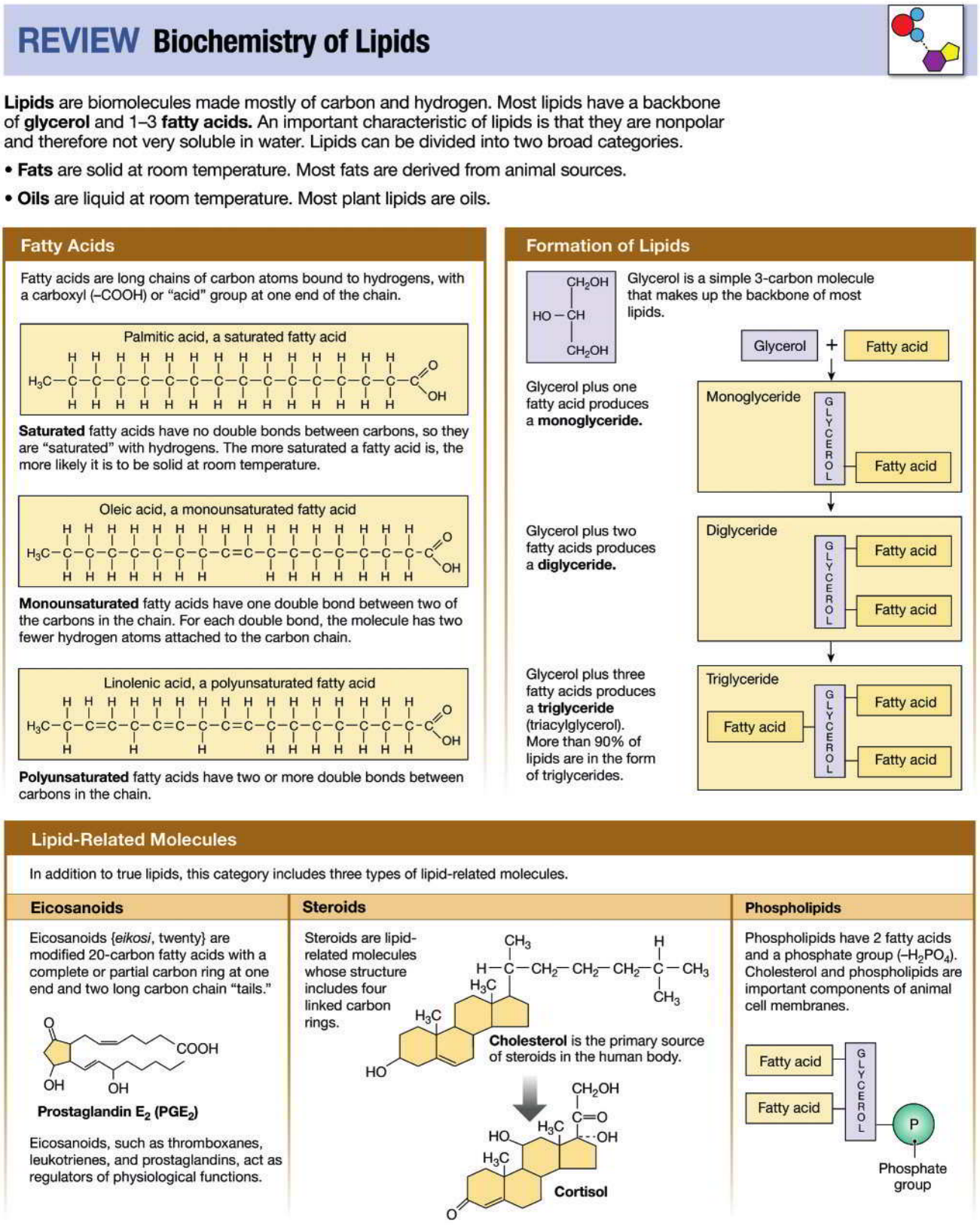


Fig. 2.2 REVIEW Biochemistry of Carbohydrates

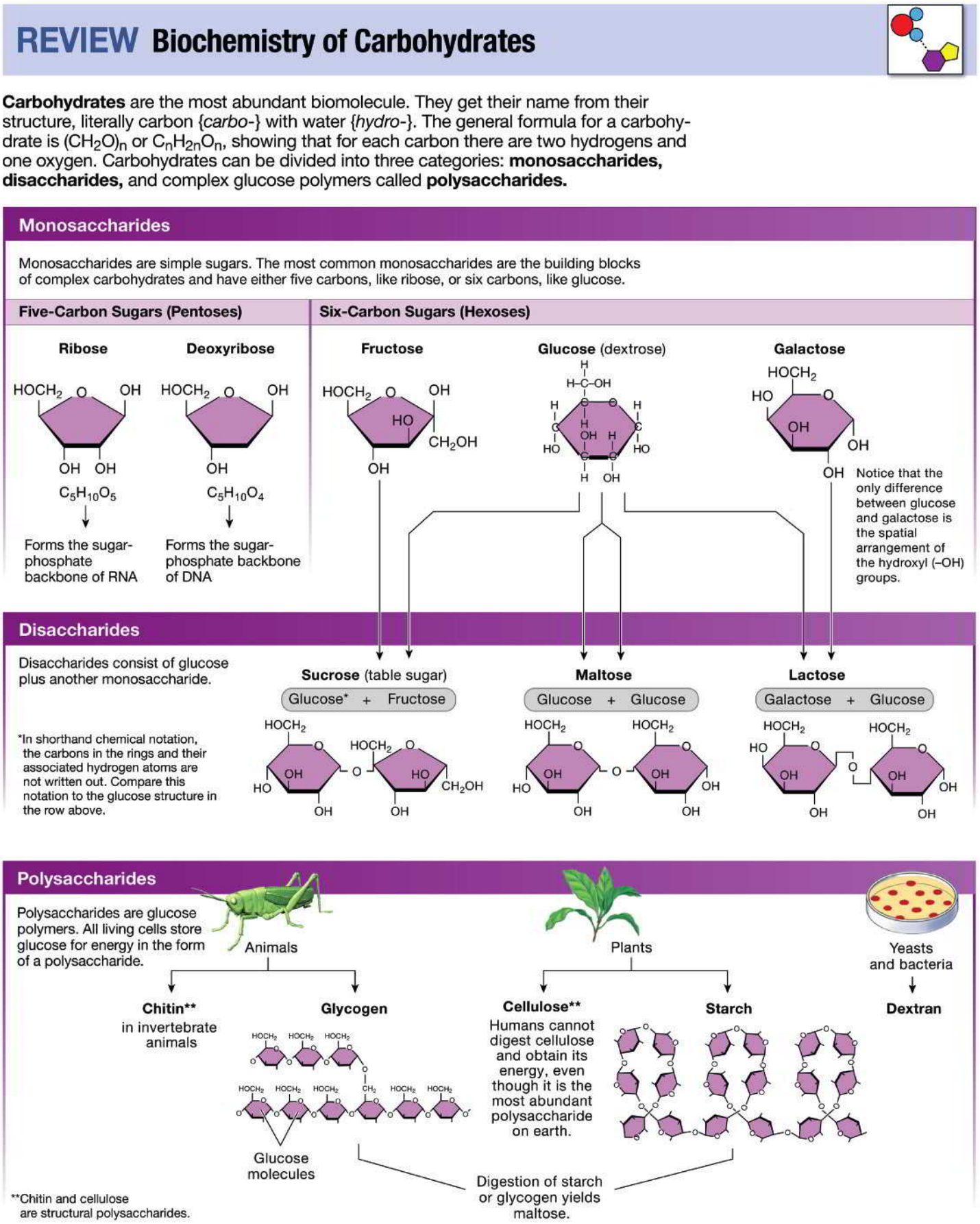


Fig. 2.3 REVIEW Biochemistry of Proteins

REVIEW Biochemistry of Proteins

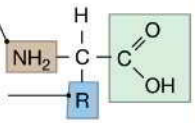
Proteins are polymers of smaller building-block molecules called **amino acids.**

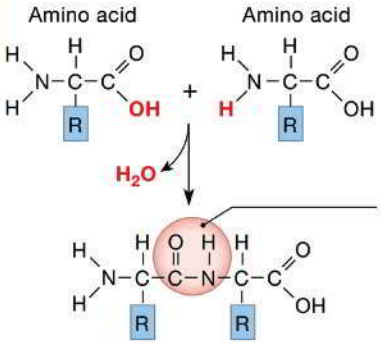
Amino Acids

All amino acids have a carboxyl group (–COOH), an amino group ($–NH_2$), and a hydrogen attached to the same carbon. The fourth bond of the carbon attaches to a variable "R" group.

The nitrogen (N) in the amino group makes proteins our major dietary source of nitrogen.

The R groups differ in their size, shape, and ability to form hydrogen bonds or ions. Because of the different R groups, each amino acid reacts with other molecules in a unique way.





In a **peptide bond,** the amino group of one amino acid joins the carboxyl group of the other, with the loss of water.

Amino Acids in Natural Proteins

Twenty different amino acids commonly occur in natural proteins. The human body can synthesize most of them, but at different stages of life some amino acids must be obtained from diet and are therefore considered *essential amino acids*. Some physiologically important amino acids are listed below.

Amino Acid	Three-Letter Abbreviation	One-Letter Symbol
Arginine	Arg	R
Aspartic acid (aspartate)*	Asp	D
Cysteine	Cys	C
Glutamic acid (glutamate)*	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Tryptophan	Trp	W
Tyrosine	Tyr	Y

*The suffix -ate indicates the anion form of the acid.

Note:

A few amino acids do not occur in proteins but have important physiological functions.

- *Homocysteine*: a sulfur-containing amino acid that in excess is associated with heart disease
- *γ-amino butyric acid* (gamma-amino butyric acid) or *GABA*: a chemical made by nerve cells
- *Creatine*: a molecule that stores energy when it binds to a phosphate group

Structure of Peptides and Proteins

Primary Structure

The 20 protein-forming amino acids assemble into polymers called peptides. The sequence of amino acids in a peptide chain is called the **primary structure.** Just as the 26 letters of our alphabet combine to create different words, the 20 amino acids can create an almost infinite number of combinations.

Peptides range in length from two to two million amino acids:

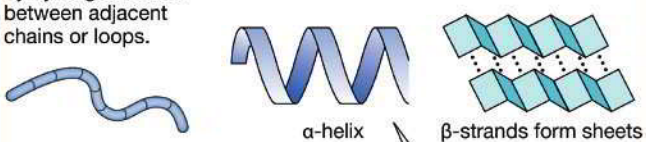
- **Oligopeptide** {*oligo-*, few}: 2–9 amino acids
- **Polypeptide:** 10–100 amino acids
- **Proteins:** >100 amino acids

Sequence of amino acids

Secondary Structure

Secondary structure is created primarily by hydrogen bonds between adjacent chains or loops.

Covalent bond angles between amino acids determine secondary structure.



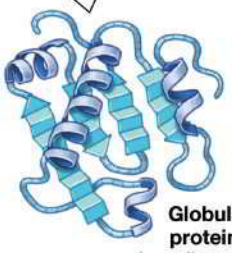
α-helix

β-strands form sheets

Tertiary Structure

Tertiary structure is the protein's three-dimensional shape.

Fibrous proteins
(usually insoluble)
Collagen

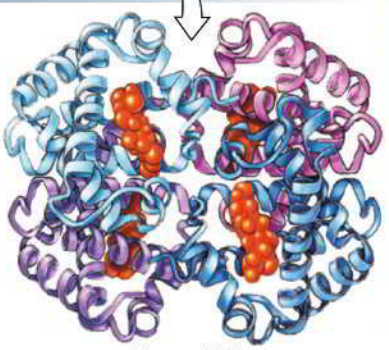


Globular proteins
(usually soluble)

Tertiary structures can be a mix of secondary structures. Beta-sheets are shown as flat ribbon arrows and alpha helices are shown as ribbon coils.

Quaternary Structure

Multiple subunits combine with noncovalent bonds. Hemoglobin molecules are made from four globular protein subunits.



Hemoglobin

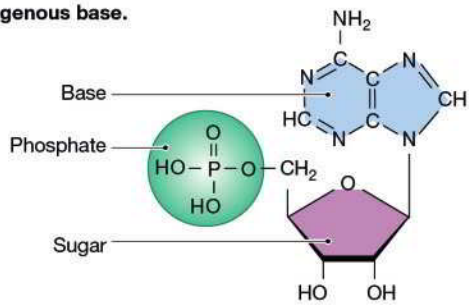
Fig. 2.4 REVIEW Nucleotides and Nucleic Acids

REVIEW Nucleotides and Nucleic Acids

Nucleotides are biomolecules that play an important role in energy and information transfer. Single nucleotides include the energy-transferring compounds **ATP** (adenosine triphosphate) and **ADP** (adenosine diphosphate), as well as **cyclic AMP,** a molecule important in the transfer of signals between cells. **Nucleic acids** (or nucleotide polymers) such as **RNA** and **DNA** store and transmit genetic information.

Nucleotide

A nucleotide consists of (1) one or more phosphate groups, (2) a 5-carbon sugar, and (3) a carbon-nitrogen ring structure called a **nitrogenous base.**



consists of

Nitrogenous Bases

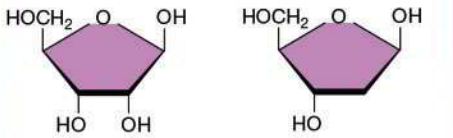
Purines have a double ring structure.

Pyrimidines have a single ring.

Adenine (A) | Guanine (G) | Cytosine (C) | Thymine (T) | Uracil (U)

Five-Carbon Sugars

Ribose | **Deoxyribose** {*de-*, without; *oxy-*, oxygen}



Phosphate

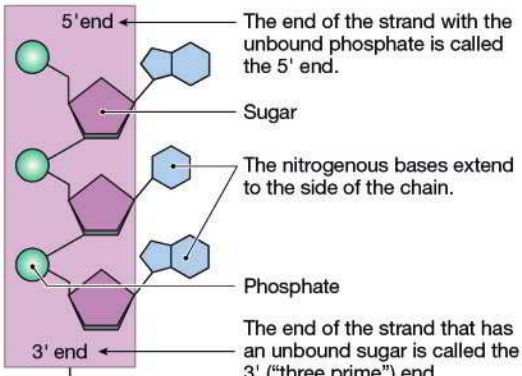
Adenine + Ribose → Adenosine

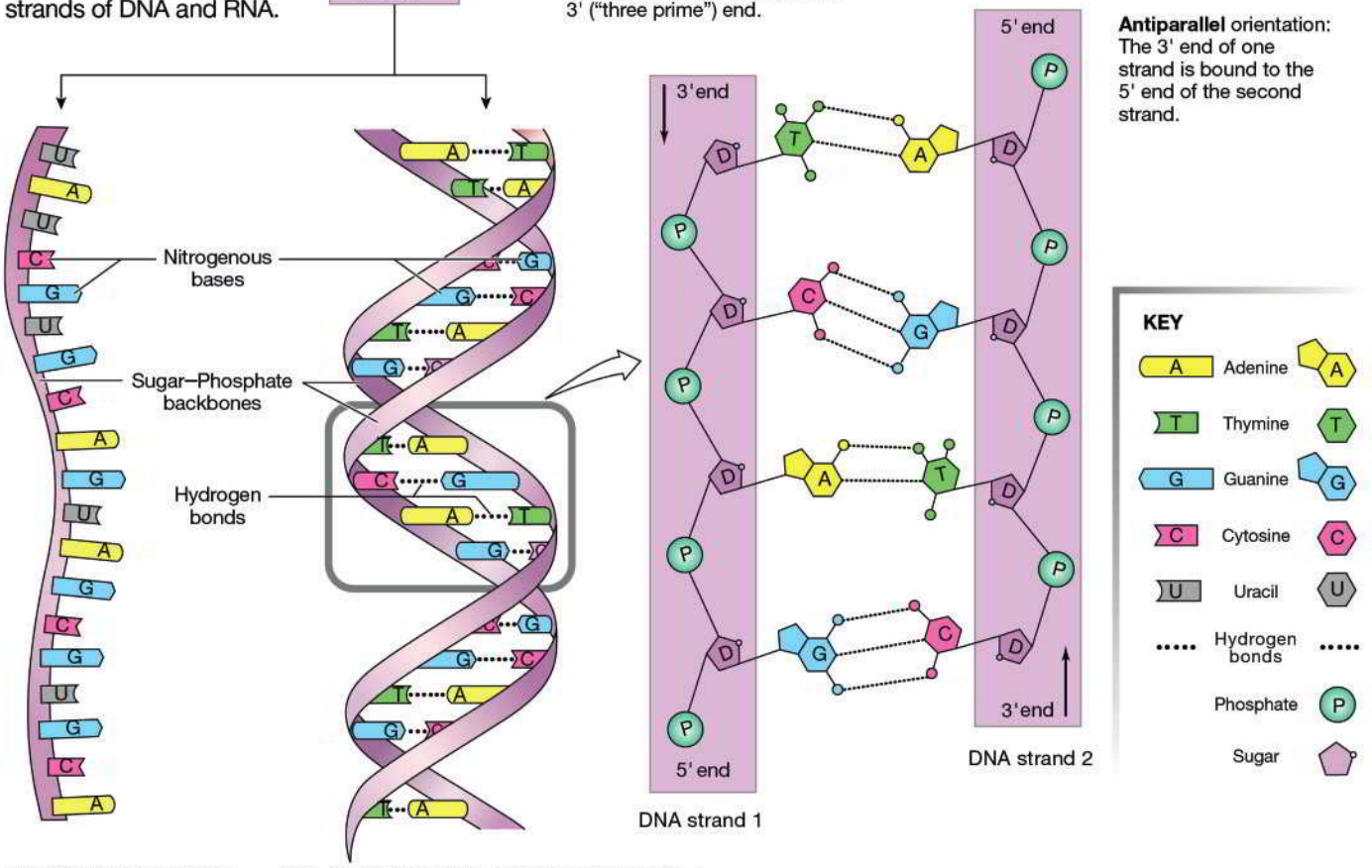
Single Nucleotide Molecules

Single nucleotide molecules have two critical functions in the human body: (1) Capture and transfer energy in high-energy electrons or phosphate bonds, and (2) aid in cell-to-cell communication.

Nucleotide	*consists of*	Base	+	Sugar	+	Phosphate Groups	+	Other Component	Function
ATP	=	Adenine	+	Ribose	+	3 phosphate groups			Energy capture and transfer
ADP	=	Adenine	+	Ribose	+	2 phosphate groups			
NAD	=	Adenine	+	2 Ribose	+	2 phosphate groups	+	Nicotinamide	
FAD	=	Adenine	+	Ribose	+	2 phosphate groups	+	Riboflavin	
cAMP	=	Adenine	+	Ribose	+	1 phosphate group			Cell-to-cell communication

Nucleic acids (nucleotide polymers) function in information storage and transmission. The sugar of one nucleotide links to the phosphate of the next, creating a chain of alternating sugar–phosphate groups. The sugar–phosphate chains, or backbone, are the same for every nucleic acid molecule. Nucleotide chains form strands of DNA and RNA.





RNA (ribonucleic acid) is a single-strand nucleic acid with ribose as the sugar in the backbone, and four bases—adenine, guanine, cytosine, and uracil.

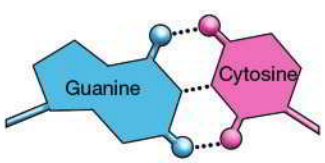
DNA (deoxyribonucleic acid) is a double helix, a three-dimensional structure that forms when two DNA strands link through hydrogen bonds between complementary base pairs. Deoxyribose is the sugar in the backbone, and the four bases are adenine, guanine, cytosine, and thymine.

Base-Pairing

Bases on one strand form hydrogen bonds with bases on the adjoining strand. This bonding follows very specific rules:

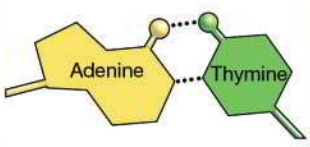
- Because purines are larger than pyrimidines, space limitations always pair a purine with a pyrimidine.
- Guanine (G) forms three hydrogen bonds with cytosine (C).
- Adenine (A) forms two hydrogen bonds with thymine (T) or uracil (U).

Guanine-Cytosine Base Pair



More energy is required to break the triple hydrogen bonds of G≡C than the double bonds of A=T or A=U.

Adenine-Thymine Base Pair



Not all biomolecules are pure protein, pure carbohydrate, or pure lipid, however. **Conjugated proteins** are protein molecules combined with another kind of biomolecule. For example, proteins combine with lipids to form **lipoproteins.** Lipoproteins are found in cell membranes and in the blood, where they act as carriers for less soluble molecules, such as cholesterol.

Glycosylated molecules are molecules to which a carbohydrate has been attached. Proteins combined with carbohydrates form **glycoproteins.** Lipids bound to carbohydrates become **glycolipids.** Glycoproteins and glycolipids, like lipoproteins, are important components of cell membranes [Fig. 3.2].

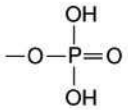
Many biomolecules are **polymers,** large molecules made up of repeating units {*poly-*, many + *-mer*, a part}. For example, **glycogen** and **starch** are both **glucose** polymers. They differ in the way the glucose molecules attach to each other, as you can see at the bottom of Figure 2.2.

Some combinations of elements, known as **functional groups,** occur repeatedly in biological molecules. The atoms in a functional group tend to move from molecule to molecule as a single unit. For example, *hydroxyl groups*, –OH, common in many biological molecules, are added and removed as a group rather than as single hydrogen or oxygen atoms. **Amino groups**, $-NH_2$, are the signature of amino acids. The phosphate group, $-H_2PO_4$, plays a role in many important cell processes, such as energy transfer and protein regulation. Addition of a phosphate group is called *phosphorylation*; removal of a phosphate group is **dephosphorylation**.

The most common functional groups are listed in **TABLE 2.1**.

Table 2.1 Common Functional Groups

Notice that oxygen, with two electrons to share, sometimes forms a double bond with another atom.

	Shorthand	Bond Structure
Amino	$-NH_2$	
Carboxyl (acid)	—COOH	
Hydroxyl	—OH	—O—H
Phosphate	$-H_2PO_4$	

Concept Check

1. List three major essential elements found in the human body.
2. What is the general formula of a carbohydrate?
3. What is the chemical formula of an amino group? Of a carboxyl group?

Electrons Have Four Important Biological Roles

An atom of any element has a unique combination of protons and electrons that determines the element's properties (**FIG. 2.5**). We are particularly interested in the electrons because they play four important roles in physiology:

1. **Covalent bonds.** The arrangement of electrons in the outer energy level (*shell*) of an atom determines an element's ability to bind with other elements. Electrons shared between atoms form strong covalent bonds that bind atoms together to form molecules
2. **Ions.** If an atom or molecule gains or loses one or more electrons, it acquires an electrical charge and becomes an **ion.** Ions are the basis for electrical signaling in the body. Ions may be single atoms, like the sodium ion Na^+ and chloride ion Cl^-. Other ions are combinations of atoms, such as the bicarbonate ion HCO_3^-. Important ions of the body are listed in **TABLE 2.2**.
3. **High-energy electrons.** The electrons in certain atoms can capture energy from their environment and transfer it to other atoms. This allows the energy to be used for synthesis, movement, and other life processes. The released energy may also be emitted as radiation. For example, bioluminescence in fireflies is visible light emitted by high-energy electrons returning to their normal low-energy state.
4. **Free radicals.** Free radicals are unstable molecules with an unpaired electron. They are thought to contribute to aging and to the development of certain diseases, such as some cancers. Free radicals and high-energy electrons are discussed in Chapter 23.

The role of electrons in molecular bond formation is discussed in the next section. There are four common bond types, two strong and two weak. Covalent and ionic bonds are strong bonds because they require significant amounts of energy to make or break. Hydrogen bonds and van der Waals forces are weaker bonds that require much less energy to break. Interactions between molecules with different bond types are responsible for energy use and transfer in metabolic reactions as well as a variety of other reversible interactions.

Table 2.2 Important Ions of the Body

Cations		Anions	
Na^+	Sodium	Cl^-	Chloride
K^+	Potassium	HCO_3^-	Bicarbonate
Ca^{2+}	Calcium	HPO_4^{2-}	Phosphate
H^+	Hydrogen	SO_4^{2-}	Sulfate
Mg^{2+}	Magnesium		

Covalent Bonds between Atoms Create Molecules

Molecules form when atoms share pairs of electrons, one electron from each atom, to create **covalent bonds.** These strong bonds require the input of energy to break them apart. It is possible to predict how many covalent bonds an atom can form by knowing how many unpaired electrons are in its outer shell, because an atom is most stable when all of its electrons are paired (**FIG. 2.6**).

For example, a hydrogen atom has one unpaired electron and one empty electron place in its outer shell. Because hydrogen has only one electron to share, it always forms one covalent bond, represented by a single line (—) between atoms. Oxygen has six electrons in an outer shell that can hold eight. That means oxygen can form two covalent bonds and fill its outer shell with electrons. If adjacent atoms share two pairs of electrons rather than just one pair, a **double bond,** represented by a double line (=), results. If two atoms share three pairs of electrons, they form a triple bond.

Running Problem 2.2

What is chromium picolinate? Chromium (Cr) is an essential element that has been linked to normal glucose metabolism. In the diet, chromium is found in brewer's yeast, broccoli, mushrooms, and apples. Because chromium in food and in chromium chloride supplements is poorly absorbed from the digestive tract, a scientist developed and patented the compound chromium picolinate. Picolinate, derived from amino acids, enhances chromium uptake at the intestine. The recommended adequate intake (AI) of chromium for men ages 19–50 is 35 μg/day. (For women, it is 25 μg/day.) As we've seen, Malik takes more than 10 times this amount.

Q1: *Locate chromium on the periodic table of the elements. What is chromium's atomic number?* ***Atomic mass****? How many electrons does one atom of chromium have?*

Q2: *Which elements close to chromium are also essential elements?*

Polar and Nonpolar Molecules

Some molecules develop regions of partial positive and negative charge when the electron pairs in their covalent bonds are not evenly shared between the linked atoms. When electrons are shared unevenly, the atom(s) with the stronger attraction for electrons develops a slight negative charge (indicated by δ^-), and the atom(s) with the weaker attraction for electrons develops a slight positive charge (δ^+). These molecules are called **polar molecules** because they can be said to have positive and negative ends, or poles. Certain elements, particularly nitrogen and oxygen, have a strong attraction for electrons and are often found in polar molecules.

A good example of a polar molecule is water (H_2O). The larger and stronger oxygen atom pulls the hydrogen electrons toward itself (Fig. 2.6b). This pull leaves the two hydrogen atoms of the molecule with a partial positive charge, and the single oxygen atom with a partial negative charge from the unevenly shared electrons. Note that the net charge for the entire water molecule is zero. The polarity of water makes it a good solvent, and all life as we know it is based on **aqueous solutions**, with water as the solvent.

A **nonpolar molecule** is one whose shared electrons are distributed so evenly that there are no regions of partial positive or negative charge. For example, molecules composed mostly of carbon and hydrogen, such as the **fatty acid** shown in Figure 2.6a, tend to be nonpolar. This is because carbon does not attract electrons as strongly as oxygen does. As a result, the carbons and hydrogens share electrons evenly, and the molecule has no regions of partial charge.

Noncovalent Bonds Facilitate Reversible Interactions

Ionic bonds, hydrogen bonds, and van der Waals forces are noncovalent bonds. They play important roles in many physiological processes, including pH, molecular shape, and the reversible binding of molecules to each other.

Ionic Bonds

Ions form when one atom has such a strong attraction for electrons that it pulls one or more electrons completely away from another atom. For example, a chlorine atom needs only one electron to fill the last of eight places in its outer shell, so it pulls an electron from a sodium atom, which has only one weakly held electron in its outer shell (Fig. 2.6c). The atom that gains electrons acquires one negative charge (−1) for each electron added, so the chlorine atom becomes a chloride ion Cl^-. Negatively charged ions are called **anions**.

An atom that gives up electrons has one positive charge (+1) for each electron lost. For example, the sodium atom becomes a sodium ion Na^+. Positively charged ions are called **cations**.

Ionic bonds, also known as *electrostatic attractions*, result from the attraction between ions with opposite charges. (Remember the basic principle of electricity that says that opposite charges attract and like charges repel.) In a crystal of table salt, the solid form of ionized NaCl, ionic bonds between alternating Na^+ and Cl^- ions hold the ions in a neatly ordered structure.

Hydrogen Bonds

A **hydrogen bond** is a weak attractive force between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. No electrons are gained, lost, or shared in a hydrogen bond. Instead, the oppositely charged regions in polar molecules are attracted to each other. Hydrogen bonds may occur between atoms in neighboring molecules or between atoms in different parts of the same molecule. For example, one water molecule may hydrogen-bond with as many as four other water molecules. As a result, the molecules line up with their neighbors in a somewhat ordered fashion (Fig. 2.6d).

Hydrogen bonding between molecules is responsible for the **surface tension** of water. Surface tension is the attractive force between water molecules that causes water to form spherical

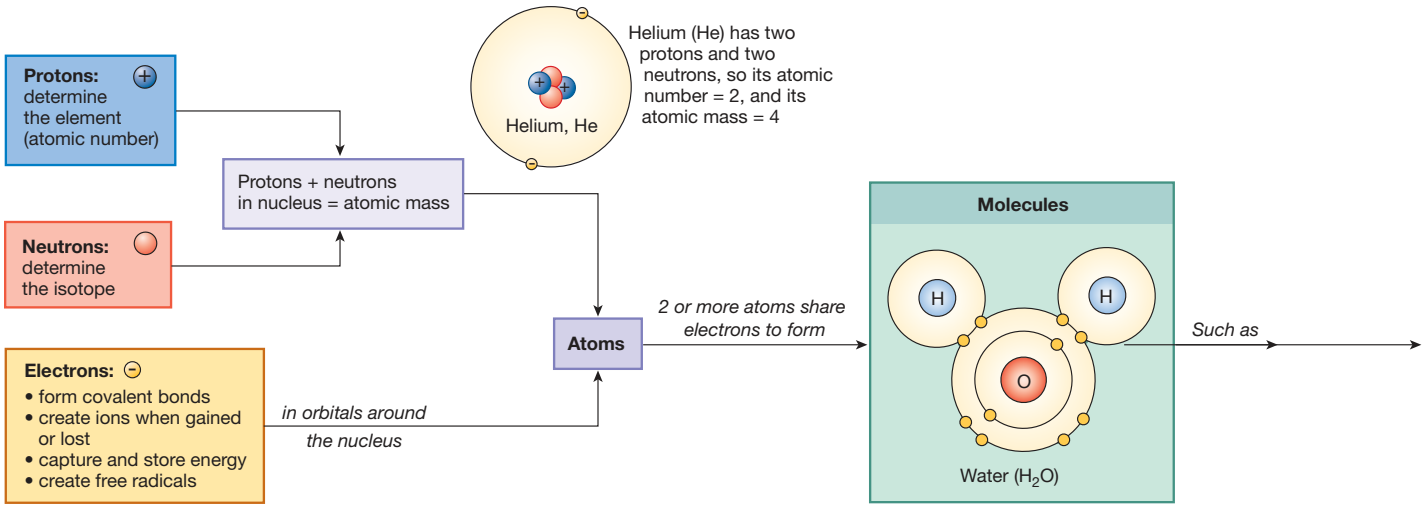
Fig. 2.5 REVIEW Atoms and Molecules

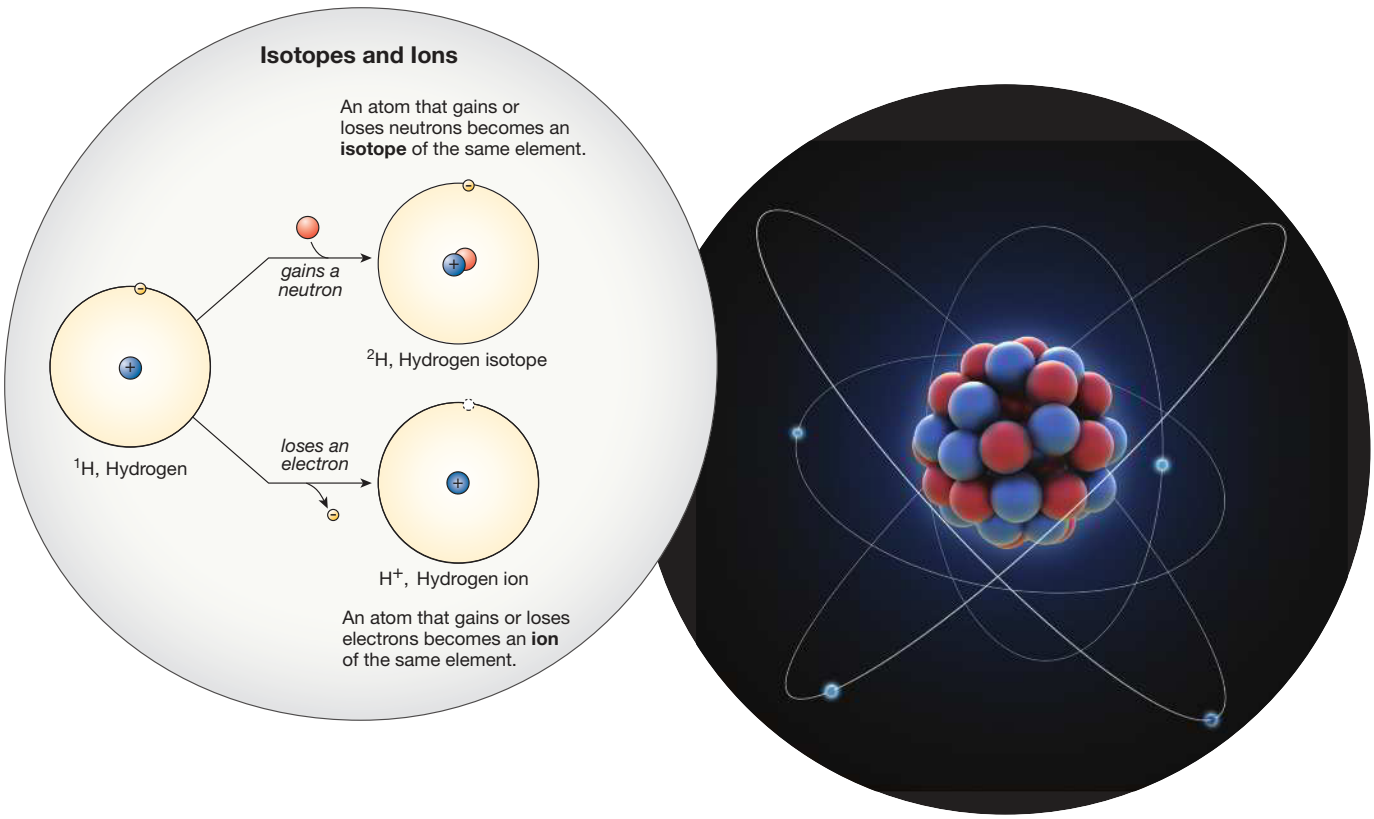
REVIEW Atoms and Molecules

Elements are the simplest type of matter. There are over 100 known elements,* but only three—oxygen, carbon, and hydrogen—make up more than 90% of the body's mass. These three plus eight additional elements are *major essential elements*. An additional 19 *minor essential elements* are required in trace amounts. The smallest particle of any element is an **atom** {*atomos*, indivisible}. Atoms link by sharing electrons to form molecules.

Major Essential Elements	Minor Essential Elements
H, C, O, N, Na, Mg, K, Ca, P, S, Cl	Li, F, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Y, I, Zr, Nb, Mo, Tc, Ru, Rh, La

* A periodic table of the elements can be found inside the back cover of the book.





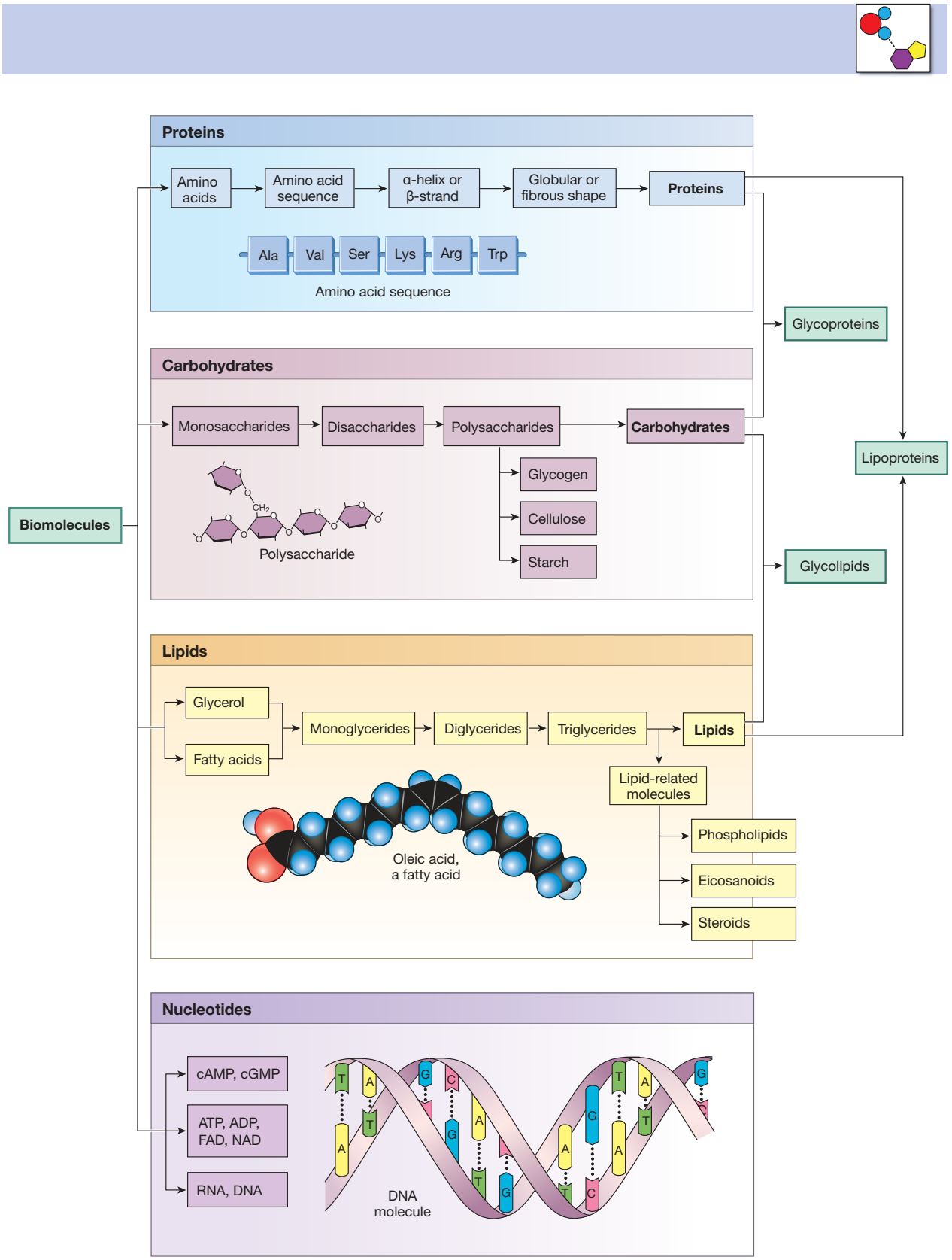
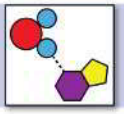


Fig. 2.6 REVIEW Molecular Bonds

REVIEW Molecular Bonds



When two or more atoms link by sharing electrons, they make units known as **molecules.** The transfer of electrons from one atom to another or the sharing of electrons by two atoms is a critical part of forming **bonds,** the links between atoms.

Bonds

Covalent Bonds

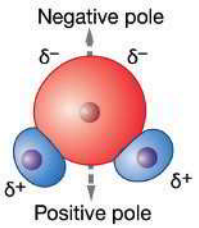
Covalent bonds result when atoms share electrons. These bonds require the most energy to make or break.

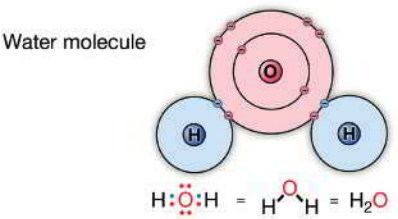
(a) Nonpolar Molecules

Nonpolar molecules have an even distribution of electrons. For example, molecules composed mostly of carbon and hydrogen tend to be nonpolar.

(b) Polar Molecules

Polar molecules have regions of partial charge (δ+ or δ−). The most important example of a polar molecule is water.

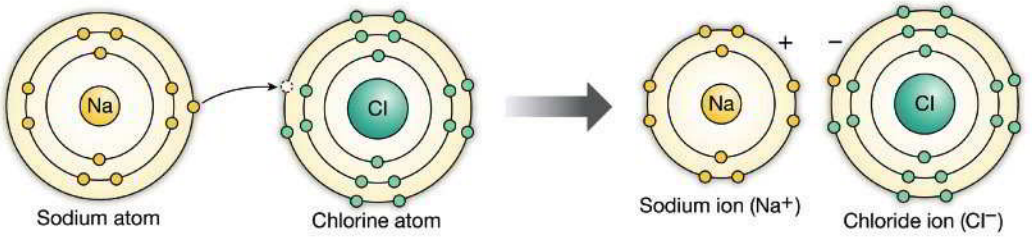




Noncovalent Bonds

(c) Ionic Bonds

Ionic bonds are electrostatic attractions between ions. A common example is sodium chloride.

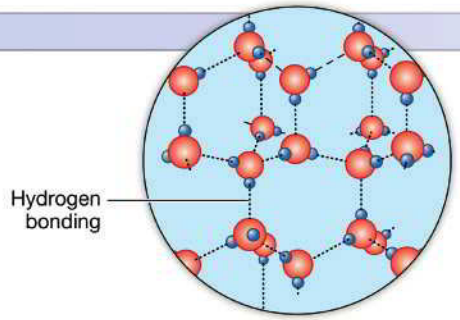


Sodium gives up its one weakly held electron to chlorine, creating sodium and chloride ions, Na^+ and Cl^-.

The sodium and chloride ions both have stable outer shells that are filled with electrons. Because of their opposite charges, they are attracted to each other and, in the solid state, the ionic bonds form a sodium chloride (NaCl) crystal.

(d) Hydrogen Bonds

Hydrogen bonds form between a hydrogen atom and a nearby oxygen, nitrogen, or fluorine atom. So, for example, the polar regions of adjacent water molecules allow them to form hydrogen bonds with one another.



Hydrogen bonding between water molecules is responsible for the surface tension of water.

(e) Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between atoms.

droplets when falling or to bead up when spilled onto a nonabsorbent surface (Fig. 2.6d). The high cohesiveness {*cohaesus*, to cling together} of water is due to hydrogen bonding and makes it difficult to stretch or deform, as you may have noticed in trying to pick up a wet glass that is "stuck" to a slick table top by a thin film of water. The surface tension of water influences lung function (described in Chapter18).

Van der Waals Forces

Van der Waals forces are weak, nonspecific attractions between the nucleus of any atom and the electrons of nearby atoms. Two atoms that are weakly attracted to each other by van der Waals forces move closer together until they are so close that their electrons begin to repel one another. Consequently, van der Waals forces allow atoms to pack closely together and occupy a minimum amount of space. A single van der Waals attraction between atoms is very weak.

Running Problem 2.3

One advertising claim for chromium is that it improves the transfer of glucose—the simple sugar that cells use to fuel all their activities—from the bloodstream into cells. In people with diabetes mellitus, cells are unable to take up glucose from the blood efficiently. It seemed logical, therefore, to test whether the addition of chromium to the diet would enhance glucose uptake in people with diabetes. In one Chinese study, diabetic patients receiving 500 micrograms (μg) of chromium picolinate twice a day showed significant improvement in their glucose uptake, but patients receiving 100 micrograms or a placebo did not.

Q3: *If people have a chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*

Q4: *From the results of the Chinese study, can you conclude that all people with diabetes suffer from a chromium deficiency?*

Concept Check

4. Are electrons in an atom or molecule most stable when they are paired or unpaired?
5. When an atom of an element gains or loses one or more electrons, it is called a(n) _____ of that element.
6. Match each type of bond with its description:

(a) covalent bond	1. weak attractive force between hydrogen and oxygen or nitrogen
(b) ionic bond	2. formed when two atoms share one or more pairs of electrons
(c) hydrogen bond	3. weak attractive force between atoms
(d) van der Waals force	4. formed when one atom loses one or more electrons to a second atom

2.2 Noncovalent Interactions

Many different kinds of noncovalent interactions can take place between and within molecules as a result of the four different types of bonds. For example, the charged, uncharged, or partially charged nature of a molecule determines whether that molecule can dissolve in water. Covalent and noncovalent bonds determine molecular shape and function. Finally, noncovalent interactions allow proteins to associate reversibly with other molecules, creating functional pairings such as enzymes and substrates, or signal receptors and molecules.

Hydrophilic Interactions Create Biological Solutions

Life as we know it is established on water-based, or *aqueous*, **solutions** that resemble dilute seawater in their ionic composition. The adult human body is about 60% water. Na^+, K^+, and Cl^- are the main ions in body fluids, with other ions making up a lesser proportion. All molecules and cell components are either dissolved or suspended in these solutions. For these reasons, it is useful to understand the properties of solutions, which are reviewed in **FIGURE 2.7**.

The degree to which a molecule is able to dissolve in a **solvent** is the molecule's **solubility:** the more easily a molecule dissolves, the higher its solubility. Water, the biological solvent, is polar, so molecules that dissolve readily in water are polar or ionic molecules whose positive and negative regions readily interact with water. For example, if NaCl crystals are placed in water, polar regions of the water molecules disrupt the ionic bonds between sodium and chloride, which causes the crystals to dissolve (**FIG. 2.8a**). Molecules that are soluble in water are said to be **hydrophilic** {*hydro-*, water + *-philic*, loving}.

In contrast, molecules such as oils that do not dissolve well in water are said to be **hydrophobic** {*-phobic*, hating}. Hydrophobic substances are usually nonpolar molecules that cannot form hydrogen bonds with water molecules. The lipids (fats and oils) are the most hydrophobic group of biological molecules.

When placed in an aqueous solution, lipids do not dissolve. Instead they separate into distinct layers. One familiar example is salad oil floating on vinegar in a bottle of salad dressing. Before hydrophobic molecules can dissolve in body fluids, they must combine with a hydrophilic molecule that will carry them into solution.

For example, **cholesterol**, a common animal fat, is a hydrophobic molecule. Fat from a piece of meat dropped into a glass of warm water will float to the top, undissolved. In the blood, cholesterol will not dissolve unless it binds to special water-soluble carrier molecules. You may know the combination of cholesterol with its hydrophilic carriers as **HDL-cholesterol** and LDL-cholesterol, the "good" and "bad" forms of cholesterol associated with heart disease.

Some molecules, such as the **phospholipids**, have both polar and nonpolar regions (Fig. 2.8b). This dual nature allows them to associate both with each other (hydrophobic interactions) and

Fig. 2.7 REVIEW Solutions

REVIEW Solutions

Life as we know it is established on water-based, or aqueous, solutions that resemble dilute seawater in their ionic composition. The human body is 60% water. Sodium, potassium, and chloride are the main ions in body fluids. All molecules and cell components are either dissolved or suspended in these saline solutions. For these reasons, the properties of solutions play a key role in the functioning of the human body.

Terminology

A **solute** is any substance that dissolves in a liquid. The degree to which a molecule is able to dissolve in a solvent is the molecule's solubility. The more easily a solute dissolves, the higher its **solubility**.

A **solvent** is the liquid into which solutes dissolve. In biological solutions, water is the universal solvent.

A **solution** is the combination of solutes dissolved in a solvent. The **concentration** of a solution is the amount of solute per unit volume of solution.

Concentration = solute amount/volume of solution

Expressions of Solute Amount

- **Mass** (weight) of the solute before it dissolves. Usually given in grams (g) or milligrams (mg).
- **Molecular mass** is calculated from the chemical formula of a molecule. This is the mass of one molecule, expressed in atomic mass units (amu) or, more often, in daltons (Da), where 1 amu = 1 Da.

Molecular mass = SUM [atomic mass of each element × the number of atoms of each element]

Example

What is the molecular mass of glucose, $C_6H_{12}O_6$?

Answer

Element	# of Atoms	Atomic Mass of Element
Carbon	6	12.0 amu × 6 = 72
Hydrogen	12	1.0 amu × 12 = 12
Oxygen	6	16.0 amu × 6 = 96

Molecular mass of glucose = 180 amu (or Da)

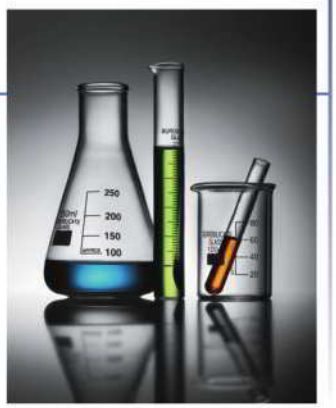
- **Moles** (mol) are an expression of the number of solute molecules, without regard for their weight. One mole = 6.02×10^{23} atoms, ions, or molecules of a substance. One mole of a substance has the same number of particles as one mole of any other substance, just as a dozen eggs has the same number of items as a dozen roses.
- **Gram molecular weight.** In the laboratory, we use the molecular mass of a substance to measure out moles. For example, one mole of glucose (with 6.02×10^{23} glucose molecules) has a molecular mass of 180 Da and weighs 180 grams. The molecular mass of a substance expressed in grams is called the gram molecular weight.
- **Equivalents** (Eq) are a unit used for ions, where 1 equivalent = molarity of the ion × the number of charges the ion carries. The sodium ion, with its charge of +1, has one equivalent per mole. The hydrogen phosphate ion (HPO_4^{2-}) has two equivalents per mole. Concentrations of ions in the blood are often reported in milliequivalents per liter (mEq/L).

FIGURE QUESTIONS

1. What are the two components of a solution?
2. The concentration of a solution is expressed as:
   (a) amount of solvent/volume of solute
   (b) amount of solute/volume of solvent
   (c) amount of solvent/volume of solution
   (d) amount of solute/volume of solution
3. Calculate the molecular mass of water, H_2O.
4. How much does a mole of KCl weigh?

Expressions of Volume

Volume is usually expressed as liters (L) or milliliters (mL) {*milli-*, 1/1000}. A volume convention common in medicine is the deciliter (dL), which is 1/10 of a liter, or 100 mL.



Prefixes

deci- (d)	1/10	1×10^{-1}
milli- (m)	1/1000	1×10^{-3}
micro- (μ)	1/1,000,000	1×10^{-6}
nano- (n)	1/1,000,000,000	1×10^{-9}
pico- (p)	1/1,000,000,000,000	1×10^{-12}

Useful Conversions

- 1 liter of water weighs 1 kilogram (kg) {*kilo-*, 1000}
- 1 kilogram = 2.2 pounds

Expressions of Concentration

- **Percent solutions.** In a laboratory or pharmacy, scientists cannot measure out solutes by the mole. Instead, they use the more conventional measurement of weight. The solute concentration may then be expressed as a percentage of the total solution, or percent solution. A 10% solution means 10 parts of a solute per 100 parts of total solution. Weight/volume solutions, used for solutes that are solids, are usually expressed as g/100 mL solution or mg/dL. An out-of-date way of expressing mg/dL is mg% where % means per 100 parts or 100 mL. A concentration of 20 mg/dL could also be expressed as 20 mg%.

Example

Solutions used for intravenous (IV) infusions are often expressed as percent solutions. How would you make 500 mL of a 5% dextrose (glucose) solution?

Answer

5% solution = 5 g glucose dissolved in water to make a final volume of 100 mL solution.

5 g glucose/100 mL = ? g/500 mL

25 g glucose with water added to give a final volume of 500 mL

- **Molarity** is the number of moles of solute in a liter of solution, and is abbreviated as either mol/L or M. A one molar solution of glucose (1 mol/L, 1 M) contains 6.02×10^{23} molecules of glucose per liter of solution. It is made by dissolving one mole (180 grams) of glucose in enough water to make one liter of solution. Typical biological solutions are so dilute that solute concentrations are usually expressed as **millimoles** per liter (mmol/L or mM).

Example

What is the molarity of a 5% dextrose solution?

Answer

5 g glucose/100 mL = 50 g glucose/1000 mL (or 1 L)

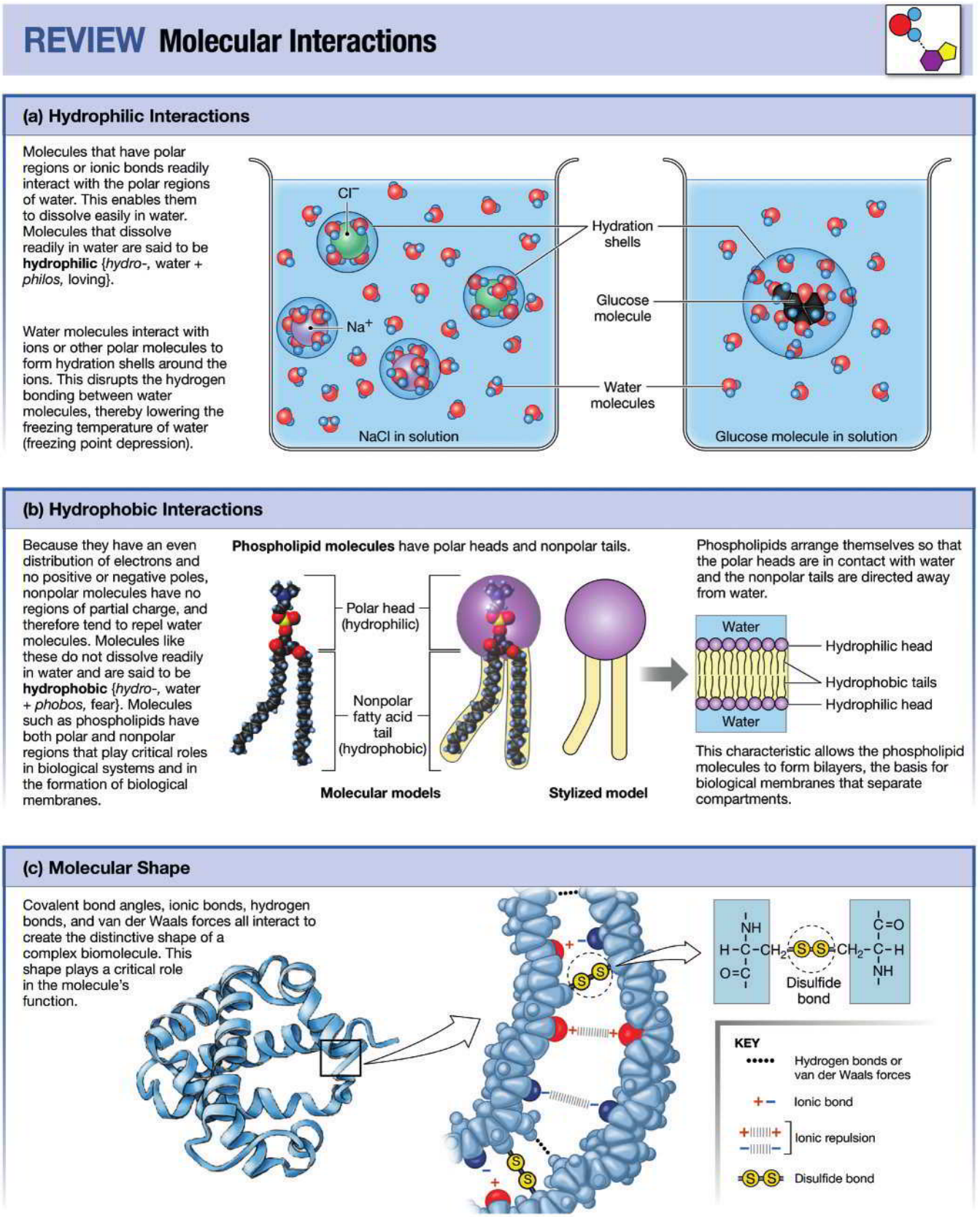
1 mole glucose = 180 g glucose

50 g/L × 1 mole/180 g = 0.278 moles/L or 278 mM

FIGURE QUESTIONS

5. Which solution is more concentrated: a 100 mM solution of glucose or a 0.1 M solution of glucose?
6. When making a 5% solution of glucose, why don't you measure out 5 grams of glucose and add it to 100 mL of water?

Fig. 2.8 REVIEW Molecular Interactions



with polar water molecules (hydrophilic interactions). Phospholipids are the primary component of biological membranes.

Concept Check

7. Which dissolve more easily in water, polar molecules or nonpolar molecules?
8. A molecule that dissolves easily is said to be hydro__ic.
9. Why does table salt (NaCl) dissolve in water?

Molecular Shape Is Related to Molecular Function

A molecule's shape is closely related to its function. Molecular bonds—both covalent bonds and weak bonds—play a critical role in determining molecular shape. The three-dimensional shape of a molecule is difficult to show on paper, but many molecules have characteristic shapes due to the angles of covalent bonds between the atoms. For example, the two hydrogen atoms of the water molecule shown in Figure 2.6b are attached to the oxygen with a bond angle of 104.5°. Double bonds in long carbon chain fatty acids cause the chains to kink or bend, as shown by the three-dimensional model of oleic acid in Figure 2.5.

Weak noncovalent bonds also contribute to molecular shape. The complex double helix of a **DNA** molecule, shown in Figure 2.4, results both from covalent bonds between adjacent **nitrogenous bases** in each strand and the hydrogen bonds connecting the two strands of the helix.

Proteins have the most complex and varied shapes of all the biomolecules. Their shapes are determined both by the sequence of amino acids in the protein chain (the **primary structure of a protein**) plus varied noncovalent interactions as long **polypeptide** chains loop and fold back on themselves. The stable **secondary structures** of proteins are formed by covalent bond angles between amino acids in the polypeptide chain.

The two common protein **secondary structures** are the **α – helix (alpha-helix)** spiral and the zigzag shape of **β – sheets (beta-sheet)** (Fig. 2.3). Adjacent β-*strands* in the polypeptide chain associate into sheetlike structures held together by hydrogen bonding, shown as dotted lines (. . .) in Figure 2.3. The sheet configuration is very stable and occurs in many proteins destined for structural uses. Proteins with other functions may have a mix of β-strands and α-helices. Protein secondary structure is illustrated by ribbon diagrams (or Richardson diagrams), with beta-sheets shown as flat arrows and α-helices as ribbon spirals (Fig. 2.3).

The **tertiary structure** of a protein is its three-dimensional shape, created through spontaneous folding as the result of covalent bonds and noncovalent interactions. Proteins are categorized into two large groups based on their shape: globular and fibrous (see Fig. 2.3). **Globular proteins** can be a mix of α-helices, β-sheets, and amino acid chains that fold back on themselves. The result is a complex tertiary structure that may contain pockets, channels, or protruding knobs. The tertiary structure of globular proteins arises partly from the angles of covalent bonds between amino acids and partly from hydrogen bonds, van der Waals forces, and ionic bonds that stabilize the molecule's shape.

In addition to covalent bonds between adjacent amino acids, covalent **disulfide bonds** (S–S) play an important role in the shape of many globular proteins (Fig. 2.8c). The amino acid *cysteine* contains sulfur as part of a *sulfhydryl group* (–SH). Two cysteines in different parts of the polypeptide chain can bond to each other with a disulfide bond that pulls the sections of chain together.

Fibrous proteins can be β-strands or long chains of α-helices. Fibrous proteins are usually insoluble in water and form important structural components of cells and tissues. Examples of fibrous proteins include *collagen*, found in many types of connective tissue, such as skin, and *keratin*, found in hair and nails.

Hydrogen Ions in Solution Can Alter Molecular Shape

Hydrogen bonding is an important part of molecular shape. However, free hydrogen ions, H^+, in solution can also participate in hydrogen bonding and van der Waals forces. If free H^+ disrupts a molecule's noncovalent bonds, the molecule's shape, or *conformation*, can change. A change in shape may alter or destroy the molecule's ability to function.

Running Problem 2.4

Chromium is found in several ionic forms. The chromium usually found in biological systems and in dietary supplements is the cation Cr^{3+}. This ion is called trivalent because it has a net charge of $+3$. The hexavalent cation, Cr^{6+}, with a charge of $+6$, is used in industry, such as in the manufacturing of stainless steel and the chrome plating of metal parts.

Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*

The concentration of free H^+ in body fluids, or *acidity*, is measured in terms of **pH. FIGURE 2.9** reviews the chemistry of pH and shows a pH scale with the pH values of various substances. The typical pH of blood in the human body is 7.40, slightly alkaline. Regulation of the body's pH within a narrow range is critical because a blood pH more acidic than 7.00 ($pH < 7.00$) or more alkaline than 7.70 ($pH > 7.70$) is incompatible with life.

Where do hydrogen ions in body fluids come from? Some of them come from the separation of water molecules (H_2O) into H^+ and OH^- ions. Others come from **acids,** molecules that release H^+ when they dissolve in water (Fig. 2.9). Many of the molecules made during metabolism are acids. For example, acid is made in the body from CO_2 (carbon dioxide) and water.

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

Note that when the hydrogen is part of the water molecule, it does not contribute to acidity. *Only free H^+ contributes to the hydrogen ion concentration.*

We are constantly adding acid to the body through metabolism, so how does the body maintain an acceptable pH? One

Fig. 2.9 REVIEW pH

REVIEW pH

Acids and Bases

An **acid** is a molecule that contributes H^+ to a solution.

- The carboxyl group, –COOH, is an acid because in solution it tends to lose its H^+:

$$R\text{–}COOH \longrightarrow R\text{–}COO^- + H^+$$

A **base** is a molecule that decreases the H^+ concentration of a solution by combining with free H^+.

- Molecules that produce hydroxide ions, OH^-, in solution are bases because the hydroxide combines with H^+ to form water:

$$R\text{–}OH \longrightarrow R^+ + OH^- \longrightarrow OH^- + H^+ \longrightarrow H_2O$$

- Another molecule that acts as a base is ammonia, NH_3. It reacts with a free H^+ to form an ammonium ion:

$$NH_3 + H^+ \longrightarrow NH_4^+$$

pH

The concentration of H^+ in body fluids is measured in terms of **pH.**

- The expression pH stands for "power of hydrogen."

(1) $pH = -\log [H^+]$

This equation is read as "pH is equal to the negative log of the hydrogen ion concentration." Square brackets are shorthand notation for "concentration" and by convention, concentration is expressed in Eq/L.

- Using the rule of logarithms that says $-\log x = \log(1/x)$, pH equation (1) can be rewritten as:

(2) $pH = \log (1/[H^+])$

This equation shows that pH is inversely related to H^+ concentration. In other words, as the H^+ concentration goes up, the pH goes down.

Example

What is the pH of a solution whose hydrogen ion concentration $[H^+]$ is 10^{-7} Eq/L?

Answer

$pH = -\log [H^+]$
$pH = -\log [10^{-7}]$

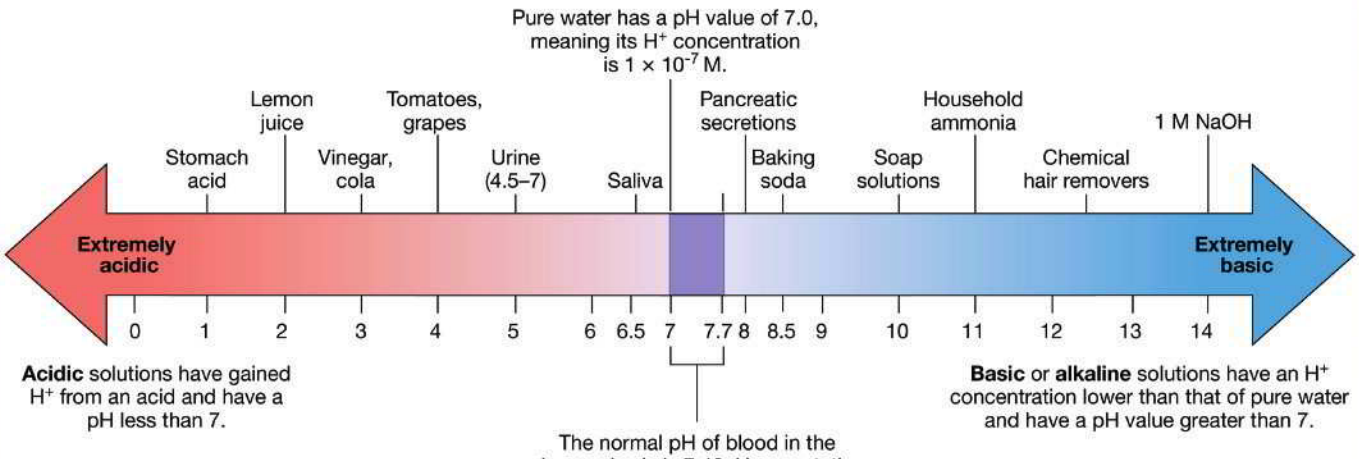
Using the rule of logs, this can be rewritten as

$pH = \log (1/10^{-7})$

Using the rule of exponents that says $1/10^x = 10^{-x}$

$pH = \log 10^7$

the log of 10^7 is 7, so the solution has a pH of 7.



The pH of a solution is measured on a numeric scale between 0 and 14. The pH scale is logarithmic, meaning that a change in pH value of 1 unit indicates a 10-fold change in $[H^+]$. For example, if a solution changes from pH 8 to pH 6, there has been a 100-fold (10^2 or 10 × 10) increase in $[H^+]$.

FIGURE QUESTIONS

1. When the body becomes more acidic, does pH increase or decrease?
2. How can urine, stomach acid, and saliva have pH values outside the pH range that is compatible with life and yet be part of the living body?

answer is buffers. A **buffer** is any substance that moderates changes in pH. Many buffers contain anions that have a strong attraction for H^+ molecules. When free H^+ is added to a buffer solution, the buffer's anions bond to the H^+, thereby minimizing any change in pH.

The bicarbonate anion, HCO_3^-, is an important buffer in the human body. The following equation shows how a sodium bicarbonate solution acts as a buffer when hydrochloric acid (HCl) is added. When placed in plain water, hydrochloric acid separates, or dissociates, into H^+ and Cl^- and creates a high H^+ concentration (low pH). When HCl dissociates in a sodium bicarbonate solution, however, some of the bicarbonate ions combine with some of the H^+ to form undissociated carbonic acid. "Tying up" the added H^+ in this way keeps the free H^+ concentration of the solution from changing significantly and minimizes the pH change.

$$\underset{\text{Hydrochloric acid}}{H^+ + Cl^-} + \underset{\text{Sodium bicarbonate}}{HCO_3^- + Na^+} \rightleftharpoons \underset{\text{Carbonic acid}}{H_2CO_3} + \underset{\text{Sodium chloride (table salt)}}{Cl^- + Na^+}$$

Concept Check

10. To be classified as an acid, a molecule must do what when dissolved in water?
11. pH is an expression of the concentration of what in a solution?
12. When pH goes up, acidity goes _____.

2.3 Protein Binding Interactions

Noncovalent molecular interactions occur between proteins and many different biomolecules. For example, biological membranes are formed by the noncovalent associations of proteins and phospholipids. And glycoproteins join glycolipids in cell membranes to create a "sugar coat" on cell surfaces that assists cell **aggregation** {*aggregare*, to join together} and adhesion {*adhaerere*, to stick}.

Proteins play important roles in so many cell functions that we can consider them the "workhorses" of the body. Most proteins fall into nine broad categories:

1. **Enzymes.** Some proteins act as **enzymes,** biological catalysts that speed up chemical reactions. Enzymes are crucial players in metabolism and you will learn more about their properties in Chapter 4.
2. **Membrane transporters.** Proteins in cell membranes help substances move between the intracellular and extracellular compartments. These proteins may form channels in the cell membrane, or they may bind to ions and molecules and carry them through the membrane. Membrane transporters are discussed in detail in Chapter 5.
3. **Signal molecules.** Some proteins and smaller **peptides** act as hormones and other signal molecules. Signal molecules are described in Chapters 6 and 8.
4. **Receptors.** Proteins that bind signal molecules and initiate cellular responses are called *receptors*. Receptors are discussed along with signal molecules in Chapter 6.
5. **Binding proteins.** These proteins, found mostly in the extracellular fluid, bind to and transport molecules throughout the body. Examples you may be familiar with include cholesterol-binding lipoproteins such as LDL (low-density lipoprotein) and the oxygen-transporting protein *hemoglobin* found inside red blood cells.
6. **Immunoglobulins.** These extracellular immune proteins, also called *antibodies*, help protect the body from foreign invaders and substances. Immune functions are discussed in Chapter 7.
7. **Motor proteins.** Motor proteins use energy from ATP to create movement. Examples include *myosin* that plays a role in muscle contraction, proteins that propel cilia and flagella, and protein fibers inside cells that move organelles and help in cell division.
8. **Structural proteins.** Fibrous proteins play an important role in creating the shape and structure of cells, tissues, and organs, as you will learn in Chapter 3. Some of the key structural proteins include *collagen*, *keratin*, and *elastin*.
9. **Regulatory proteins.** Regulatory proteins turn cell processes on and off or up and down. For example, the regulatory proteins known as *transcription factors* bind to DNA and alter gene expression and protein synthesis. The details of regulatory proteins can be found in cell biology textbooks.

Although proteins are quite diverse in shape and function, they share one common feature: they all bind to other molecules through noncovalent interactions. The interaction takes place at a location on the protein molecule called the **binding site.** The binding site depends on the three-dimensional shape of the protein, and its properties can be altered or *modulated* by factors that affect protein structure. The unique shapes of different binding sites give rise to three important properties of protein binding that are discussed below: specificity, affinity, and competition.

Running Problem 2.5

The hexavalent form of chromium used in industry is known to be toxic to humans. In 1992, officials at California's Hazard Evaluation System and Information Service warned that inhaling chromium dust, mist, or fumes placed chrome and stainless steel workers at increased risk for lung cancer. Officials found no risk to the public from normal contact with chrome surfaces or stainless steel. In 1995 and 2002, a possible link between the biological trivalent form of chromium (Cr^{3+}) and cancer came from *in vitro* studies {*vitrum*, glass—that is, a test tube} in which mammalian cells were kept alive in tissue culture. In these experiments, cells exposed to moderately high levels of chromium picolinate developed potentially cancerous changes.[1, 2]

Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*

Any molecule or ion that binds to another molecule is called a **ligand** {*ligare*, to bind or tie}. Ligands that bind to enzymes and membrane transporters are usually called **substrates** {*sub-*, below + *stratum*, a layer}. Proteins can also be ligands. Protein signal molecules bind to receptors, and protein transcription factors bind to DNA. Immunoglobulins bind ligands called *antigens*, but the immunoglobulin-antigen complex itself can then become a ligand [Fig. 7.8].

Proteins Are Selective about the Molecules They Bind

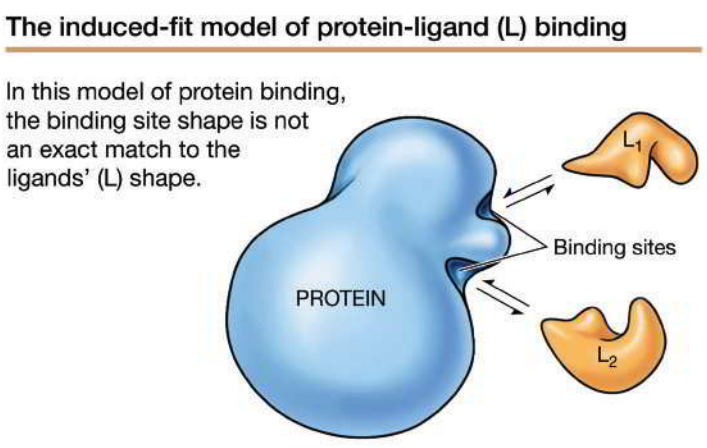
The ability of a protein to bind to a particular ligand or a group of related ligands is called **specificity.** Some proteins are very specific about the ligands they bind, while others bind to whole groups of molecules. For example, the enzymes known as **peptidases** bind to polypeptide ligands and break apart their **peptide bonds**, no matter which two amino acids are joined by those bonds. For this reason the action of peptidases is not very specific. In contrast, **aminopeptidases** also break peptide bonds but are more specific. They will bind to only one end of a protein chain (the end with an unbound amino group) and can act only on the last peptide bond in the chain.

Ligand binding requires **molecular complementarity**. In other words, the ligand and the protein binding site must be complementary, or compatible. In protein binding, when the ligand and protein come close to each other, noncovalent interactions between the ligand and the protein's binding site allow the two molecules to bind. From studies of enzymes and other binding proteins, scientists have discovered that a protein's binding site and the shape of its ligand do not need to fit one another exactly. When the binding site and the ligand come close to each other, they begin to interact through hydrogen and ionic bonds and van der Waals forces. The protein's binding site then changes shape (*conformation*) to fit more closely to the ligand. This is known as the **induced-fit model of protein-ligand interaction** and is shown in **FIGURE 2.10**.

When one protein binds to several related ligands, the related ligands that compete for the binding sites are said to be **competitors.** Competition between ligands is a universal property of protein binding. Competing ligands that mimic each other's actions are called **agonists** {*agonist*, contestant}. Agonists may occur in nature, such as *nicotine*, the chemical found in tobacco, which mimics the activity of the neurotransmitter *acetylcholine* by binding to the same receptor protein. Agonists can also be synthesized using what scientists learn from the study of protein–ligand binding sites.

Competing ligands that bind to the protein and block the binding site without causing a response are **antagonists**, also called inhibitors. Antagonists act like someone slipping into the front of a box office line to chat with their friend, the cashier. They are not interested in buying a ticket, but prevent the people waiting in line from getting their tickets. The ability of agonist and antagonist molecules to mimic or decrease the activity of naturally occurring ligands has led to the development of many drugs.

Fig. 2.10 The induced-fit model of protein-ligand (L) binding



Isoforms

Closely related proteins whose function is similar but whose affinity for ligands differs are called **isoforms** of one another. For example, the oxygen-transporting protein *hemoglobin* has multiple isoforms. One hemoglobin molecule has a **quaternary structure** consisting of four subunits (see Fig. 2.3). In the developing fetus, the hemoglobin isoform has two α (alpha) chains and two γ (gamma) chains that make up the four subunits. Shortly after birth, fetal hemoglobin molecules are broken down and replaced by adult hemoglobin. The adult hemoglobin isoform retains the two α chain isoforms but has two β (beta) chains in place of the γ chains. Both adult and fetal isoforms of hemoglobin bind oxygen, but the fetal isoform has a higher affinity for oxygen. This makes it more efficient at picking up oxygen across the placenta.

Protein-Binding Reactions Are Reversible

The degree to which a protein is attracted to a particular ligand is called the protein's **affinity** for the ligand. If a protein has a high affinity for a given ligand, the protein is more likely to bind to that ligand than to other ligands for which the protein has lower affinity.

Protein binding to a ligand can be written using the same notation that we use to represent chemical reactions:

$$P + L \rightleftharpoons PL$$

where P is the protein, L is the ligand, and PL is the bound protein-ligand complex. The double arrow indicates that binding is reversible.

Reversible binding reactions reach a state of **equilibrium**, where the rate of binding ($P + L \rightarrow PL$) is exactly equal to the rate of unbinding, or *dissociation* ($P + L \leftarrow PL$) When a reaction is at equilibrium, the ratio of the product concentration, or protein-ligand complex [PL], to the reactant concentrations [P][L] is always the same. This ratio is called the **equilibrium constant** K_{eq}, and it applies to all reversible chemical reactions:

$$K_{eq} = \frac{[PL]}{[P][L]}$$

The square brackets [ ] around the letters indicate concentrations of the protein, ligand, and protein-ligand complex.

In protein-binding reactions, the equilibrium constant K_{eq} is a quantitative representation of the protein's binding affinity for the ligand: high affinity for the ligand means a larger K_{eq}.[3] If one protein binds to several related ligands, a comparison of their K_{eq} values tells us which ligand is more likely to bind to the protein.

Binding Reactions Obey the Law of Mass Action

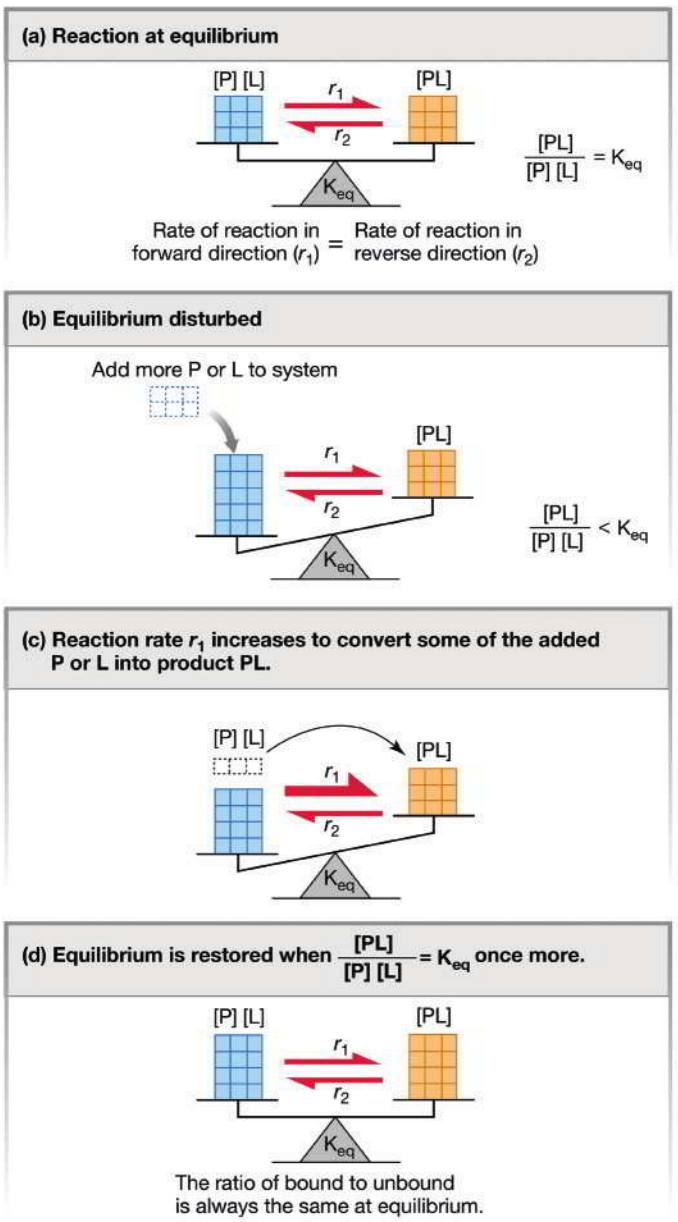
Reversible reactions at equilibrium have a constant ratio of bound protein to free protein and ligand. However, equilibrium is not a static state. In the living body, concentrations of protein or ligand change constantly through synthesis, breakdown, or movement from one compartment to another. So what restores equilibrium when it is disturbed?

When the concentration of protein or ligand changes, the reaction follows the **law of mass action**, which you may have learned in chemistry as *Le Châtelier's principle*. The law of mass action says that reaction rates are proportional to the concentration of the reactants. If the concentration of one of the participants changes, the reaction rates will increase or decrease to restore the equilibrium condition.

An example of this is shown in **FIGURE. 2.11**, which begins with a reaction at equilibrium (Fig 2.11a). The equilibrium is disturbed when more protein or ligand is added to the system (Fig. 2.11b). Now the ratio of [PL] to [P][L] differs from the K_{eq}. In response, the rate of the binding reaction increases to convert some of the added P or L into the bound protein-ligand complex (Fig. 2.11c). As the ratio approaches its equilibrium value again, the rate of the forward reaction slows until finally the system reaches the equilibrium ratio once more (Fig. 2.11d). [P], [L], and [PL] have all increased over their initial values, but the equilibrium ratio has been restored.

One example of this principle at work is the transport of **steroid** hormones in the blood. Steroids are hydrophobic, so more than 99% of steroid hormone in the blood is bound to carrier proteins. The equilibrium ratio [PL]/[P][L] is 99% bound:1% unbound hormone. However, only the unbound or "free" hormone can cross the cell membrane and enter cells. As unbound hormone leaves the blood, the equilibrium ratio is disturbed. The binding proteins then release some of the bound hormone until the 99:1 ratio is again restored. The same principle applies to enzymes and metabolic reactions. Changing the concentration of one participant in a chemical reaction has a chain-reaction effect that alters the concentrations of other participants in the reaction.

Fig. 2.11 The law of mass action



Concept Check

13. Consider the carbonic acid reaction, which is reversible:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

If the concentration of carbon dioxide in the body increases, what happens to the pH?

14. A researcher is trying to design a drug to bind to a particular cell receptor protein. Candidate molecule A has a K_{eq} of 0.9 for the receptor. Molecule B has a K_{eq} of 4.3. Which molecule has the most potential to be successful as the drug?

Running Problem 2.6

Malik has been taking chromium picolinate because he heard that it would increase his strength and muscle mass. Then a friend told him that the Food and Drug Administration (FDA) said there was no evidence to show that chromium would help build muscle. In one study,[4] a group of researchers gave high daily doses of chromium picolinate to football players during a two-month training period. By the end of the study, the players who took chromium supplements had not increased muscle mass or strength any more than players who did not take the supplement.

Use Google Scholar (*http://scholar.google.com*) and search for *chromium picolinate AND muscle*. Look for articles on body composition or muscle strength in humans before you answer the next question.

Q7: *Based on the papers you found, the Hallmark et al. study (which did not support enhanced muscle development from chromium supplements), and the studies that suggest that chromium picolinate might cause cancer, do you think that Malik should continue taking chromium picolinate?*

Multiple Factors Alter Protein Binding

A protein's affinity for a ligand is not always constant. Chemical and physical factors can alter, or *modulate*, binding affinity or can even eliminate it totally. Some proteins must be activated before they have a functional binding site. In this section we discuss some of the processes that have evolved to allow activation, modulation, and inactivation of protein binding. **TABLE 2.3** summarizes the different types of activation and modulation.

Activation

Some proteins are synthesized in the cell in an inactive state. Before these proteins can become active, enzymes must chop off one or more portions of the protein molecule (**FIG. 2.12a**). Protein hormones (a type of signal molecule) and enzymes are two groups that commonly undergo such *proteolytic activation* {*lysis*, to release}. The inactive forms of these proteins are often identified with the prefix *pro-* {before}: prohormone, proenzyme, proinsulin, for example. Some inactive enzymes have the suffix *-ogen* added to the name of the active enzyme instead, as in **trypsinogen**, the inactive form of trypsin.

The activation of some proteins requires the presence of a **cofactor,** which is an ion or small organic functional group. Cofactors must attach to the protein before the binding site is able to bind to a ligand (Fig. 2.12b). Ionic cofactors include Ca^{2+}, Mg^{2+}, and Fe^{2+}. Many enzymes do not function without their cofactors.

Table 2.3 Factors That Affect Protein Binding

Essential for Binding Activity	
Cofactors	Required for ligand binding at binding site
Proteolytic activation	Converts inactive to active form by removing part of molecule. Examples: digestive enzymes, protein hormones
Modulators and Factors That Alter Binding or Activity	
Competitive inhibitor	Competes directly with ligand by binding reversibly to active site
Irreversible inhibitor	Binds to binding site and cannot be displaced by competition
Allosteric modulator	Binds to protein away from binding site and changes activity; may be inhibitors or activators
Covalent modulator	Binds covalently to protein and changes its activity. Example: phosphate groups
pH and temperature	Alter three-dimensional shape of protein by disrupting hydrogen or S–S bonds; may be irreversible if protein becomes denatured

Modulation

The ability of a protein to bind a ligand and initiate a response can be altered by various factors, including temperature, pH, and molecules that interact with the protein. **Chemical modulators** are molecules that bind to proteins and alter their binding ability or their activity. Chemical modulators can be classified in several ways:

- By whether they enhance or inhibit the protein's activity,
- By whether their effect is reversible or irreversible,
- By where they bind to the protein (at the binding site or to another part of the protein), and
- By how they bind to the protein (noncovalent interactions or covalent bonds).

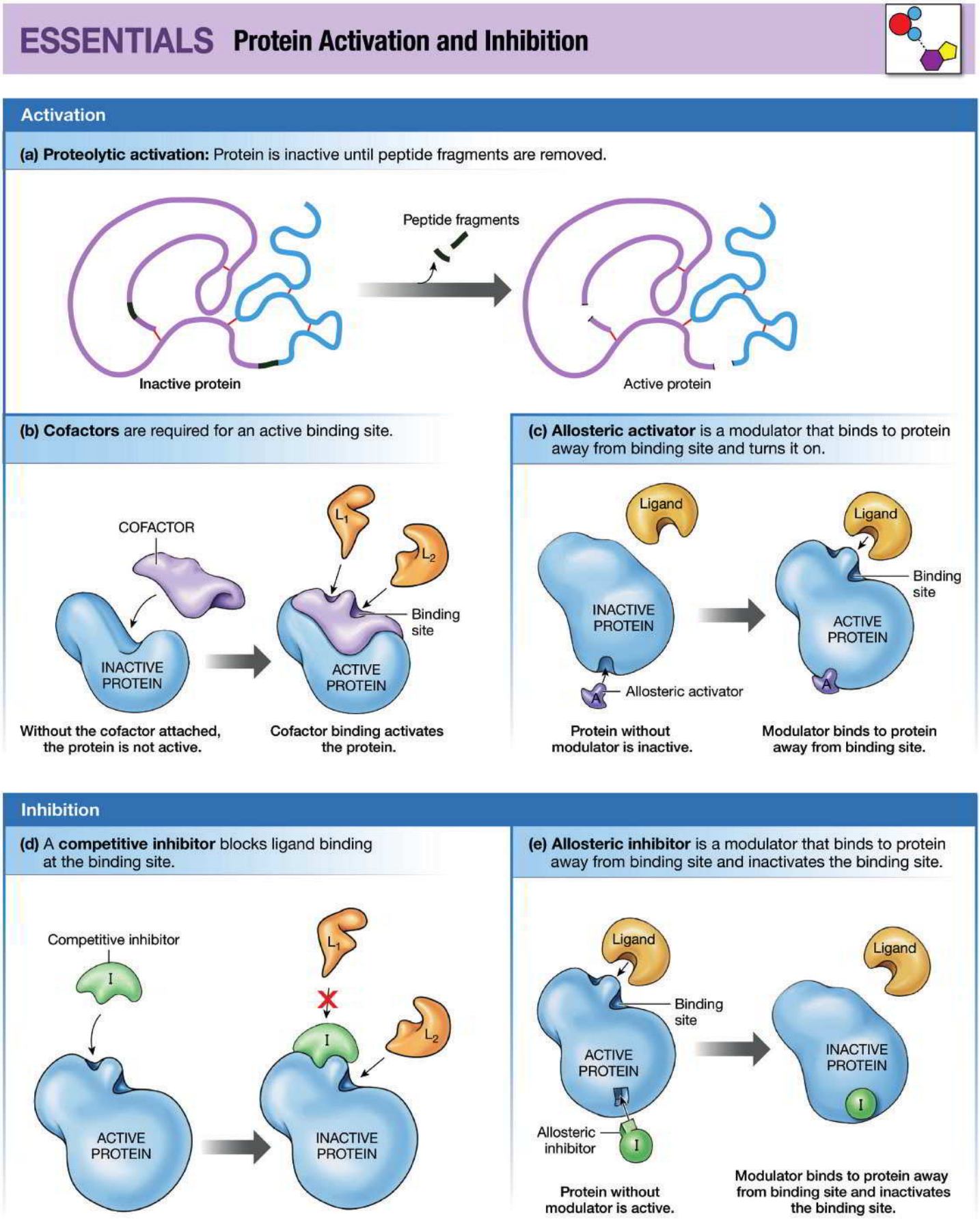
Inhibitors are chemical modulators that bind to a protein and decrease or stop its activity. The action of inhibitors may be reversible (competitive inhibitors) or irreversible (irreversible antagonists). **Competitive inhibitors** are reversible antagonists that compete with the typical ligand for the binding site (Fig. 2.12d). The degree of inhibition depends on the relative concentrations of the competitive inhibitor and the customary ligand, as well as on the protein's affinities for the ligand and inhibitor. The binding of competitive inhibitors is reversible: increasing the concentration of the customary ligand can displace the competitive inhibitor and decrease the inhibition.

Irreversible antagonists, on the other hand, bind tightly to the protein and cannot be displaced by competition. Antagonist drugs have proven useful for treating many conditions. For example, tamoxifen, an estrogen receptor antagonist, is used in the treatment of hormone-dependent cancers of the breast.

Allosteric modulators {*allos*, other + *stereos*, solid (as a shape)} bind to a protein at a regulatory site away from the binding site, and by doing so change the shape of the binding site. The effects of allosteric modulators may be reversible or irreversible. *Allosteric inhibitors* are antagonists that decrease the affinity of the binding site for the ligand and inhibit protein activity (Fig. 2.12e). *Allosteric activators* increase the probability of protein-ligand binding and enhance protein activity (Fig. 2.12c). For example, the oxygen-binding ability of hemoglobin changes with allosteric modulation by carbon dioxide, H^+ and several other factors [Fig. 19.9].

Covalent modulators are atoms or functional groups that bind covalently to proteins and alter the proteins' properties. Like allosteric modulators, covalent modulators may either increase or decrease a protein's binding ability or its activity. One of the most common covalent modulators is the phosphate group. Many proteins in the cell are activated or inactivated when a phosphate group forms a covalent bond with them, a process known as

Fig. 2.12 ESSENTIALS Protein Activation and Inhibition



phosphorylation. Phosphorylation can be reversed by enzymes that break the covalent bond.

One of the best known covalent inhibitor drugs is the antibiotic penicillin. Alexander Fleming discovered this compound in 1928, when he noticed that *Penicillium* mold inhibited bacterial growth in a petri dish. By 1938, researchers had extracted the active ingredient penicillin from the mold and used it to treat infections in humans. But it was not until 1965 that researchers figured out exactly how the antibiotic works. Penicillin is an irreversible antagonist that binds covalently to a key bacterial protein by mimicking the normal ligand. Because penicillin forms unbreakable bonds with the protein, the protein is irreversibly inhibited. Without the protein, the bacterium is unable to make a rigid cell wall. Without a rigid cell wall, the bacterium swells, ruptures, and dies.

Physical Factors

Physical conditions such as temperature and pH (acidity) can have dramatic effects on protein structure and function. Small changes in pH or temperature act as modulators to increase or decrease the activity of proteins such as enzymes (**FIG. 2.13a**). However, once these physical factors exceed some critical value, they disrupt the noncovalent bonds holding the protein in its tertiary conformation. The protein loses its shape and, along with that, its activity. When the protein loses its conformation, it is said to be *denatured*.

If you have ever fried an egg, you have watched this transformation happen to the egg white proteins as they change from a slithery clear state to a firm white state. Hydrogen ions in high enough concentration to be called acids have a similar effect on protein structure. During preparation of ceviche, a popular dish in several Latin American countries, raw fish is marinated in lime juice. The acidic lime juice contains hydrogen ions that disrupt hydrogen bonds in the muscle proteins of the fish, causing the proteins to become denatured. As a result, the meat becomes firmer and opaque, just as it would if it were cooked with heat.

In a few cases, protein activity can be restored if the original temperature or pH returns. The protein then resumes its original shape as if nothing had happened. Usually, however, denaturation produces a permanent loss of activity. There is certainly no way to unfry an egg or uncook a piece of fish. The potentially disastrous influence of temperature and pH on proteins is one reason these variables are so closely regulated by the body.

Concept Check

15. Match each chemical to its action(s).

(a) Allosteric modulator	**1.** Bind away from the binding site
(b) Competitive inhibitor	**2.** Bind to the binding site
(c) Covalent modulator	**3.** Inhibit activity only
	4. Inhibit or enhance activity

The Body Regulates the Amount of Protein in Cells

The final characteristic of proteins in the human body is that the amount of a given protein varies over time, often in a regulated fashion. The body has mechanisms that enable it to monitor whether it needs more or less of certain proteins. Complex signaling pathways, many of which themselves involve proteins, direct particular cells to make new proteins or to break down (*degrade*) existing proteins. This programmed production of new proteins (receptors, enzymes, and membrane transporters, in particular) is called **up-regulation.** Conversely, the programmed removal of proteins is called **down-regulation.** In both instances, the cell is directed to make or remove proteins to alter its response.

The amount of protein present in a cell has a direct influence on the magnitude of the cell's response. For example, the graph in Figure 2.13b shows the results of an experiment in which the amount of ligand is held constant while the amount of protein is varied. As the graph shows, an increase in the amount of protein present causes an increase in the response.

As an analogy, think of the checkout lines in a supermarket. Imagine that each cashier is an enzyme, the waiting customers are ligand molecules, and people leaving the store with their purchases are products. One hundred customers can be checked out faster when there are 25 lines open than when there are only 10 lines. Likewise, in an enzymatic reaction, the presence of more protein molecules (enzyme) means that more binding sites are available to interact with the ligand molecules. As a result, the ligands are converted to products more rapidly.

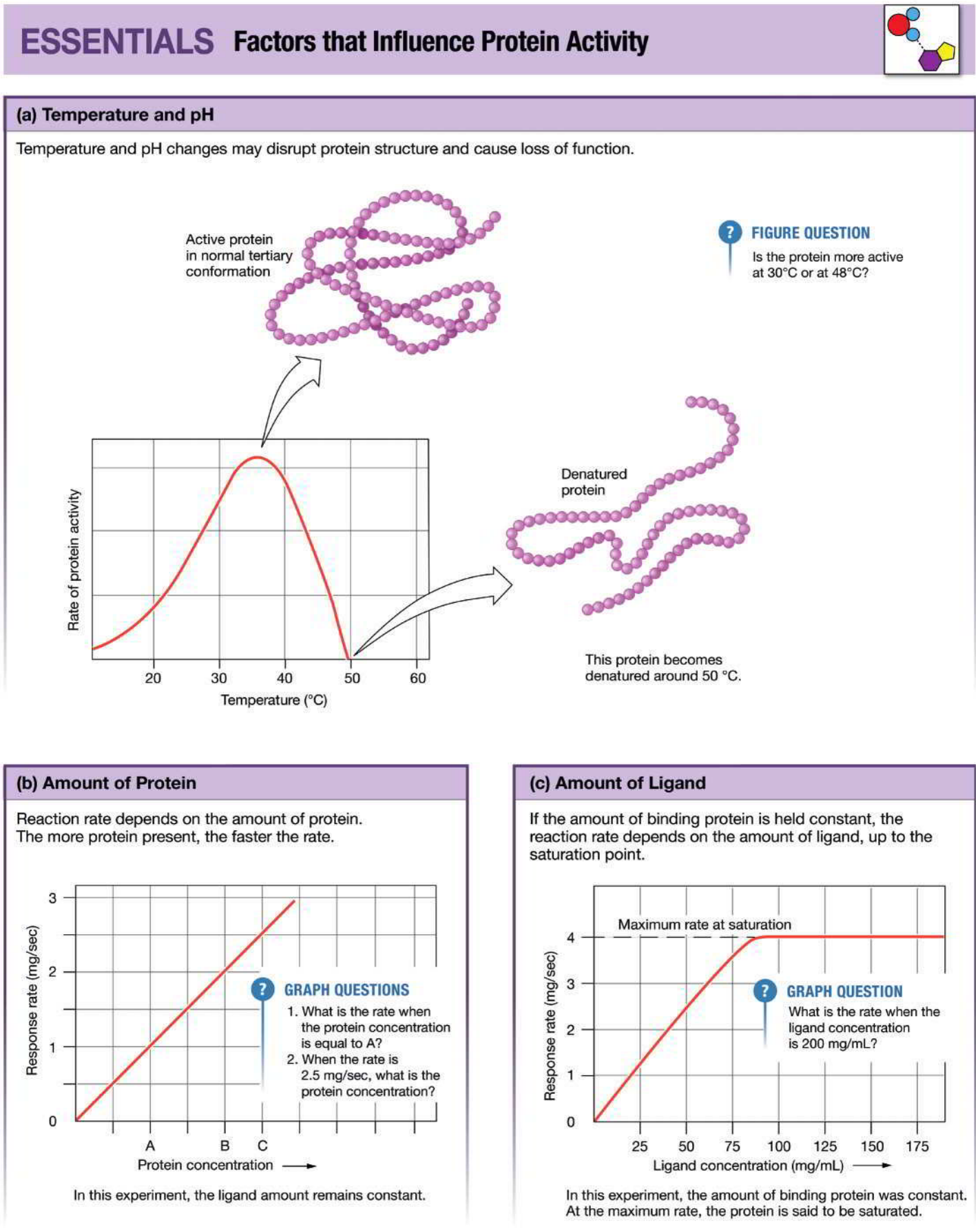
Regulating protein concentration is an important strategy that cells use to control their physiological processes. Cells alter the amount of a protein by influencing both its synthesis and its breakdown. If protein synthesis exceeds breakdown, protein accumulates and the reaction rate increases. If protein breakdown exceeds synthesis, the amount of protein decreases, as does the reaction rate. Even when the amount of protein is constant, there is still a steady turnover of protein molecules.

Reaction Rate Can Reach a Maximum

If the concentration of a protein in a cell is constant, then the concentration of the ligand determines the magnitude of the response. Fewer ligands activate fewer proteins, and the response is low. As ligand concentrations increase, so does the magnitude of the response, up to a maximum where all protein binding sites are occupied.

Figure 2.13c shows the results of a typical experiment in which the protein concentration is constant but the concentration of ligand varies. At low ligand concentrations, the response rate is directly proportional to the ligand concentration. Once the concentration of ligand molecules exceeds a certain level, the protein molecules have no more free binding sites. The proteins are fully occupied, and the rate reaches a maximum value. This condition is known as **saturation.** Saturation applies to enzymes, membrane transporters, receptors, binding proteins, and immunoglobulins.

Fig. 2.13 ESSENTIALS Factors That Influence Protein Activity



An analogy to saturation appeared in the early days of television on the *I Love Lucy* show and can be viewed today by searching YouTube (https://www.youtube.com/watch?v=AnHiAWlrYQc). Lucille Ball's character was working at the conveyor belt of a candy factory, wrapping chocolates to go into a candy box. Initially, the belt moved slowly, and she had no difficulty wrapping the candy. Gradually, the belt brought candy to her more rapidly, and she had to increase her wrapping speed to keep up. Finally, the belt brought candy to her so fast that she could not wrap it all because she was working at her maximum rate. That was Lucy's saturation point.

In conclusion, you have now learned about the important and nearly universal properties of proteins: shape-function relationships, ligand binding, specificity, competition, activation/inhibition, and saturation. You will revisit these concepts many times as you work through the organ systems of the body.

Concept Check

16. What happens to the rate of an enzymatic reaction as the amount of enzyme present decreases?
17. What happens to the rate of an enzymatic reaction when the enzyme has reached saturation?

Running Problem 2.7 Conclusion: Chromium Supplements

In this running problem, you learned that claims of chromium picolinate's ability to enhance muscle mass have not been supported by evidence from controlled scientific experiments. You also learned that studies suggest that the biological trivalent form of chromium may damage cells. In 2022 the NIH *Chromium Fact Sheet for Health Professionals*[5] says evidence indicates chromium may not be an essential nutrient as previously believed and there is insufficient research at this time to support its use as a nutritional supplement. Now compare your answers with those in the summary table.

Question	Facts	Integration and Analysis
Q1: *What is chromium's atomic number? Atomic mass? How many electrons does one atom of chromium have?*	Reading from the table, chromium (Cr) has an atomic number of 24 and an average atomic mass of 52. Atomic number is the number of protons in one atom. An atom has equal numbers of protons and electrons.	The atomic number of chromium is 24; therefore, one atom of chromium has 24 protons and 24 electrons.
Q2: *Which elements close to chromium are also essential elements?*	Molybdenum, manganese, and iron.	N/A
Q3: *If people have chromium deficiency, would you predict that their blood glucose level would be lower or higher than normal?*	Chromium helps move glucose from blood into cells.	If chromium is absent or lacking, less glucose would leave the blood and blood glucose would be higher than normal.
Q4: *From the result of the Chinese study, can you conclude that all people with diabetes suffer from chromium deficiency?*	Higher doses of chromium supplements lowered elevated blood glucose levels, but lower doses have no effect. This is only one study, and no information is given about similar studies elsewhere.	We have insufficient evidence from the information presented to draw a conclusion about the role of chromium deficiency in diabetes.
Q5: *How many electrons have been lost from the hexavalent ion of chromium? From the trivalent ion?*	For each electron lost from an ion, a positively charged proton is left behind in the nucleus of the ion.	The hexavalent ion of chromium, Cr^{6+}, has six unmatched protons and therefore has lost six electrons. The trivalent ion, Cr^{3+}, has lost three electrons.
Q6: *From this information, can you conclude that hexavalent and trivalent chromium are equally toxic?*	The hexavalent form is used in industry and, when inhaled, has been linked to an increased risk of lung cancer. Enough studies have shown an association that California's Hazard Evaluation System and Information Service has issued warnings to chromium workers. Evidence to date for toxicity of trivalent chromium in chromium picolinate comes from studies done on isolated cells in tissue culture.	Although the toxicity of Cr^{6+} is well established, the toxicity of Cr^{3+} has not been conclusively determined. Studies performed on cells in vitro may not be applicable to humans. Additional studies need to be performed in which animals are given reasonable doses of chromium picolinate for an extended period of time.
Q7: *Based on the study that did not support enhanced muscle development from chromium supplements and the studies that suggest that chromium picolinate might cause cancer, do you think Malik should continue taking picolinate?*	No research evidence supports a role for chromium picolinate in increasing muscle mass or strength in humans. Other research suggests that chromium picolinate may cause cancerous changes in isolated cells.	The evidence presented suggests that for Malik, there is no benefit from taking chromium picolinate, and there may be risks. Using risk–benefit analysis, the evidence supports stopping the supplements. However, the decision is Malik's personal responsibility. He should keep himself informed of new developments that would change the risk–benefit analysis.

Chemistry Review Quiz

Use this quiz to see what areas of chemistry and basic biochemistry you might need to review. The title above each set of questions refers to a review figure on this topic. Answers are in Appendix A.

Atoms and Molecules (Fig. 2.5)

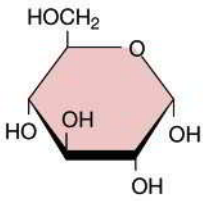
Match each subatomic particle in the left column with all the phrases in the right column that describe it. A phrase may be used more than once.

1. electron	(a) one has atomic mass of 1 amu
2. neutron	(b) found in the nucleus
3. proton	(c) negatively charged
	(d) changing the number of these in an atom creates a new element
	(e) adding or losing these makes an atom into an ion
	(f) gain or loss of these makes an isotope of the same element
	(g) determine(s) an element's atomic number
	(h) contribute(s) to an element's atomic mass

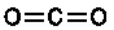
4. Isotopes of an element have the same number of _____ and _____, but differ in their number of _____. Unstable isotopes emit energy called _____.
5. Name the element associated with each of these symbols: C, O, N, and H.
6. Write the one- or two-letter symbol for each of these elements: phosphorus, potassium, sodium, sulfur, calcium, and chlorine.
7. Use the periodic table of the elements to answer the following questions:
   (a) Which element has 30 protons?
   (b) How many electrons are in one atom of calcium?
   (c) Find the atomic number and average atomic mass of iodine.
   (d) What is the letter symbol for iodine?
8. A magnesium ion, Mg^{2+}, has (*gained/lost*) two (*protons/ neutrons/ electrons*).
9. H^+ is also called a proton. Why is it given that name?
10. Use the periodic table of the elements to answer the following questions about an atom of sodium.
    (a) How many electrons does the atom have?
    (b) What is the electrical charge of the atom?
    (c) How many neutrons does the average atom have?
    (d) If this atom loses one electron, it would be called a(n) *anion/cation*.
    (e) What would be the electrical charge of the substance formed in (d)?
    (f) Write the chemical symbol for the ion referred to in (d).
    (g) What does the sodium atom become if it loses a proton from its nucleus?
    (h) Write the chemical symbol for the atom referred to in (g).

11. Write the chemical formulas for each molecule depicted. Calculate the molecular weight of each molecule.

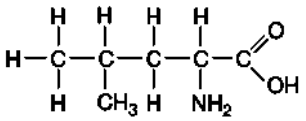
(a)



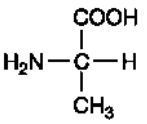
(b)



(c)



(d)



Lipids (Fig. 2.1)

12. Match each lipid with its best description.

(a) triglyceride	**1. most common form of lipid in the body**
(b) eicosanoid	**2. liquid at room temperature, usually from plants**
(c) steroid	**3. important component of cell membrane**
(d) oil	**4. structure composed of carbon rings**
(e) phospholipids	**5. modified 20-carbon fatty acid**

13. Use the chemical formulas given to decide which of the following fatty acids is most **unsaturated**:
    (a) $C_{18}H_{36}O_2C_{18}H_{36}O_2$
    (b) $C_{18}H_{34}O_2$
    (c) $C_{18}H_{30}O_2$

Carbohydrates (Fig. 2.2)

14. Match each carbohydrate with its description.

(a) starch	1. monosaccharide
(b) chitin	2. disaccharide, found in milk
(c) glucose	3. storage form of glucose for animals
(d) lactose	4. storage form of glucose for plants
(e) glycogen	5. structural polysaccharide of invertebrates

Proteins (Fig. 2.3)

15. Match these terms pertaining to proteins and amino acids:

(a) the building blocks of proteins	1. essential amino acids
(b) must be included in our diet	2. primary structure
(c) protein catalysts that speed the rate of chemical reactions	3. amino acids
	4. globular proteins
(d) sequence of amino acids in a protein	5. enzymes
(e) protein chains folded into a ball-shaped structure	6. tertiary structure
	7. fibrous proteins

16. What aspect of protein structure allows proteins to have more versatility than lipids or carbohydrates?
17. Peptide bonds form when the _____ group of one amino acid joins the _____ of another amino acid.

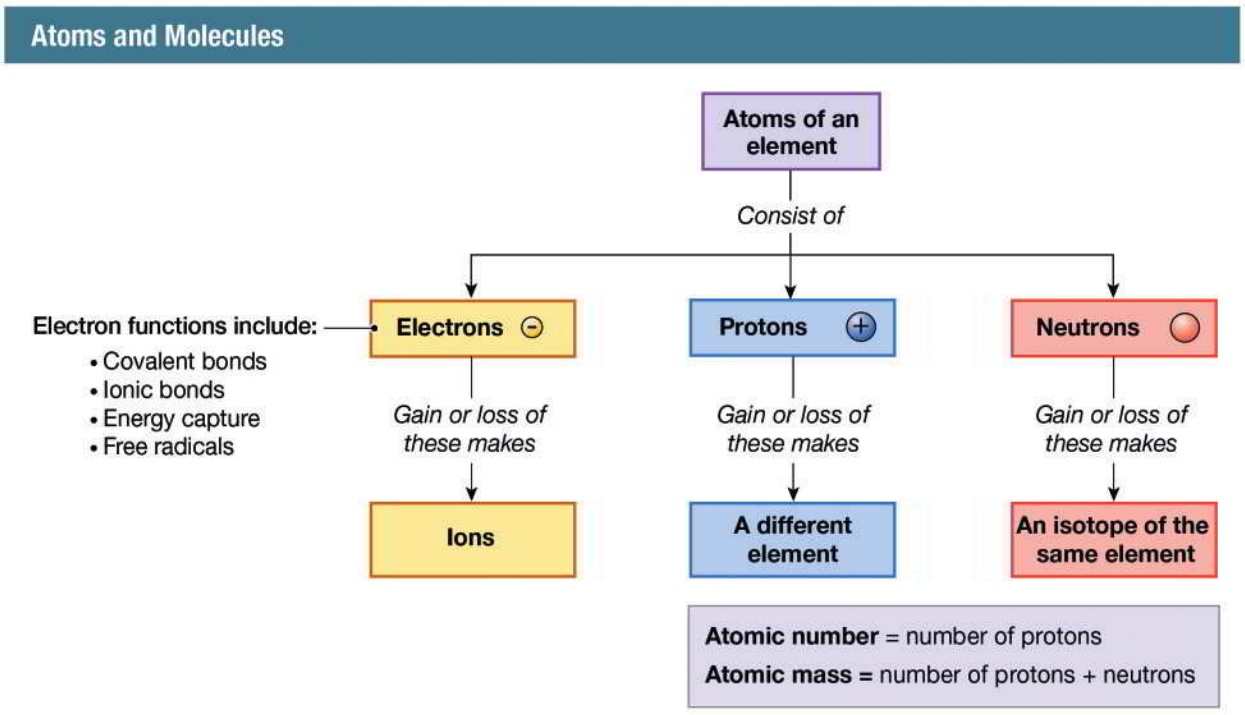
Nucleotides (Fig. 2.4)

18. List the three components of a nucleotide.
19. Compare the structure of DNA with that of RNA.
20. Distinguish between purines and pyrimidines.

Chapter Summary

This chapter has focused on the core concept of molecular interactions. Key ideas that will occur repeatediy in your study of physiology include:

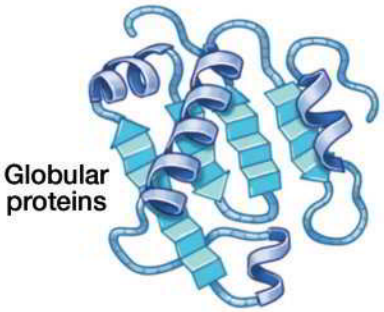
- The four main classes of **biomolecules**, their building blocks and variations. Fig. 2.1-2.4
- Key elements, **functional groups**, and **ions**. Tbl. 2.1, 2.2, Fig. 2.5
- The importance of **noncovalent interactions** in molecular shape and **solubility**. Fig. 2.6, 2.8
- **Solutions** and how to express concentration. Fig. 2.7
- Acids, bases, and **pH** Fig. 2.9
- The importance of **protein binding interactions** that play a role in nearly every physiological process. Fig. 2.8, 2.10



Functional Categories of Proteins

- Enzymes
- Membrane transporters
- Signal molecules
- Receptors
- Binding proteins
- Immunoglobulins
- Molecular motors
- Structural proteins
- Regulatory proteins

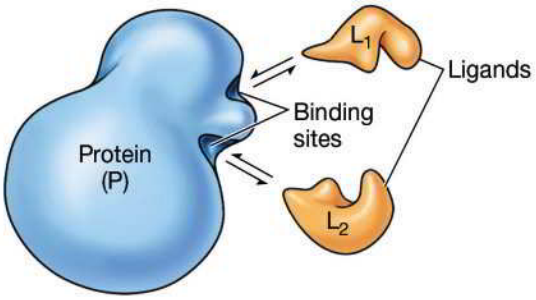
Fibrous proteins

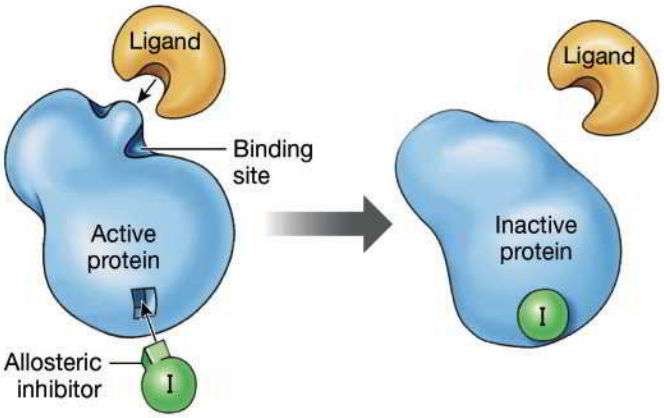


Protein Binding Interactions

Proteins (P) bind to Ligands (L)

$P + L \rightleftharpoons PL$

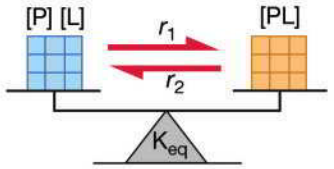




Protein binding demonstrates:

- **Specificity** and **affinity** for ligands
  - **Isoforms** of proteins
- **Competition** for the binding site
  - From **agonists**
  - From **antagonists** (competitive inhibitors)
- **Modulation** Fig. 2.12, 2.13
  - Activate, enhance, or inhibit
  - Reversible or irreversible
  - Noncovalent interaction or covalent bonding
  - At binding site or allosteric
  - Molecular or temperature, pH

Law of Mass Action Fig. 2.11



Rate of reaction in forward direction (r_1) = Rate of reaction in reverse direction (r_2)

At equilibrium

Equilibrium Constant K_{eq}

$$K_{eq} = \frac{[PL]}{[P]\,[L]}$$

Larger K_{eq} means higher affinity of the protein for the ligand.

Links to Resources

[1]DM Stearns *et al*. Chromium(III) picolinate produces chromosome damage in Chinese hamster ovary cells. *FASEB J* 9: 1643–1648, 1995. *https://doi.org/10.1096/fasebj.9.15.8529845*

[2]DM Stearns *et al*. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. *Mutat Res Genet Toxicol Environ Mutagen* 513: 135–142, 2002.*https://doi.org/10.1016/S1383-5718(01)00301-1*

[3]The reciprocal of the equilibrium constant is called the **dissociation constant** (K_d).

$$K_d = \frac{[P][L]}{[PL]}$$

A large K_d indicates low binding affinity of the protein for the ligand, with more P and L remaining in the unbound state. Conversely, a small K_d indicates higher protein affinity for the ligand.

[4]MA Hallmark *et al*. Effects of chromium and resistive training on muscle strength and body composition. *Med Sci Sports Exerc* 28(1):139–144,1996.*https://doi.org/10.1097/00005768-199601000-00025*

[5]National Institutes of Health (NIH) Office of Dietary Supplements (ODS). *Chromium: Fact sheet for health professionals*. 2022. *https://ods.od.nih.gov/factsheets/Chromium-HealthProfessional/*

Review Questions

In addition to working through these questions and checking your answers, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. List the four kinds of biomolecules. Give an example of each kind that is relevant to physiology.
2. True or false? All organic molecules are biomolecules.
3. When atoms bind tightly to one another, such as H_2O or O_2, one unit is called a(n) _____.
4. An atom of carbon has four unpaired electrons in an outer shell with space for eight electrons. How many covalent bonds will one carbon atom form with other atoms?
5. Fill in the blanks with the correct bond type.

   In a(n) _____ bond, electrons are shared between atoms. If the electrons are attracted more strongly to one atom than to the other, the molecule is said to be a(n) _____ molecule. If the electrons are evenly shared, the molecule is said to be a(n) _____ molecule.
6. Name two elements whose presence contributes to a molecule becoming a polar molecule.
7. Based on what you know from experience about the tendency of the following substances to dissolve in water, predict whether they are polar or nonpolar molecules: table sugar, vegetable oil.
8. A negatively charged ion is called a(n) _____, and a positively charged ion is called a(n) _____.
9. Define the pH of a solution. If pH is less than 7, the solution is _____; if pH is greater than 7, the solution is _____.
10. A molecule that moderates changes in pH is called a _____.
11. Proteins combined with fats are called _____, and proteins combined with carbohydrates are called _____.
12. A molecule that binds to another molecule is called a(n) _____.
13. Match these definitions with their terms (not all terms are used):

(a) the ability of a protein to bind one molecule but not another	1. irreversible inhibition
(b) the part of a protein molecule that binds the ligand	2. induced fit
(c) the ability of a protein to alter shape as it binds a ligand	3. binding site
	4. specificity
	5. saturation

14. An ion, such as Ca^{2+} or Mg^{2+}, that must be present in order for an enzyme to work is called a(n) _____.
15. A protein whose structure is altered to the point that its activity is destroyed is said to be _____.

Level Two Reviewing Concepts

16. Mapping exercise: Make the list of terms into a map describing solutions.

• concentration	• nonpolar molecule
• equivalent	• polar molecule
• hydrogen bond	• solubility
• hydrophilic	• solute
• hydrophobic	• solvent
• molarity	• water
• mole	

17. A solution in which $[H^+] = 10^{-3}$ M is (acidic/basic), whereas a solution in which $[H^+] = 10^{-10}$ M is (acidic/basic). Give the pH for each of these solutions.
18. Name three nucleotides or nucleic acids, and tell why each one is important.
19. You know that two soluble proteins are isoforms of each other. What can you predict about their structures, functions, and affinities for ligands?

20. You have been asked to design some drugs for the purposes described next. Choose the desirable characteristic(s) for each drug from the numbered list.

(a) Drug A must bind to an enzyme and enhance its activity.	1. antagonist
(b) Drug B should mimic the activity of a normal nervous system signal molecule.	2. competitive inhibitor
(c) Drug C should block the activity of a membrane receptor protein.	3. agonist
	4. allosteric activator
	5. covalent modulator

Level Three Problem Solving

21. You have been summoned to assist with the autopsy of an alien being whose remains have been brought to your lab. The chemical analysis returns with 33% C, 40% O, 4% H, 14% N, and 9% P. From this information, you conclude that the cells contain nucleotides, possibly even DNA or RNA. Your assistant is demanding that you tell him how you knew this. What do you tell him?

22. The harder a cell works, the more CO_2 it produces. CO_2 is carried in the blood according to the following equation:

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

What effect does hard work by your muscle cells have on the pH of the blood?

Level Four Quantitative Problems

23. Calculate the amount of NaCl you would weigh out to make one liter of 0.9% NaCl. Explain how you would make a liter of this solution.

24. A 1.0 M NaCl solution contains 58.5 g of salt per liter.

a. How many molecules of NaCl are present in 1 L of this solution?

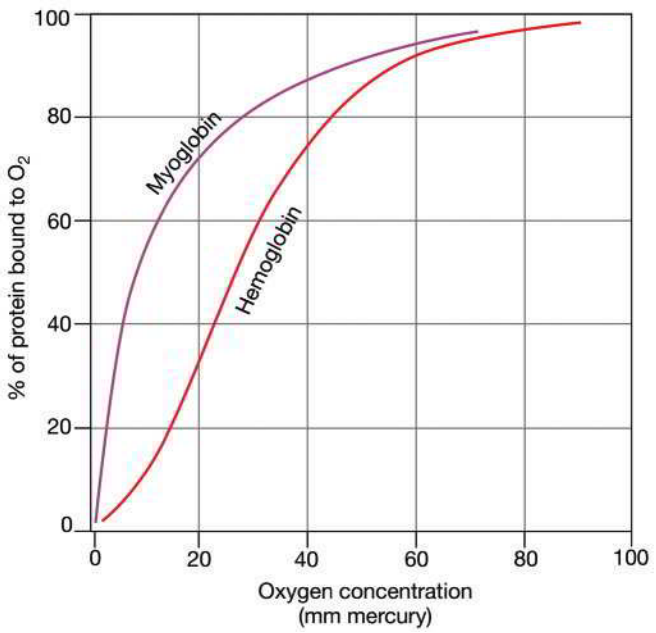
b. How many millimoles of NaCl are present?

c. How many **equivalents** of Na^+ are present?

d. Express 58.5 g of NaCl per liter as a **percent solution**.

25. How would you make 200 mL of a 10% glucose solution? Calculate the molarity of this solution. How many millimoles of glucose are present in 500 mL of this solution? (*Hint:* What is the molecular mass of glucose?)

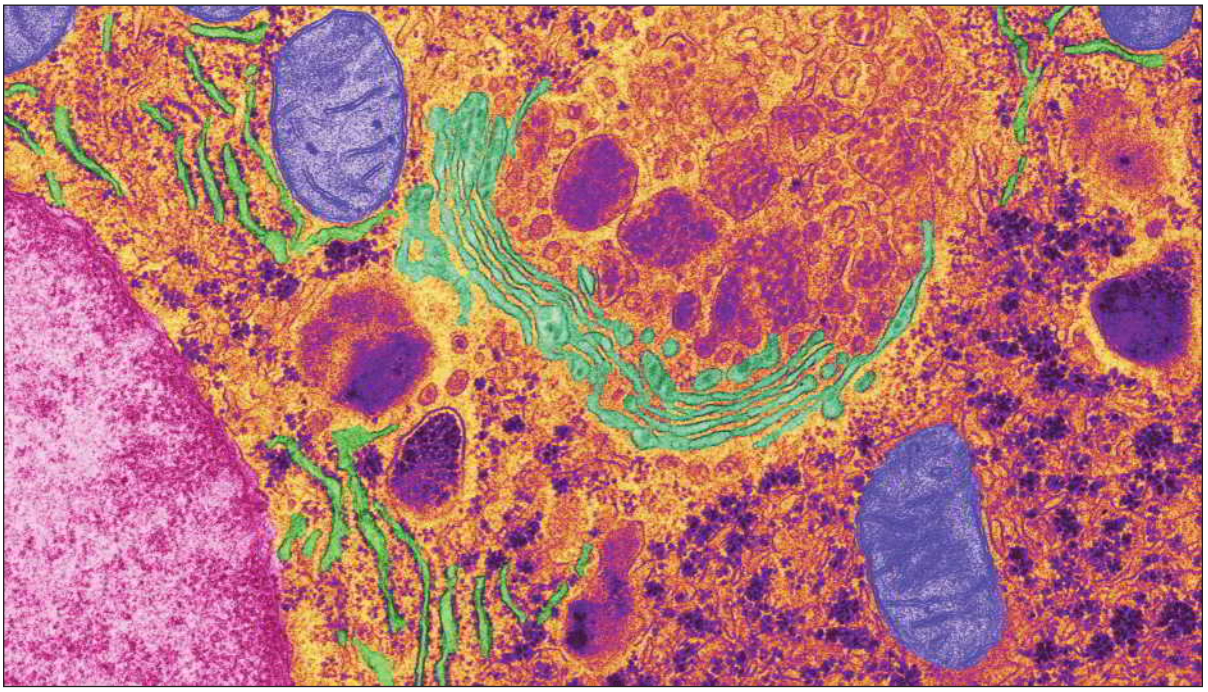
26. The graph shown below represents the binding of oxygen molecules (O_2) to two different proteins, myoglobin and hemoglobin, over a range of oxygen concentrations. Based on the graph, which protein has the higher affinity for oxygen? Explain your reasoning.



Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A.

3

Compartmentation: Cells and Tissues



Colored electron micrograph of liver organelles

Cells are organisms, and entire animals and plants are aggregates of these organisms.

Theodor Schwann, 1839

This chapter focuses on the core concept of compartmentation. The human body has functional compartments at all levels of organization, from the large body cavities like the abdomen to nearly invisible compartments within cells. Compartments serve a vital function by allowing physiological and biochemical processes to be separated in space.

Compartmentation

Photo Credits

Cover: Susumu Nishinaga/Science Source.

About the Authors: Jennifer L. Thompson; Kathleen Wilcox; Jennifer L. Thompson; Kelly Donato; Amber Rose Monroe; Dee U. Silverthorn.

Chapter 1 Opener: vectorfusionart/Shutterstock.

Chapter 2 Opener: Juan Gaertner/Shutterstock; **2.5:** Mopic/Shutterstock; **2.6d:** skyblue16/Shutterstock; **2.7 (top to bottom):** Sergio Ponomarev/Shutterstock; Charles D. Winters/Science Source; Tim Hawley/Getty Images; Gurpal Singh Datta/Indiapicture/Alamy Stock Photo.

Chapter 3 Opener: Keith R. Porter/Science Source; **3.3:** From Lipid Rafts: Feeling is Believing. Robert M. Henderson, J. Michael Edwardson, Nicholas A. Geisse, and David E. Saslowsky. *Physiology* 2004 19:2, 39-43; **3.6a:** Steve Gschmeissner/www.sciencephoto.com/Shutterstock. **3.8b:** Don W. Fawcett/Science Source Don W. Fawcett; **3.8e:** Dr. Holger Jastrow; **3.10c, e:** Dee Silverthorn; **3.13:** Robert Tallitsch/Pearson Education, Inc.; **3.14:** Komsan Loonprom/Shutterstock; **Clinical Focus:** James Stevenson/Science Source.

Chapter 4 Opener: Thomas Deerinck, NCMIR/Science Source.

Chapter 5 Opener: National Institutes of Health/Science Source; **5.4:** Tetra Images/Getty Images. **5.18 (top to bottom):** Krijnse Locker J, Schmid SL (2013) Integrated Electron Microscopy: Super-Duper Resolution. *PLoS Biol* 11(8): e1001639. https://doi.org/10.1371/journal.pbio.1001639; Michael Chirillo, The University of Texas at Austin.

Chapter 6 Opener: HAWOONG JEONG, UNIVERSITY OF NOTRE DAME/Science Source.

Chapter 7 Opener: Steve Gschmeissner/Science Source.

Chapter 8 Opener: Jose Luis Calvo/Shutterstock; **8.1:** Dee Silverthorn; **8.16:** William C. Ober.

Chapter 9 Opener: Steve Gschmeissner/Science Source; **9.2:** Ed Reschke/Photolibrary/Getty Images; **9.4:** SPL/Science Source; **9.5:** Todd Derksen; **Try It:** monphoto/123RF; **9.18:** Don W. Fawcett/Science Source; **9.22d:** David Becker/Science Source.

Chapter 10 Opener: Zephyr/Science Source; **10.5a:** Medical Body Scans/Science Source; **10.20c:** WDCN/Univ College London/Science Source.

Chapter 11 Opener: Science Source; **11.13a:** Dee Silverthorn; **Try It:** Valentyn Volkov/Shutterstock; **11.24b:** James Cavallini/Science Source; **11.26j:** stalnyk/123RF.

Chapter 12 Opener: Steve Gschmeissner/Science Source.

Chapter 13 Opener: Jose Calvo/Science Source; **13.14:** Dee Silverthorn; **13.20a:** Ljupco/iStock/Getty Images.

Chapter 14 Opener: Hawoong Jeong, University of Notre Dame/Science Source.

Chapter 15 Opener: Omikron/Science Source.

Chapter 16 Opener: Susumu Nishinaga/Science Source; **16.17c:** William C. Ober; **16.20:** Science History Images/Alamy Stock Photo.

Chapter 17 Opener: Steve Gschmeissner/Science Source; **17.5a:** Sebastian Kaulitzki/123RF; **17.5c:** David M. Phillips/Science Source; **17.5d:** David M. Phillips/Science Source; **17.5e:** Eye of Science/Science Source; **17.8:** Dee Silverthorn; **17.12b:** Susumu Nishinaga/Science Source.

Chapter 18 Opener: Jose Calvo/Science Source; **18.6:** totophotos/Shutterstock.

Chapter 19 Opener: David Phillips/Science Source.

Chapter 20 Opener: Steve Gschmeissner/Science Source; **20.1h:** Dee Silverthorn; **20.5b:** Dee Silverthorn.

Chapter 21 Opener: Titz B, Rajagopala SV, Goll J, Hauser R, McKevitt MT, et al. (2008) The Binary Protein Interactome of Treponema pallidum, The Syphilis Spirochete. *PLoS ONE* 3(5): e2292. doi:10.1371/journal.pone.0002292.

Chapter 22 Opener: MICROSCAPE/Science Source; **22.3:** William C. Ober.

Chapter 23 Opener: Thermal Vision Research/Wellcome Images/Science Source; **23.13b:** Dee Silverthorn.

Chapter 24 Opener: Jose Luis Calvo/Science Source; **24.3a:** Biophoto Associates/Science Source; **24.3b:** Clinical Photography, Central Manchester University Hospitals NHS Foundation Trust, UK/Science Source; **24.6a:** Alison Wright / Science Source; **24.6b:** Braden Gunem/Alamy Stock Photo; **24.6c:** Dr P. Marazzi/Science Source; **24.9:** Clinical Photography, Central Manchester University Hospitals NHS Foundation Trust, UK/Science Source; **24.10a:** Science Photo Library/Shutterstock; **24.11:** David Gregory & Debbie Marshall/Wellcome Images/Science Source.

Chapter 25 Opener: HAWOONG JEONG, UNIVERSITY OF NOTRE DAME/Science Source; **25.7:** lzf/Shutterstock; **Chapter Summary:** Rido/Shutterstock.

Chapter 26 Opener: ZEPHYR/Science Source; **26.1:** CNRI/Science Source; **26.14:** AJPhoto/Science Source; **26.16d:** William C. Ober.

Glossary

2,3-bisphosphoglycerate (2,3-BPG) A metabolite of red blood cells that lowers the binding affinity of hemoglobin for oxygen

5α–reductase Enzyme that converts testosterone to DHT

A band Band of striated muscle sarcomere whose length equals that of the thick filament

Absorption (1) Transfer of substances from the lumen of the kidney or gastrointestinal tract to the extracellular space; (2) Bulk flow of fluid from the ECF into the capillary lumen

Acclimation Physiological adjustment to environmental change in a laboratory setting

Acclimatization The adaptation of physiological processes to a given set of environmental conditions

Accommodation The process by which the eye adjusts the shape of the lens to keep objects in focus

Acetyl coenzyme A (Acetyl CoA) Metabolic intermediate that links glycolysis and beta-oxidation to the citric acid cycle

Acetylcholine (ACh) Neurotransmitter used by neurons of the central and peripheral nervous system

Acetylcholinesterase (AChE) Enzyme that breaks down acetylcholine in the synapse

Acid Molecule that ionizes and contributes an H^+ to a solution

Acidosis Extracellular pH less than 7.38

Acromegaly Abnormal growth of cartilage and soft tissues due to excess growth hormone secretion in an adult

Acrosomal reaction Release of enzymes from the sperm head when it contacts an egg

Acrosome Lysosome-like vesicle of sperm that contains powerful enzymes essential for fertilization

Actin A globular protein (G-actin) that polymerizes to form thin filaments (F-actin)

Action potentials Rapid and uniform electrical signal conducted down a cell membrane

Activation energy (1) The energy required to initiate a reaction; (2) The initial input of energy required to bring reactants into a position that allows them to react with one another

Activation gate Sodium channel gate that opens to initiate an action potential

Active hyperemia An increase in blood flow that accompanies an increase in metabolism

Active transport Movement across a membrane that requires the input of energy from ATP

Activins Peptide hormone from the gonads that stimulates FSH secretion

Acuity Keenness of vision

Acute Sudden onset of a condition

Acute-phase proteins Liver proteins that act as opsonins and enhance the inflammatory response

Adaptation of receptors Process in which sensory receptors decrease their response to a stimulus over time

Adaptive immunity Immune responses directed at specific invaders and mediated by antibodies

Addition reaction Reaction in which a functional group is added to one or more of the substrates

Adenosine Nucleoside composed of adenine and ribose

Adenylyl cyclase-cAMP system The enzyme that converts ATP to cyclic AMP

Adequate stimulus The form of energy to which a particular receptor is most responsive

Adherens junctions Bands that link actin microfilaments in adjacent cells together with the help of cadherins

Adipocytes Fat cells

Adipokines Cytokine released by adipose tissue

ADP (Adenosine diphosphate) Composed of adenine, ribose, and two phosphates

Adrenal cortex Outer portion of adrenal gland that produces steroid hormones

Adrenal gland Endocrine and neuroendocrine gland that sits on top of the kidney

Adrenal medulla Modified sympathetic ganglion, the inner portion of the adrenal gland that produces catecholamines

Adrenergic Adjective pertaining to epinephrine (adrenaline) or norepinephrine

Adrenergic neurons Neuron that secretes norepinephrine

Adrenergic receptors Membrane receptor that binds to norepinephrine and epinephrine

Adrenocorticotrophic hormone (ACTH) Anterior pituitary hormone that regulates secretion of cortisol from the adrenal cortex

Aerobic Adjective pertaining to a process that requires oxygen

Affective behaviors Behaviors related to feeling and emotion

Afferent The input pathway that connects a sensor to an integrating center

Afferent arteriole Renal arterioles that bring blood to the glomerulus

Affinity The degree to which a protein is attracted to its ligand

Agglutinate Antibody-induced clumping of red blood cells together

Aggregation Process in which cells stick to each other

Agonist Molecules that combine with a receptor and mimic a response

Airways Anatomical structures from mouth to bronchioles that carry air to the alveoli

Albumins Plasma protein made in the liver

Aldosterone A steroid hormone that stimulates Na^+ reabsorption and K^+ secretion in the kidney

Alkalosis Extracellular pH greater than 7.42

Allantois Extraembryonic membrane that becomes part of the umbilical cord

Allergen Any substance capable of triggering an allergic reaction

Allosteric modulators Binds to an enzyme away from the binding site and changes the shape of the active site

Alpha motor neurons Neurons that innervate extrafusal muscle fibers and cause muscle contraction

Alpha-helix Spiral configuration formed by some amino acid chains

Alternative splicing The processing of mRNA to make different proteins from a single strand of DNA

Alveolar macrophages Immune cells that patrol the alveoli

Alveolar ventilation The volume of fresh air that reaches the alveoli each minute

Alveoli The exchange surface of the lungs, where oxygen and carbon dioxide transfer between air and the blood

Amination Addition of an amino group to a molecule

Amine neurotransmitters Neurotransmitters made from amino acids, including the catecholamines, histamine, and serotonin

Amino acids Molecules with a central carbon atom linked to a hydrogen atom, an amino group, a carboxyl group, and a variable group of atoms designated "R." The building blocks of proteins

Amino groups Functional group whose composition is $-NH_2$

Aminopeptidases Digestive enzyme that removes amino acids from the amino terminal end of a peptide

Amnion Extraembryonic membrane that secretes amniotic fluid

AMPA receptors Glutamate receptor-channel that allows net Na^+ influx

Amplifier enzyme A membrane enzyme that creates two or more second messengers during signal transduction

Amygdala Portion of the brain linked to emotion and memory

Amylase Enzyme that digests starch to maltose

Anabolism Metabolic pathways that require a net input of energy and that synthesize small molecules into larger ones

Anaerobic Adjective pertaining to a process that does not require oxygen

Anatomic dead space The portions of the airways that do not exchange gases with the blood

Anatomy The study of structure

Anchoring junctions Form of cell-cell or cell-matrix junctions

Androgen-binding protein (ABP) Sertoli cell protein that binds testosterone to keep it in the lumen of the seminiferous tubule

Androgens Steroid hormone produced in the gonads and adrenal cortex; dominant hormone in males

Anemia Pathological state with low hemoglobin

Angiogenesis The process by which new blood vessels develop, especially after birth

Angiotensin II (ANG II) Trophic hormone that regulates aldosterone secretion; also raises blood pressure and causes thirst and ADH secretion

Angiotensin-converting enzyme (ACE) Membrane-bound endothelial enzyme that converts ANG I into ANG II

Anions Negatively charged ions

Anosmia Loss of sense of smell

Antagonistic control Hormones or neurons with opposing effects on some homeostatic function

Antagonistic muscle groups Flexor-extensor pairs of muscles attached to the same set of bones

Antagonists One substance opposes the action of another

Anterior horns (Ventral horns) Region of the spinal cord that contains cell bodies of motor neurons that carry efferent signals

Anterior pituitary An endocrine gland in the brain that secretes multiple hormones

Anterograde amnesia Inability to remember newly acquired information

Anti-Müllerian hormone (Mullerian inhibiting substance) Glycoprotein that causes the Mullerian ducts to degenerate during embryonic development

Antibodies Extracellular immune proteins keyed to a particular pathogen that help target the pathogen for destruction. Synonym: immunoglobulin

Antibody-dependent cell-mediated cytotoxicity Process in which natural killer cells kill a target cell by binding to the Fc portion of antibodies that are coating the cell

Anticoagulants Any chemical that inhibits blood coagulation

Anticodon The tRNA base triplet that pairs with the mRNA codon for an amino acid

Antidiuretic hormone (ADH) Posterior pituitary hormone that regulates water reabsorption in the kidney. Alternate name: vasopressin

Antigen-presenting cells (APC) Immune cells that ingest and digest pathogens, then insert a fragment of the pathogen into a surface protein

Antigens Substances that trigger an immune response from the body and that can react with products of that response

Antiport carriers A membrane transport protein that moves two or more molecules in opposite directions across a membrane

Antrum (1) Distal portion of the stomach; (2) Fluid-filled cavity of mature ovarian follicle

Aorta The main artery taking blood from the left ventricle to the body

Aortic baroreceptors Blood pressure-sensing receptors in the aorta

Aortic bodies Regions of the aortic wall that contain baro- and chemoreceptors

Aortic valve The valve between the left ventricle and the aorta

Apical membrane The surface of transporting epithelial cells that faces the lumen of an organ

Apnea Cessation of breathing

Apoptosis (Cell suicide) Programmed cell death

Aquaporins (AQP) Family of membrane water channels

Aqueous humor Plasma-like fluid filling the compartment of the eye between the cornea and the lens

Aqueous solutions Solution in which water is the solvent

Arachidonic acid 20-carbon fatty acid precursor of eicosanoid signal molecules

Arachnoid membrane The middle membrane layer of the meninges

Aromatase An enzyme that converts androgens to estrogens

Arteries Blood vessels that carry blood away from the heart

Arterioles The smallest arteries and site of variable resistance in the circulatory system

Ascending limb (Of loop of Henle) Portion of the nephron where dilute fluid is produced

Ascending tracts Spinal neurons that carry signals to the brain

Aspartate Amino acid that also acts as an excitatory neurotransmitter

Association areas Parts of the cerebrum that translate sensory information into perception

Associative learning Learning that occurs by association of two stimuli

Asthma Lung disease characterized by bronchoconstriction

Astigmatism Blurred vision caused by an irregularly shaped cornea

Astrocytes Glial cells in the CNS that contact both neurons and blood vessels

Asynchronous recruitment Alternation of active motor units to prevent fatigue

Atherosclerosis Pathological condition in which lipids and calcium deposit beneath the vascular endothelium

Atomic mass The mass of protons and neutrons in one atom of an element

Atoms The smallest particle of an element

ATP (Adenosine triphosphate) An energy-storing compound composed of adenine, ribose, and three phosphate groups

ATP-gated K^+ channel (K_{ATP} channel) Channel that closes when the ATP/ADP ratio increases

Atresia Apoptosis of ovarian follicles

Atrial natriuretic peptide (ANP) Peptide hormone from atria of the heart that increases renal Na^+ and water excretion

Atrioventricular node (AV node) The electrical gateway to the ventricles, located near the floor of the right atrium

Atrioventricular valves (AV valve) Heart valves that separate the atria from the ventricles

Atrium (Plural: atria) Upper chamber of the heart that receives blood from the blood vessels

Autocrine signal A local chemical signal that acts on the cell that secreted it

Autoimmune diseases Diseases in which the immune system creates antibodies against the body's own tissues

Autonomic division Efferent division of the nervous system that controls smooth muscle, cardiac muscle, glands, and some adipose tissue

Autonomic neurons Efferent neurons that control smooth muscle, cardiac muscle, many glands, and some adipose tissue

Autorhythmic cells Cardiac cells that spontaneously and rhythmically depolarize and fire action potentials

Autosomes The 22 pairs of chromosomes that contain information for non-sex-related development

AV node delay (Atrioventricular node delay) Slowing of electrical conduction through the AV node that allows atria to complete contraction before the ventricles begin

Axon hillock Region of the axon where it joins the cell body. Often contains the trigger zone

Axon terminal The distal end of a neuron where neurotransmitter is released into a synapse

Axonal transport Movement of material between the axon terminal and the cell body

Axons An extension of a neuron that carries signals to the target cell

B lymphocytes (B cells) White blood cell that secretes antibodies

Baroreceptor reflex The primary reflex pathway for homeostatic control of blood pressure

Baroreceptors Stretch-sensitive mechanoreceptors that respond to changes in pressure

Barr body The inactivated X chromosome in each female cell

Basal ganglia Nuclei surrounding the thalamus that help with planning movement

Basal lamina An acellular layer of extracellular matrix that lies beneath an epithelium, holding the epithelial cells to underlying cell layers

Basal metabolic rate (BMR) An individual's lowest metabolic rate

Basement membrane Fusion of the epithelial basal lamina with matrix of the supporting connective tissue

Bases Molecules that combine with free hydrogen ions

Basilar membrane Membrane that separates the cochlear duct from the tympanic duct. It supports the organ of Corti

Basolateral membrane The sides of transporting epithelial cells that face the extracellular fluid. Synonym: serosal membrane

Basophils Leukocyte that releases histamine, heparin

Beta cells of the pancreas Endocrine cells that secrete insulin

Beta-blockers Drugs that are beta-adrenergic receptor antagonists. Used to treat hypertension

Beta-sheet Sheet-like structure formed from adjacent strands of amino acids held together with hydrogen bonds

Bicuspid valve The left AV valve of the heart. Synonym: mitral valve

Bile A solution secreted by the liver and composed primarily of bile acids, bile pigments and cholesterol

Bile acids Steroid detergents made from cholesterol by the liver

Bile salts Bile acids conjugated with amino acids

Bilirubin Breakdown product of heme groups from hemoglobin

Binding site Region of an enzyme or transport protein to which the substrate binds

Binocular vision Three-dimensional vision from overlapping visual fields of two eyes

Bioenergetics The study of energy flow through biological systems

Biological rhythms The cyclic variation of a biological process

Biomolecular condensates Functional compartments without walls, such as nucelolus. Made of proteins or combinations of RNA and protein

Biomolecules Organic molecules associated with living organisms

Bipolar neurons Neuron with a single axon and single dendrite

Bipotential Early embryonic gonads that cannot be identified as male or female

Blastocyst Early embryo, consisting of a hollow ball of cells

Blind spot Region of the retina with no photoreceptors because the optic nerve and blood vessels exit the eye. Synonym: optic disk

Blind study An experiment in which the subject does not know if he or she is receiving the experimental treatment

Blood The circulating portion of the extracellular fluid

Blood pressure The pressure exerted by blood on the walls of the blood vessels. Usually measured in the systemic arteries

Blood-brain barrier Tight junctions in the brain capillaries that prevent free exchange of many substances between the blood and the cerebrospinal fluid

Blood-testis barrier Tight junctions between Sertoli cells that prevent free exchange between the extracellular fluid and the lumen of the seminiferous tubules

Body temperature Normal human body temperature is 37 °C or 98.6 °F

Bohr effect The effect of a change in pH on hemoglobin binding of oxygen

Bolus A mass

Bone Calcified connective tissue

Bone marrow A soft tissue that fills the hollow centers of bones; site of hematopoiesis

Bowman's capsule The initial segment of the renal tubule. Receives filtered fluid from the glomerular capillaries

Boyle's Law If the volume of a gas increases, the pressure decreases, and vice versa. $P_1V_1 = P_2V_2$

Bradycardia Slow heart rate

Brain stem Portion of the brain closest to the spinal cord; contains centers for many unconscious body functions

Broca's area Speech center in the frontal lobe

Bronchioles Small collapsible airways with smooth muscle walls

Brown fat Adipose cells that contain multiple lipid droplets

Brush border Name given to microvilli covering the luminal surface of intestinal and renal tubule epithelia

Buffer A molecule that moderates changes in pH

Bulbourethral glands (Cowper's) Male accessory gland that produces components of semen

Bulk flow Mass movement of water or air as the result of pressure gradients

Bundle branches Two branches of the bundle of His that carry electrical signals to each ventricle

Bundle of His (Atrioventricular bundle) Specialized electrical conducting cells of the heart that carry signals into the ventricles

C cells Thyroid gland cells that secrete calcitonin

Ca^{2+}-ATPase Membrane transporter that moves calcium ions against their concentration gradient

Cadherins Membrane-spanning protein of adhesive junctions that links two cells together

Calcitonin Thyroid gland hormone that decreases plasma Ca^{2+} concentrations in lower animals

Calcitonin gene-related peptide (CGRP) Neuronal peptide that is coded by the same gene as calcitonin

Calcium channel Ion channel that allows movement of calcium ions across a membrane

Calcium channel blockers Drugs that block calcium channels; used to treat high blood pressure

Calcium-induced calcium release (CICR) Process in which calcium ion entry into a muscle fiber triggers release of additional calcium ions from the sarcoplasmic reticulum

Calmodulin Intracellular second messenger that binds Ca^{2+}

Candidate hormones Molecules that have not been shown to fulfill all the qualifications of a hormone

Capacitation Changes in sperm that confer the ability to swim rapidly and fertilize an egg

Capacity (Lung capacity) The sum of two or more lung volumes

Capillary Smallest blood vessels where blood exchanges material with the interstitial fluid

Carbaminohemoglobin Hemoglobin with bound carbon dioxide

Carbohydrates Molecules of carbon, hydrogen, and oxygen in the ratio CH_2O

Carbon dioxide (CO_2) Gaseous product of aerobic respiration

Carbonic anhydrase (CA) Enzyme that catalyzes the conversion of carbon dioxide and water into hydrogen and bicarbonate ions

Carboxypeptidases Enzymes that break peptide bonds at the carboxy terminal end of a peptide

Cardiac cycle The period of time from the end of one heartbeat through the end of the next beat

Cardiac glycosides Drugs such as ouabain and digitalis that block the sodium-potassium-ATPase

Cardiac muscle Striated muscle of the heart

Cardiac output (CO) The amount of blood pumped per ventricle per unit time

Cardiovascular control center (CVCC) Neurons in the medulla oblongata that integrate sensory information and direct autonomic responses aimed at maintaining adequate blood pressure

Cardiovascular system The heart and blood vessels

Carotid bodies Peripheral chemoreceptors in the carotid arteries that respond to low arterial oxygen, decreased pH, or increased carbon dioxide

Carrier proteins Membrane protein that binds to the molecule it transports. Synonym: transporter

Cartilage Firm, elastic connective tissue with collagen fibers

Cascade Response in which a series of inactive molecules convert to active forms until a product is formed

Castration Removal of the gonads

Catabolism Reactions that release energy and result in the breakdown of large biomolecules

Catalase Enzyme that converts peroxide to oxygen and water

Catalysts Molecules that speed up the rate of a chemical reaction without being changed

Catecholamines Signal molecule formed from tyrosine; includes epinephrine, norepinephrine, and dopamine

Cations Positively charged ions

Cecum The initial section of the large intestine

Cell adhesion molecules (CAMs) Membrane proteins that link cells to each other and to the extracellular matrix

Cell body Part of the cell that contains the nucleus and many organelles. Synonym: cell soma

Cell junctions Membrane proteins and extracellular matrix that hold cells together to form tissues

Cell membrane The phospholipid bilayer that serves as both a gateway and a barrier for substances moving into and out of the cell

Cell-mediated immunity Immune reaction that requires T lymphocytes to come in contact with the antigen

Cell-to-cell communication Chemical and electrical processes by which cells coordinate their functions

Cells The basic functional unit of most living organisms

Cellular mechanism of action The intracellular events through which a signal molecule's message is carried out inside the target cell

Cellular respiration Intracellular reaction of oxygen with organic molecules to produce CO_2, water, and energy in the form of ATP

Central chemoreceptor Chemoreceptor in the medulla oblongata that monitors plasma P_{CO_2}

Central fatigue Subjective feeling of fatigue during exercise

Central nervous system (CNS) Brain and spinal cord

Central pattern generators (CPGs) Networks of CNS neurons that function spontaneously to control certain rhythmic muscle movements

Central receptors Sensory receptors located in or closely linked to the brain

Centrosome The cell's microtubule-organizing center

Cephalic phase Digestive reflexes triggered by stimuli received in the brain, such as the smell or sight of food

Cerebellum Portion of the brain that coordinates the execution of movement

Cerebral cortex Outer portion of the cerebrum that carries out higher cognitive functions

Cerebral lateralization Asymmetrical distribution of function between the left and right sides of the brain

Cerebrospinal fluid (CSF) A salty solution that is continuously secreted into the ventricles of the brain

Cerebrum Largest region of the brain

Cervix Neck of the uterus that opens into the vagina

Channel proteins A membrane protein that forms water-filled channels to link intracellular and extracellular compartments

Chemical bonds The physical forces that attract and hold atoms together

Chemical equilibrium Process in which the forward and reverse rates are equal so that there is no net change in the concentrations of products or reactants

Chemical reaction A substance undergoes a chemical change to become a different substance by breaking existent covalent bonds or making new bonds

Chemical synapses Synapse that uses neurotransmitters to pass information to the target cell

Chemical work Making and breaking of chemical bonds that enable cells and organisms to grow, maintain a suitable internal environment, and store information

Chemically gated channels Channels whose open gate is controlled by binding to a chemical ligand

Chemoreceptors A sensory receptor that is activated by binding of a chemical substance

Chemotaxins A molecule that attracts cells such as white blood cells

Chief cells A cell of the stomach that secretes pepsinogen

Chloride shift Process in which red blood cells exchange HCO_3^- for Cl^-

Cholecystokinin (CCK) Intestinal hormone that regulates digestive function and may play a role in appetite

Cholesterol A steroid that serves as the basis for steroid hormones; also a key component of membranes

Cholinergic Neurons that secrete acetylcholine

Chondrocytes Cells that produce cartilage

Chordae tendineae Collagenous cords that prevent the atrioventricular valves from being pushed back into the atria during ventricular contraction

Choroid plexus A transporting epithelium that secretes cerebrospinal fluid

Chromaffin cells Modified postganglionic sympathetic neurons in the adrenal medulla that secrete epinephrine

Chronic An ongoing condition

Chronic obstructive pulmonary disease (COPD) Pulmonary diseases characterized by nonreversible decreased air flow through bronchioles; emphysema and chronic bronchitis

Chylomicrons Large droplets of triglycerides, cholesterol, proteins, and lipoproteins that are synthesized in cells of the small intestine

Chyme A soupy substance produced by digestion in the digestive tract

Cilia Short, hair-like structures whose movement creates currents that move fluids or secretions across the cell surface

Ciliary muscle Muscle in the eye whose contraction slackens zonules and rounds the lens

Ciliated epithelia Epithelia covered with cilia that move fluid over the surface

Circulatory system The heart and blood vessels

Circumcision Removal of the foreskin of the penis

Citric acid cycle Key metabolic pathway of aerobic respiration. Synonyms: Krebs cycle, tricarboxylic cycle, TCA cycle

Clearance A measurement of the disappearance of a substance from the blood, expressed as milliliters of plasma cleared of solute per unit time

Clonal expansion Reproduction of one type of lymphocyte following exposure to an antigen

Clone A group of cells that are genetically identical

Closed system A system where nothing enters and nothing leaves

Co-secretion Secretion of more than one compound from a secretory vesicle

Coagulation Process in which fluid blood forms a gelatinous clot

Cochlea Coiled structure of ear that contains receptors for hearing

Coenzymes Organic cofactors for enzymes; they do not alter the enzyme's binding site as inorganic cofactors do

Cofactor An inorganic or nonprotein organic molecule required for activation of protein

Cognitive behaviors Behaviors that deal with thought processes rather than emotion

Colipase A protein cofactor that allows lipase to break through the bile salt coating of an emulsion

Collagen Flexible but inelastic protein fibers of connective tissue

Collaterals Branch of an axon

Collecting duct Terminal region of the kidney tubule

Colloid osmotic pressure (π) Osmotic pressure that due to the presence of plasma proteins that cannot cross the capillary endothelium. Synonym: oncotic pressure

Colon Proximal portion of the large intestine

Colonocytes Transporting epithelial cell of the large intestine

Colony-stimulating factors (CSF) Cytokines made by endothelial cells and white blood cells that direct the production and development of white blood cells

Compartmentation The internal division of the body or cell into compartments so that functions can be isolated from one another

Competitive inhibitors Molecules that bind to the active site of the enzyme, preventing substrate binding

Complement A group of plasma enzymes that are involved in immune function

Complete tetanus (fused tetanus) Sustained maximal contraction of a muscle in response to repeated stimuli

Compliance The ability of the lung or other tissue to stretch

Concentration The amount of solute per unit volume of solution

Concentration gradient A difference in the concentration of a substance between two places

Conductive hearing loss Hearing loss due to failure of sound transmission though outer or middle ear

Cones A photoreceptor for high acuity vision and color vision during the daytime

Congenital adrenal hyperplasia Hereditary defects in the enzymes needed for adrenal steroid production

Congestive heart failure (CHF) Pathological condition in which the left ventricle fails to pump blood adequately, causing backup of fluid into the lungs

Conjugated proteins Molecules of protein combined with either lipid or carbohydrate

Connexins Membrane-spanning cylindrical proteins that form gap junctions; capable of opening and closing

Connexon The protein channel of a gap junction, made of connexins

Consensual reflex Light shined in one pupil constricts both pupils

Consolidation Process that converts short-term memory to long-term memory

Constitutively active Any essential bodily function that is always taking place

Contact-dependent signals Cell-cell signals that require surface molecule binding between two cells

Continuous capillaries Capillaries whose endothelial cells are joined with leaky junctions

Contraction Process by which a muscle creates force

Contralateral On the opposite side from

Control Part of an experiment designed to ensure that any observed changes are due to the experimental manipulation and not to an outside factor

Controlled variables A variable that controlled to be the same for both experimental and control groups

Convergence A number of presynaptic neurons provide input to a smaller number of postsynaptic neurons

Cornea The clear covering of the anterior surface of the eye

Coronary arteries Arteries supplying blood to the heart muscle

Coronary circulation Arteries supplying blood to the heart muscle

Corpora cavernosa Two columns of erectile tissue in the penis

Corpus albicans The remnants of a degenerated corpus luteum

Corpus callosum The central region where neurons pass from one hemisphere of the cerebrum to the other

Corpus luteum Ovarian structure that produces estrogen and progesterone after ovulation

Corpus spongiosum A column of spongy erectile tissue in the penis

Cortex Literally, bark; the outer or surface portion of an organ

Cortical granules Cytoplasmic granules in the egg that contain chemicals to prevent polyspermy

Cortical reaction Chemical reaction that changes the zona pellucida after fertilization so that additional sperm cannot reach the egg

Corticospinal tract Neurons from motor cortex to spinal cord

Corticotropin-releasing hormone (CRH) Hypothalamic hormone that regulates secretion of ACTH from the anterior pituitary

Cortisol Steroid hormone from the adrenal cortex that regulates metabolism, particularly during stress

Cotransporter A protein that moves more than one kind of molecule at one time

Countercurrent exchange systems Anatomical arrangement of vessels so that flow in one vessel is in the opposite direction from flow in the adjacent vessel

Countercurrent multiplier Anatomical arrangement of the loop of Henle that concentrates solute in the renal medulla

Covalent bonds Bonds created by two atoms that share one or more pairs of electrons.

Covalent modulators Atoms or functional groups bind to proteins and affect their activity

Cranial nerves 12 pairs of peripheral nerves that originate primarily from the brain stem

Creatine kinase (CK) Enzyme that transfers a high-energy phosphate group from phosphocreatine to ADP

Creatinine The breakdown product of phosphocreatine

Crista Sensory structure at the base of each semicircular canal

Cross-sectional studies These examine a population for the prevalence of a disease or condition

Crossbridges Connection formed when mobile myosin heads bind to actin molecules in muscle

Crossed extensor reflex A postural reflex that helps maintain balance during flexion reflexes

Crossover study Experimental design in which the subjects spend half the time on the experimental treatment and half the time on placebo

Cryptorchidism Failure of one or both testes to descend into the scrotum

Crypts Deep pockets created by the highly folded surface of the intestine

Cupula Gelatinous mass in the vestibular apparatus that contains cilia of hair cells

Cyanosis Blue or gray appearance to mucous membranes due to excessive amounts of reduced hemoglobin

Cyclic AMP (CAMP/cyclic adenosine monophosphate) Nucleotide that participates in the transfer of signals between the external environment and the cell

Cyclooxygenase (COX) Enzyme that converts arachidonic acid to prostanoids

Cystic fibrosis transmembrane conductance regulator (CFTR channel) Nucleotide-gated chloride channel in epithelia that is defective in cystic fibrosis

Cytokines Regulatory peptides that control cell development, differentiation, and the immune response

Cytoplasm All material inside the cell membrane except for the nucleus

Cytoskeleton The internal scaffolding of the cell, composed of microfilaments, intermediate filaments, and microtubules

Cytosol Semi-gelatinous intracellular fluid containing dissolved nutrients, ions, and waste products

Cytotoxic T cell (T_C cell) A lymphocyte that kills its target cells

D cells Pancreatic endocrine cells and intestinal cells that secrete somatostatin

Dalton's law The total pressure of a mixture of gases is determined by the sum of the pressures of the individual gases

Data Information or facts gathered during an experiment

Deamination Removal of an amino group from a molecule

Decibels (dB) Measure of sound wave intensity

Declarative memory (explicit) Memory that depends on the use of higher level cognitive skills such as inference, comparison, and evaluation. Synonym: explicit memory

Deglutition Swallowing

Degranulation Process in which immune cells release the contents of their granules

Dehydration reactions Reaction in which two molecules combine into one, losing water in the process

Deiodinases Tissue enzyme that converts T4 to T3 by removal of an iodine

Delayed hypersensitivity reactions Allergic reaction mediated by T cells that may take several days to develop

Delta waves High-amplitude, low-frequency brain waves of deep sleep

Dendrites Thin, branched processes that receive and transfer incoming information to an integrating region within the neuron

Dendritic cells Antigen-presenting immune cells with long, thin processes

Dendritic spines Projections of the dendrite membrane that increase surface area

Denervation hypersensitivity Up-regulation of neurotransmitter receptors following denervation creates greater than expected response to exogenous neurotransmitter

Dense bodies Attachment proteins for smooth muscle actin fibers

Dephosphorylation Removal of a phosphate group

Depolarized The membrane potential of a cell becomes less negative

Descending tracts Neurons that carry information from the brain to the spinal cord

Desensitization Reversible form of receptor down-regulation achieved using modulators

Desmopressin A form of vasopressin used to treat bed-wetting

Desmosomes A type of cell-to-cell junction

Dextrose A six-carbon sugar; also known as glucose

Diabetes insipidus Disease characterized by lack of vasopressin

Diabetes mellitus Disease characterized by lack of or abnormal action of insulin

Diabetic autonomic neuropathy Disturbances of neuronal function as a complication of diabetes mellitus

Diacylglycerol (DAG) A second messenger

Diaphragm (Muscle) The skeletal muscle that forms the floor of the thoracic cage

Diaphysis The shaft of a long bone

Diarrhea Excessive amounts of watery stool

Diastole The time during which cardiac muscle relaxes

Diastolic pressure Lowest pressure in the circulatory system, associated with relaxation of the ventricles

Diencephalon Brain portion between brain stem and cerebrum, consisting of thalamus and hypothalamus

Differentiation Developmental process during which cells take on different forms and functions

Diffuse endocrine system Hormones secreted by isolated endocrine cells rather than from glands

Diffuse modulatory systems Clusters of brain stem neurons that influence large areas of the brain

Diffusion Movement of molecules from an area of higher concentration to an area of lower concentration

Digestion Chemical and mechanical breakdown of foods into smaller units that can be absorbed

Digestive system Those structures involved in ingestion, processing, absorption, and elimination of food

Dihydropyridine receptor (DHP) Voltage-sensing receptors in the t-tubules, linked to Ca^{2+} channels

Dipalmitoylphosphatidylcholine Surfactant in the alveoli that decreases surface tension

Direct calorimetry A procedure in which food is burned and the heat released is trapped and measured

Disaccharidases Enzyme that digests disaccharides

Disaccharides Sugars composed of two sugar monomers

Distal nephron The distal tubule and collecting duct

Disulfide bonds (S—S) A weak bond between two sulfur atoms

Diuresis Loss of water in the urine

Diuretics Drugs that cause water loss in the urine

Divergence A few presynaptic neurons branch to affect a larger number of postsynaptic neurons

DNA (Deoxyribonucleic acid) Nucleotide that stores genetic information in the nucleus

Dopamine (DA) Amine CNS neurotransmitter

Dorsal root Branch of a spinal nerve that carries sensory information

Dorsal root ganglia Collections of sensory cell bodies found on the dorsal roots just before they enter the spinal cord

Double bond Bonds formed when two atoms share two pairs of electrons

Double-blind crossover study Double-blind experiment in which the subjects switch between experimental treatment and placebo halfway through the study

Double-blind studies Experimental design in which neither the subject nor the researcher knows who is getting the experimental treatment and who is getting the placebo

Down-regulation Decrease in protein number or binding affinity that lessens response

Ducts Open tubes through which most exocrine glands release their products

Duodenum Initial segment of the small intestine

Dura mater Outer membrane of the meninges

Dwarfism A condition of short stature caused by inadequate growth hormone during childhood

Dynamic equilibrium An equilibrium state where individual particles continue to move without disturbing the equilibrium

Dyneins A motor protein

Dysgeusia Loss of sense of taste

Dyspnea A subjective feeling of not being able to breathe or get air

Dystrophin Muscle protein that links actin to the cell membrane

Ectohormone Signal molecules secreted to the external environment

Ectosomes Extracellular vesicles created by outward budding at the cell surface

Edema The accumulation of fluid in the interstitial space

Effector The cell or tissue that carries out the homeostatic response

Efferent Output signal that goes from the integrating center to an effector

Efferent neurons A peripheral neuron that carries signals from the central nervous system to the target cells

Eicosanoids Modified 20-carbon fatty acids that act as regulators of physiological functions

Einthoven's triangle The triangle formed by the three lead electrodes of the simple ECG

Ejaculation Semen in the urethra is expelled to the exterior

Ejection fraction Percentage of ventricular volume ejected in one contraction (stroke volume/EDV)

Elastance Ability of a stretched substance to return to its unstretched state

Elastin A coiled, wavy protein that returns to its original length after being stretched

Electrical gradient Uneven distribution of electrical change, especially across a membrane

Electrical synapses Synapse where electrical signals pass directly from cell to cell through gap junctions

Electrocardiograms (ECG) A recording of the summed electrical events of the cardiac cycle

Electrochemical gradient The combined concentration and electrical gradients for an ion

Electrolyte An ion, because ions carry electricity

Emergent properties Properties that cannot be predicted to exist based only on knowledge of the system's individual components

Emesis Vomiting

Emission Movement of sperm from vas deferens to the urethra

Emphysema Lung disease characterized by loss of elastance and alveolar surface area

Emulsion Small droplets suspended in a liquid, such as lipid droplets in an aqueous solution

Encapsulated lymphoid tissues Lymph nodes and the spleen

End-diastolic volume (EDV) The maximum volume of blood that the ventricles hold during a cardiac cycle

End-plate potential (EPP) Depolarization at the motor end plate due to acetylcholine

End-systolic volume (ESV) The amount of blood left in the ventricle at the end of contraction

Endergonic A reaction that requires net input of energy from an outside source

Endocrine glands A ductless gland or single cell that secretes a hormone

Endocrine system The cells and tissues of the body that secrete hormones

Endolymph High K^+, low Na^+ fluid that fills the cochlear duct of the ear

Endometrium The secretory inner lining of the uterus

Endopeptidases An enzyme that attacks peptide bonds in the interior of an amino acid chain

Endoplasmic reticulum (ER) A network of interconnected membrane tubes in the cytoplasm; site of protein and lipid synthesis

Endosome Vesicle formed by endocytosis

Endothelium Layer of thin epithelial cells that line the lumen of the heart and blood vessels

Energy The capacity to do work

Enteric nervous system Neurons in the wall of the gastrointestinal tract that are capable of sensing and integrating information and carrying out a response without input from the CNS

Enterochromaffin-like cells (ECL cells) Stomach cells that secrete histamine

Enterocytes Transporting epithelial cells of the small intestine

Enteroendocrine cells (EEC) Isolated endocrine cells of the gut

Enteropeptidase Intestinal enzyme that activates trypsin

Entropy A condition of randomness or disorder. *See also* second law of thermodynamics

Enzymes Protein catalysts that speed up reactions by lowering their activation energy

Eosinophils Leukocytes associated with parasitic infections and allergic reactions

Epididymis Duct from seminiferous tubules to vas deferens where sperm complete their maturation

Epinephrine Catecholamine neurohormone secreted by the adrenal medulla

Epiphyseal plates Region of long bones where active bone growth takes place

Epiphysis The end of a long bone

Epithelia Tissue that protects surface of the body, lines hollow organs, and manufactures and secretes substances. (Singular: epithelium)

Epithelial transport Movement of material from one side of an epithelium to the other

Equilibrium potential (E_{ion}) The membrane potential that exactly opposes the concentration gradient of an ion

Equivalents (Eq) Molarity of an ion times the number of charges the ion carries

Erection Blood trapped within spongy tissues of the penis causes it to lengthen and harden

Erythroblasts Large, nucleated immature red blood cells

Erythrocytes Red blood cells that transport oxygen and carbon dioxide between the lungs and the tissues

Erythropoiesis Red blood cell production

Erythropoietin (EPO) Hormone made in the kidneys that regulates red blood cell production

Esophagus The passageway connecting the mouth and stomach

Essential elements Those elements necessary for life

Estradiol Form of estrogen produced when aromatase acts on testosterone

Estrogen Steroid hormone produced in ovary and adrenal cortex; dominant steroid in females

Etiology The cause or origin of a disease

Excess postexercise oxygen consumption (EPOC) Increased oxygen consumption following exercise that represents metabolism to replace ATP and other stores consumed during exercise

Exchange epithelia Thin epithelia designed for easy transfer of material from one compartment to another

Excitation-contraction coupling (E-C coupling) The sequence of action potentials and calcium release that initiate contraction

Excitatory postsynaptic potential (EPSPs) Depolarizing graded potentials that make a neuron more likely to fire an action potential

Excretion The elimination of material from the body, usually through the urine, feces, lungs, or skin

Exergonic reaction Chemical reaction that releases energy

Exocrine glands A gland that releases secretions into the external environment through ducts

Exocytosis Process in which intracellular vesicles fuse with the cell membrane and release their contents into the extracellular fluid

Exopeptidases Enzymes that release single amino acids from peptides by chopping them off the ends

Exophthalmos Bulging eyes in hyperthyroidism due to enlargement of tissue in the eye socket

Exosomes Extracellular vesicles created from endosomes

Expiration The movement of air out of the lungs

Expiratory reserve volume (ERV) The amount of air that can be exhaled after the end of a normal expiration

Expressive aphasia Inability to speak coherently as a result of damage to Broca's area

Extensor A muscle that moves bones away from each other when the muscle contracts

External environment The outside world surrounding the body

External lamina Thin matrix layer supporting nerve and muscle cells

External respiration The interchange of gases between the environment and the body's cells

Extracellular fluid (ECF) The internal fluid that surrounds the cells

Extracellular matrix Extracellular material synthesized and secreted by cells

Extracellular vesicles (EVs) Tiny membrane-bound bodies that cells release into the ECF

Extrafusal muscle fibers The normal contractile fibers of a muscle

Extrapyramidal tract (extrapyramidal system) Neural network associated with basal ganglia that influences body position and movement

Extrinsic pathway Coagulation pathway that starts when damaged tissues expose tissue factor

F-actin Long chains or filaments of actin molecules

Fab region The antigen-binding arms of an antibody molecule

Facilitated diffusion Movement of molecules across cell membranes in response to a concentration gradient with the aid of a membrane protein

Factor General name given to signal molecules when first discovered

$FADH_2$ (Flavin adenine dinucleotide) Nucleotide that captures and transfers energy with high-energy electrons

Fallopian tubes Tube that transport eggs from the ovary to the uterus. Synonym: oviduct

Fas A "death receptor" on cell membranes whose activation causes a cell to commit suicide by apoptosis

Fast axonal transport Rapid movement of particles along an axon using microtubules and kinesin foot proteins

Fast pain Sharp, rapidly transmitted pain

Fast synaptic potential Graded potential in postsynaptic cells that begins quickly and lasts only a few milliseconds

Fast-twitch glycolytic fibers Fast muscle fibers that rely on anaerobic metabolism and therefore fatigue rapidly

Fast-twitch oxidative-glycolytic fibers Fast muscle fibers that use a combination of aerobic and anaerobic metabolism and therefore do not fatigue as fast as glycolytic fibers

Fatty acid Long chain of carbon atoms bound to hydrogens and terminating with a carboxyl

Fc region Stem of antibody molecule that binds to receptors on immune cells

Feedback inhibition The end product of a metabolic pathway acts as an inhibitory modulator of the pathway. Synonym: end-product inhibition

Feedback loop Information about a homeostatic response that is sent back to the integrating center

Feedforward control Anticipatory responses that start a response loop in anticipation of a change that is about to occur

Feeding center Tonically active hypothalamic center that promotes food intake

Fenestrated capillaries Capillaries with large pores in the endothelium

Ferritin Protein that binds and stores iron in the body

Ferroportin (FPN) Membrane transporter that takes iron ions out of cells

Fibrin Plasma protein that forms polymer fibers that stabilize platelet plugs

Fibrinogen Plasma protein that becomes fibrin in blood clots

Fibrinolysis Dissolution of fibrin by plasmin

Fibronectin A protein fiber that helps connect cells to their extracellular matrix

Fick's law of diffusion Diffusion through a membrane is directly proportional to the surface area and concentration gradient and inversely proportional to the thickness of the membrane and its resistance

Filtration (1) (Renal) Bulk flow of plasma-like fluid from the glomerular capillaries into Bowman's capsule; (2) (CV) Bulk flow of fluid out of a capillary into the ECF

Filtration fraction The percentage of total plasma volume that filters at the glomerulus

Filtration slits Opening between podocyte foot processes through which renal filtration takes place

Fimbriae The fringed opening of the Fallopian tube

First heart sound Sounds created by vibrations from closure of AV valves

First law of thermodynamics The total amount of energy in the universe is constant

First messenger Chemical signal molecules that bind to protein receptors on the cell surface

Flagella Long hair-like extensions of the cell whose microtubules create movement

Flatus Intestinal gas

Flexion reflexes A polysynaptic reflex that causes an arm or leg to be pulled away from a painful stimulus

Flexor A muscle that brings connected bones closer together when it contracts

Flow rate The volume of fluid that passes one point in the system per unit time

Fluid mosaic model Membrane composed of phospholipid bilayer with proteins inserted wholly or partially into the bilayer

Fluid pressure Pressure created by the presence of fluid within an enclosed space

Fluids A substance that flows, which includes both liquids and gases

Flux Diffusion rate across a membrane per unit surface area of the membrane

Focal adhesions Junction between intracellular actin and matrix proteins

Focal length (Focal distance) The distance from the center of a lens to the focal point

Focal point The point where parallel light waves passing through a lens converge

Follicle-stimulating hormone (FSH) Anterior pituitary hormone that stimulates gamete production in the gonads

Follicular phase Phase of the menstrual cycle during which ovarian follicles mature and prepare to release an egg

Foot processes Long cytoplasmic extension of a podocyte that wraps around glomerular capillaries

Fovea The region of most acute vision and the point on which light is focused when you look at an object

Frank-Starling law of the heart The principle that within physiological limits, the heart will pump all the blood that returns to it

Free energy The potential energy stored in the chemical bonds of a molecule

Free radicals Unstable molecule with one more unpaired electrons

Frequency coding The frequency of action potentials encodes the intensity of a stimulus

Functional groups Groups of atoms that tend to move from molecule to molecule as a single unit

Functional unit The smallest structure that can carry out all the functions of a system

Fundus The upper portion of the stomach

Fusion pore Membrane complex through which secretory vesicle contents can be released

G_{olf} Protein for olfactory transduction

G cells Cell of the stomach that secretes gastrin

G protein Membrane proteins that couple membrane receptors to ion channels or membrane enzymes

G-actin Single globular molecule of actin

Galactose A hexose monosaccharide

Gallbladder Organ that stores and concentrates bile

Gametes The reproductive cells that unite to form a new individual

Gametogenesis Gamete production

Gamma globulins Name given to the immune globulins of plasma

Gamma motor neurons Small neuron that innervates intrafusal fibers within the muscle spindle

Gamma-aminobutyric acid (GABA) Inhibitory neurotransmitter of the CNS

Ganglion A cluster of nerve cell bodies in the peripheral nervous system. Plural: ganglia

Ganglion cells Neurons of the eye whose axons form the optic nerve

Gap junctions Cytoplasmic bridges between adjacent cells, created by linked membrane proteins

Gastric lipase Stomach enzyme that digests lipids

Gastrin Hormone secreted by G cells of the stomach that stimulates gastric acid secretion

Gastrointestinal tract (GI tract) Synonym: digestive tract

Gated channels A channel that opens and closes in response to stimuli

Gene A region of DNA that contains all the information needed to make a functional piece of mRNA

Genitalia The external reproductive structures

Genomic effect Any effect that occurs due to altered gene activity

Germ cells Embryonic gonadal cells that produce gametes

GIP (gastric inhibitory peptide or glucose-dependent insulinotropic peptide) GI hormone that causes feedforward release of insulin

Gland Group of epithelial cells specialized for synthesis and secretion of substances

Glial cells Nonexcitable support cells of the central nervous system

Glomerular filtration rate (GFR) The amount of fluid that filters into Bowman's capsule per unit time

Glomerulus Ball-like network of capillaries in the kidney; site of filtration

Glomus cells Cells of the carotid and aortic body that respond to low oxygen

Glucagon Pancreatic hormone that elevates plasma glucose

Glucocorticoids Adrenal steroid hormones such as cortisol that elevate plasma glucose

Gluconeogenesis Pathways through which noncarbohydrate precursors, especially amino acids, are converted into glucose

Glucose A six-carbon sugar that is a major energy source for the body. Synonym: dextrose

Glucostatic theory Theory that glucose utilization by the hypothalamic centers regulates food intake

Glucosuria (Glycosuria) Excretion of glucose in the urine

GLUT transporters Family of facilitated diffusion carriers for glucose and other hexose sugars

Glutamate Amino acid that also acts as an excitatory neurotransmitter

Glycerol A simple 3-carbon molecule that is the backbone of fatty acids

Glycine Amino acid that also acts as an inhibitory neurotransmitter

Glycocalyx Glycoproteins on the surface of cells

Glycogen Storage polysaccharide found in animal cells

Glycogenolysis The breakdown of glycogen

Glycolipids Molecule that is a combination of carbohydrate and lipid

Glycolysis Metabolic pathway that converts glucose to pyruvate (aerobic) or lactic acid (anaerobic)

Glycoproteins Molecule that is a combination of carbohydrate and protein

Glycosylated molecules A molecule that has sugar molecules attached to it

GnRH pulse generator Region of the hypothalamus that coordinates the pulsatile secretion of GnRH

Goblet cells Single exocrine cell that produces mucus

Goiter Enlarged thyroid gland

Goldman-Hodgkin-Katz equation (GHK) Calculates resting membrane potential using membrane permeability and ion concentrations gradients

Golgi apparatus Organelle that modifies and packages proteins into vesicles

Golgi tendon organ (GTO) Receptors are found at the junction of the tendons and muscle fibers that responds to contraction of the muscle

Gonadotropin-releasing hormone (GnRH) Hypothalamic hormone that stimulates release of gonadotropins from the anterior pituitary

Gonadotropins (FSH and LH) Peptide hormones from the anterior pituitary that act on the gonads

Gonads The organs (ovaries and testes) that produce gametes

Graded contractions Muscle contraction whose force varies with the amount of calcium that enters the cell

Graded potentials A change in membrane potential whose magnitude is proportional to the stimulus and that decreases with distance as it spreads through the cytoplasm

Gradient A gradual change in the value or magnitude of a function

Granular cells Specialized cells in the walls of renal arterioles that synthesize and release renin

Granulocytes White blood cell whose cytoplasmic inclusions give it a granular appearance: basophils, eosinophils, and neutrophils

Granulosa cell Cell of the ovarian follicle that secretes estrogen

Granzymes Enzyme of cytotoxic T cells that triggers apoptosis in target cells

Gray matter Nerve cell bodies, dendrites, and axon terminals

Ground substance A cellular portion of matrix consisting of glycoproteins and water

Growth hormone Protein hormone from the anterior pituitary that controls tissue growth

Growth hormone-releasing hormone (GHRH) Hypothalamic hormone that influences growth hormone secretion

Gut-associated lymphoid tissue (GALT) Immune cells and tissues of the GI tract

Gyrus A convolution of the brain's cerebral surface

H zone Region of sarcomere with only thick filaments

Habituation A decreased response to a stimulus that is repeated over and over

Hair cells Sensory cells for transduction of sound and equilibrium

Half-life The amount of time required to reduce the concentration of hormone by one-half

Haustra Bulging pockets of the large intestine wall

HDL-cholesterol (High-density-lipoprotein cholesterol) The "good" plasma carrier for cholesterol

Heart valves Connective tissue valves that prevent back flow of blood in the heart

Helper T Immune cells that secrete cytokines to help other immune cells

Hematocrit Percentage of the total blood volume that is packed red blood cells

Hematopoiesis Blood cell production in the bone marrow

Heme groups A carbon-hydrogen-nitrogen porphyrin ring with an iron atom in the center

Hemidesmosomes Strong junction that ties a cell to matrix

Hemoglobin (Hb) Oxygen-carrying pigment of red blood cells

Hemorrhage Excessive blood loss

Hemostasis Process of keeping blood within the blood vessels by repairing breaks without compromising the fluidity of the blood

Heparin An anticoagulant molecule

Hepatic portal system Specialized region of the circulation that transports material absorbed at the intestine directly to cells of the liver

Hepatocytes Liver cell

Hepcidin Peptide liver hormone that regulates iron uptake by the body

Hertz (Hz) Measure of sound wave frequency

Hexoses Six-carbon sugars

Hippocampus Portion of the brain associated with learning and memory

Histamine Paracrine secreted by mast cells and basophils; acts as a vasodilator and bronchoconstrictor

Histology The study of tissue structure and function

Homeostasis The ability of the body to maintain a relatively constant internal environment

Hormones Chemical secreted by a cell or group of cells into the blood for transport to a distant target where it acts in very low concentrations to affect growth, development, homeostasis, or metabolism. *See also* specific type

Human chorionic gonadotropin (HCG) Hormone secreted by the developing placenta

Human leukocyte antigens (HLA) Name for classification of human MHC proteins

Human placental lactogen (hPL) Peptide placental hormone that influences maternal metabolism. Synonym: human chorionic somatomammotropin (hCS)

Humoral immunity Immunity conferred by antibodies

Hydraulic pressure Pressure exerted by fluid in motion. Used synonymously with hydrostatic pressure in the circulatory system

Hydrogen bond Weak attractive forces between hydrogens and other atoms, especially oxygen and nitrogen

Hydrolysis reaction Reaction in which large molecules are broken into smaller ones by addition of water

Hydrophilic Molecules that dissolve readily in water

Hydrophobic Molecules that do not dissolve readily in water

Hydrostatic pressure The pressure exerted by a stationary column of fluid in a tube

Hydroxyapatite Calcium phosphate crystals of bone

Hypercapnia Elevated P_{CO_2} in the blood

Hyperopia Far-sightedness

Hyperplasia Increased cell number due to cell division

Hyperpnea Increase in ventilation rate to match an increase in metabolic rate

Hyperpolarized Membrane potential that is more negative than the resting potential

Hypertension Chronically elevated blood pressure

Hypertonic A solution that causes net movement of water out of a cell at equilibrium

Hypertrophies Increases cell size without a change in cell number

Hyperventilation An increase in alveolar ventilation that is not associated with an increase in metabolic rate

Hypothalamic-hypophyseal portal system Modified section of the circulation that takes neurohormones directly from the hypothalamus to the anterior pituitary

Hypothalamus Region of the brain that contains centers for behavioral drives and plays a key role in homeostasis

Hypotonic A solution that causes a net influx of water into a cell at equilibrium

Hypoventilation A decrease in alveolar ventilation without a change in metabolic rate

Hypoxia Lack of oxygen in the cells

I bands Region of the sarcomere occupied only by thin filaments

Iatrogenic A physician-caused condition

I_f channels Monovalent cation channels in cardiac autorhythmic cells that contribute to the pacemaker potential

Ileocecal valve Muscular region whose contraction separates the large and small intestines

Ileum Distal portion of the small intestine

Immediate hypersensitivity reactions Allergic reaction that occurs within minutes

Immune surveillance Theory that cancer cells develop regularly but are usually detected and destroyed by the immune system

Immune system The cells and tissues and their products that defend the body against invaders

Immunity The ability of the body to protect itself from pathogens

Immunocytes General name given to any of the immune cells

Immunoglobulins Synonym for antibody

Impermeable A membrane that does not allow a substance to cross it

Inactivation gates The slow gate of the Na^+ channel that closes to stop ion flow

Inclusions Particle of insoluble material in the cytoplasm such as glycogen granules and lipid droplets

Incontinence Inability to voluntarily control urination or defecation

Incus Middle of the three small bones of the middle ear

Induced-fit model of protein-ligand interaction The active site changes shape to fit either substrate or product molecules

Inferior vena cava Great vein that returns blood from the lower body to the right atrium

Infertility Inability to conceive

Inflammation A nonspecific reaction of the immune system to a foreign invader

Inhibins Peptide hormone from the gonads that inhibits FSH secretion

Inhibitory postsynaptic potential (IPSP) Hyperpolarizing graded potentials that make a neuron less likely to fire an action potential

Initial segment The axon hillock and first part of an axon; often the location of the neuron's trigger zone

Innate immunity The nonspecific responses of the body to invasion by foreign substances

Inner ear Portion of the ear containing the cochlea and the vestibular apparatus

Innervated Controlled by a neuron

Inositol trisphosphate (IP_3) A second messenger made from membrane

Inotropic agent Any chemical that affects cardiac contractility

Insensible water loss Water loss across the skin and in exhaled air of which we are not normally aware

Insomnia Inability to sleep well

Inspiration The movement of air into the lungs

Inspiratory muscles The external intercostals, diaphragm, scalenes, and sternocleidomastoids

Inspiratory reserve volume (IRV) The volume of air that can be inhaled in addition to a normal inspiration

Insulin Pancreatic hormone that decreases plasma glucose concentration

Integral proteins Proteins tightly bound to the membrane, and the only way they can be removed is by disrupting the membrane structure with detergents or other harsh methods that destroy the membrane's integrity

Integrating center The control center that evaluates incoming signal and decides on an appropriate response

Integrins Membrane-spanning proteins that link the cytoskeleton to extracellular matrix proteins

Intercalated cell (I cell) Cell of the collecting duct that transports H^+ and bicarbonate

Intercalated disks Specialized cell junctions in cardiac muscle that contain gap junctions

Intercostal muscles Muscles associated with the rib cage; used for breathing

Interferons Cytokines secreted by lymphocytes

Interleukins Cytokines released by one type of white blood cell to act on another

Intermediate filaments Cytoplasmic protein fiber made of myosin, keratin, neurofilament, and other proteins

Intermembrane space Region between the two outer membranes of a mitochondrion

Internal environment The extracellular fluid that surrounds the cells of the body

Interneurons A neuron that is completely contained within the central nervous system

Internodal pathway Conduction pathway from the SA node to the AV node

Interstitial cells Testicular cells that secrete androgens. Synonym: Leydig cells

Interstitial cells of Cajal (ICC) Modified smooth muscle cells of the digestive tract that initiate slow waves

Interstitial fluid Extracellular fluid that surrounds the cells and lies between the cells and the plasma

Intracellular fluid (ICF) Fluid within the cells

Intrafusal fibers Modified muscle fibers of the muscle spindle that lack myofibrils in their central portions

Intrapleural pressure Subatmospheric pressure within the pleural cavity

Intrinsic factor Protein secreted by gastric parietal cells that is required for vitamin B_{12} absorption in the intestine

Intrinsic pathway Coagulation reaction that begins with collagen exposure and uses proteins already present in plasma

Ion An atom with a net positive or negative charge due to gain or loss of one or more electrons

Ionic bonds A bond between ions attracted to each other by opposite charge

Ionotropic receptors Neurotransmitter receptor that alters ion channel function

IP_3 channels Calcium channels in smooth muscle sarcoplasmic reticulum that open in response to IP_3 binding

Ipsilateral On the same side as

Irreversible reaction A chemical reaction that proceeds in one direction but not the other

Irritant receptors Airway mucosal cells that respond to inhaled particles or noxious gases in the airway

Ischemia Lack of adequate blood flow and oxygen to a tissue

Isoforms Related forms of a molecule

Isometric contractions A contraction that creates force without movement

Isotonic A solution that results in no net water movement into or out of a cell at equilibrium

Isotonic contraction A contraction that creates force and moves a load

Isovolumic ventricular contraction Phase of the cardiac cycle when the ventricles are contracting but all valves are closed and the volume of blood in the ventricles is not changing

Isovolumic ventricular relaxation Phase of the cardiac cycle when the ventricles are relaxing but the volume of blood in them is not changing because all valves are closed

Isozymes Related forms of a single enzyme

Jaundice A yellow tint to the skin and sclera due to excessive levels of bilirubin

Jejunum The middle section of the small intestine

Joint receptors Sensory receptors that send information about the relative positioning of bones linked by flexible joints

Juxtaglomerular apparatus (JG) Region where the distal tubule of the nephron passes between afferent and efferent arterioles

Ketoacidosis A state of metabolic acidosis that results from excessive ketone production

Kilocalorie (Kcal or Calorie) Amount of energy needed to raise the temperature of 1 liter of water by 1 °C

Kinases An enzyme that adds a phosphate group to the substrate

Kinesins A motor protein

Kinetic energy The energy of motion

Kinetics (Of ion channels) The speed with which channels open, close, or deactivate

Kiss-and-run pathway Secretion in which the secretory vesicle fuses transiently with the membrane, then pulls away

L-dopa Dopamine precursor that can cross the blood-brain barrier

Labeled line coding The 1 : 1 association of a sensory receptor with a sensation

Labia majora Outer lips of the vulva

Labia minora Small inner lips of the vulva

Lacrimal apparatus Tear ducts and glands

Lactase Enzyme that breaks down the milk sugar lactose

Lactate The end product of anaerobic glycolysis

Lactation Milk production by the mammary gland

Lacteals Fingerlike projections of the lymph system that extend into the villi of the intestine to absorb lipids

Lactic acidosis A state of metabolic acidosis from the accumulation of lactate in anaerobic metabolism

Lactose Milk sugar

Laminin Insoluble protein fiber in extracellular matrix

Large intestine The terminal portion of the intestine

Larynx The "voice box" that contains vocal cords

Latent period Delay between the muscle action potential and beginning of muscle tension that represents the time required for Ca^{2+} release and binding to troponin

Lateral geniculate body Nucleus in the thalamus where optic fibers synapse with neurons going to the visual cortex

Lateral inhibition Process in which sensory neurons close to a stimulus are inhibited to intensify the perception of the stimulus

Law of conservation of electrical charge The body is electrically neutral

Law of mass action For a reaction at equilibrium, the ratio of substrates to products is always the same

Law of mass balance If the amount of a substance in the body remains constant, any gain must be offset by an equal loss

Leak channels Ion channels that spend most of their time in an open state

Left atrium Chamber of the heart that receives blood from the lungs

Left ventricle Chamber of the heart that pumps blood to the systemic circulation

Lens Portion of the eye that focuses light upon the retina

Leptin Protein hormone from adipocytes that acts as a satiety factor

Let-down reflex Neuroendocrine reflex that triggers oxytocin release and ejection of milk from the mammary gland

Leukocytes White blood cells that defend the body against foreign invaders

Leukotrienes Eicosanoid signal molecule; plays a role in the etiology of asthma

Leydig cells Testicular cells that secrete androgens. Synonym: interstitial cells

Libido Sex drive

Ligaments Connective tissue that connects one bone to another

Ligand The molecule that binds to a protein

Ligand-gated Protein channels that open when a signal molecule binds to them. Synonym: chemically gated channel

Limbic system Region of the cerebrum that acts as the link between higher cognitive functions and more primitive emotional responses

Lipases Enzyme that digests lipids

Lipids Molecules made mostly of carbon and hydrogen. Synonym: fats

Lipolysis Lipid breakdown

Lipophilic Lipid-soluble molecules that can diffuse through cell membranes

Lipophobic Water-soluble molecules that usually cannot diffuse through a membrane phospholipid bilayer

Lipoproteins Protein combined with a lipid

Liposomes Spherical structures with an exterior composed of a phospholipid bilayer, leaving a hollow center with an aqueous core

Lipostatic theory Control of food intake is based on a set point for body weight that is set by adipocytes

Lipoxygenase Enzyme that converts arachidonic acid to leukotrienes

Load A weight or force that opposes contraction of a muscle

Local control Homeostatic control that takes place strictly at the tissue or cell by using paracrine or autocrine signals

Local current flow A wave of electrical current that spreads throughout the cytoplasm

Local protein synthesis Protein synthesis in neuronal dendrites

Long reflexes A GI reflex that is integrated in the CNS rather than in the enteric nervous system

Long-loop negative feedback Negative feedback from a peripheral endocrine gland hormone to the hypothalamus and anterior pituitary

Long-term potentiation (LTP) Physical changes in a synapse that allow the response of the postsynaptic cell to a constant stimulus to be enhanced

Longitudinal studies An experiment are designed to be carried out for a long period of time

Loop of Henle Portion of the renal tubule that creates dilute urine and sets up the conditions needed to make concentrated urine

Loose connective tissues Elastic connective tissues that underlie skin and provide support for small glands

Low-density lipoprotein (LDL) The "bad" protein carrier for plasma cholesterol

Lumen The cavity of a hollow tube or organ

Lungs Organs where gases are exchanged with the blood

Luteal phase The portion of the menstrual cycle following ovulation, when the corpus luteum produces estrogen and progesterone

Luteinization Conversion of the follicle to a corpus luteum

Luteinizing hormone (LH) Anterior pituitary hormone that acts on the gonads to influence hormone production

Lymph The fluid within the lymphatic system that moves from the tissues to the venous side of the systemic circulation

Lymph capillaries Small vessels of the lymph system that dead-end in the tissues

Lymph nodes Encapsulated collections of immune cells that monitor the lymph for pathogens

Lymphatic system An anatomical system whose functions overlap with those of the cardiovascular, digestive, and immune systems

Lymphocytes A white blood cell responsible primarily for the acquired immune response

Lysozyme Antibacterial enzyme found in respiratory tract secretions and tears

M cells (1) Magnocellular ganglion cells in the retina that transmit information about movement, location, and depth perception; (2) Modified intestinal microfold cell overlying a Peyer's patch; absorbs intestinal contents by transcytosis

Macrophages Tissue phagocytes that develop from monocytes

Macula densa Specialized cells in the distal tubule wall that monitor fluid flow through the tubule

Maculae Sensory receptors of the utricle and saccule of the vestibular apparatus

Major histocompatibility complexes (MHC) Family of membrane protein complexes that participate in the immune response; play a role in foreign tissue rejection

Male accessory glands The prostate gland, bulbourethral gland, and seminal vesicles

Malignant hyperthermia A genetically linked condition in which body temperature becomes abnormally elevated

Malleus The first bone of the middle ear that sits against the tympanic membrane

Maltose A disaccharide composed of two glucose molecules

Mammary gland The exocrine glands of the breast that produce milk

Mass flow Mass flow equals concentration times volume flow

Mass movement Wave of contraction in the large intestine that triggers defecation

Mast cells A tissue cell that secretes histamine

Mastication Chewing

Matrix metalloproteinases (MMPs) Enzymes that dissolve extracellular matrix

Maximum voluntary ventilation The maximum speed and depth at which a person can voluntarily breathe

Mean arterial pressure (MAP) Average blood pressure in the arteries, estimated as diastolic pressure plus one-third of the pulse pressure

Mean cell hemoglobin (MCH) Average amount of hemoglobin in one red blood cell

Mechanical work Used for movement. Most mechanical work is mediated by motor proteins that make up certain intracellular fibers and filaments of the cytoskeleton

Mechanically gated channels A channel that opens in response to mechanical stimuli such as pressure and heat

Mechanisms This referes to physiological processes or "how" of a system

Mechanistic approach The ability to explain the mechanisms that underlie physiological events

Mechanoreceptors A sensory receptor that responds to mechanical energy such as touch or pressure

Mediated transport Movement across a membrane with the aid of a protein transporter

Medulla oblongata Portion of the brain stem that contains centers for breathing, cardiovascular control, swallowing, and other unconscious or involuntary functions

Megakaryocyte Parent cell of platelets, found in bone marrow

Meiosis Cell division that produces haploid gametes

Melanins Pigment, usually dark brown or black, found in skin and hair

Melanocytes Pigment-containing cells that create skin color in humans and coat color in rodents

Melatonin Hormone secreted by the pineal gland

Membrane (1) The phospholipid bilayer that surrounds cells and divides the cytoplasm into compartments; (2) A thin sheet of connective tissue

Membrane attack complex Proteins produced by immune cells that create membrane pores in the target cells

Membrane potential The electrical potential difference created by living cells due to uneven distribution of ions between the intracellular and extracellular fluids

Membrane recycling Process in which cell membrane is withdrawn by endocytosis and stored as vesicles in the cytoplasm until needed. At that time, the vesicle is reinserted into the membrane by exocytosis

Membrane-spanning proteins Membrane proteins whose chains extend all the way across the cell membrane

Memory cells Lymphocytes responsible for creating stronger and more rapid immune response following second exposure to an antigen

Menarche A female's first menstrual period

Meninges Three layers of membrane that lie between the spinal cord and vertebrae, or brain and skull

Menopause The time when a woman's menstrual cycles cease

Menstrual cycles The cyclic production of eggs and cyclic preparation of the uterus for pregnancy in females

Menstruation Cyclic sloughing of the endometrial lining

Merkel receptors Skin receptor for steady pressure

Mesangial cells Contractile cells in the renal corpuscle that alter glomerular blood flow

Mesentery Peritoneal membrane that hold the intestines in place

Messenger RNA (MRNA) RNA produced in the nucleus from a DNA template; travels to the cytoplasm to direct the synthesis of new proteins

Meta-analysis Statistical technique that combines data from multiple studies to look for trends

Metabolic acidosis State of acidosis resulting from overproduction of metabolic acids

Metabolic alkalosis State of alkalosis usually resulting from loss of gastric acid through vomiting or excessive ingestion of alkaline antacids

Metabolism All the chemical reactions in the body

Metabotropic receptors Neurotransmitter receptor that acts through a second messenger system

Metastasis Spread of cancer or another disease throughout the body

Micelles Small droplet of phospholipid, arranged so that the interior is filled with hydrophobic fatty acid tails

Microcirculation The arterioles, capillaries and venules

Microfilaments Thinnest protein fibers in the cytoplasm, made of the protein actin

Microglia Macrophages in the CNS

Microtubules Tubular fibers made of the protein tubulin

Microvilli Finger-like extensions of the cell membrane that increase the surface area for absorption of material

Micturition Urination

Migrating motor complex Contractions that move food remnants and bacteria from the stomach to the large intestine between meals

Mitochondria Organelles that generate ATP through oxidative phosphorylation. Singular: mitochondrion

Mitochondrial matrix Central region of a mitochondrion

Mitosis Cell division that results in two identical diploid daughter cells

Mixed nerves A nerve that carries both sensory and motor information

Modality The nature of a stimulus

Molarity (M) Solution concentration expressed as moles of solute per liter of solution

Mole (Mol) 6.02×10^{23} atoms, ions, or molecules of a substance. Avogadro's number of particles

Molecular chaperones Protein that helps a newly-made protein fold into shape

Molecular complementarity The physical compatibility of a ligand and its binding site

Molecular mass The mass of one molecule, expressed in atomic mass units or daltons

Molecules Two or more atoms link together by sharing electrons

Monoamine oxidase (MAO) The enzyme that breaks down norepinephrine

Monocular zone The portion of the visual field where vision is two-dimensional

Monocytes Blood cell that is the parent cell of tissue macrophages

Mononuclear phagocyte system Monocytes in the blood and tissue macrophages

Monosaccharides Simple sugars such as glucose

Monosynaptic reflex Reflex in which there is one synapse between neurons

Moods Relatively stable feelings related to sense of well-being

Motor proteins Proteins that create movement

Motor unit Group of skeletal muscle fibers and the somatic motor neuron that controls them

Mucins Glycoproteins of mucus

Mucociliary escalator The layer of mucus lining the respiratory tract that is moved upward by cilia so that it can be swallowed

Mucosa The inner lining of the intestinal tract

Mucous cells Cell that secretes mucus. Synonym: goblet cell

Mucus A thick, sticky exocrine secretion containing glycoproteins and proteoglycans

Müllerian ducts Embryonic structures that develop into female reproductive structures

Multipotent Undifferentiated cells in a tissue that can divide and develop into the specialized cells of that tissue

Multivesicular body An endosome filled with exosomes

Muscarine A fungal compound that is an agonist for cholinergic muscarinic receptors

Muscarinic receptors A subtype of cholinergic receptor for which muscarine is an agonist

Muscle fatigue Inability of a muscle to continue to generate or sustain tension

Muscle fibers A muscle cell

Muscle spindles Muscle receptors that send information about muscle length

Muscle tension The force created by a contracting muscle

Muscle tissue A collection of muscle cells that contract to create force and movement

Muscle tone The basal state of muscle contraction or tension that results from tonic activity of the muscle spindles

Myelin Concentric layers of cell membrane that wrap around and insulate axons

Myenteric plexus Nerve network of the enteric nervous system that lies between the muscle layers

Myocardial infarction A region of damaged myocardium caused by lack of blood flow

Myocardium Cardiac muscle

Myofibrils Bundles of contractile and elastic proteins responsible for muscle contraction

Myoglobin Oxygen-binding pigment in muscle that transfers oxygen between cell membrane and mitochondria

Myokines Cytokine released by exercising muscle cells

Myometrium Smooth muscle layer of the uterus

Myopia Near-sightedness

Myosin light chain kinase (MLCK) Enzyme that phosphorylates light protein chains of myosin in smooth muscle

Myosin light chain phosphatase Enzyme that dephosphorylates light protein chains of myosin in smooth muscle

Myosin light chains Small protein chains that make up part of the smooth muscle myosin head

Myosins Motor proteins that converts chemical bond energy of ATP into motion. They form the thick filament of striated muscles

Myotatic unit Collection of synergistic and antagonistic muscles that act in a coordinated fashion to control a single joint

NADH (Nicotinamide adenine dinucleotide) Nucleotide that captures and transfers energy with high-energy electrons

Nanoparticles Particles smaller than 100 nm

Naïve lymphocytes A lymphocyte that has not yet been exposed to its specific antigen

Natriuresis Sodium (Na^+) loss in the urine

Natriuretic peptide (NP) Peptide hormone increases renal sodium and water excretion

Natural killer cells (NK cells) A type of lymphocyte that apparently attacks certain tumor and virus-infected cells

Nebulin Inelastic giant protein that aligns filaments of the sarcomere

Necrosis Cell death due to toxins, physical damage, or lack of oxygen. The dying cell releases enzymes that may damage neighboring cells

Negative feedback A homeostatic feedback loop designed to keep the system at or near a setpoint

Nephrons Microscopic tubule that is the functional unit of the kidney

Nernst equation The equation that determines the equilibrium potential for a single ion based on the ion concentrations inside and outside the cell

Nerve-cell adhesion molecules (NCAMs) Membrane proteins in nerve cells that aid cell growth

Nerves A collection of axons running between the central nervous system and the peripheral target cells

Nervous system Network of billions or trillions of nerve cells linked together in a highly organized manner to form the rapid control system of the body

Neural crest cells Embryonic cells that form the peripheral nervous system

Neural tube Embryonic cells that develop into the CNS

Neurocrine molecules Any molecule secreted by a nerve cell

Neuroeffector junction Synapse between an autonomic neuron and its target muscle or gland

Neuroendocrine pathways Control pathways in which the efferent signal molecule is secreted by a neuron into the blood, where it functions as a hormone

Neurofilament Intermediate filament of neurons

Neurohormones A hormone that is produced and secreted by a neuron

Neuromodulator Chemicals that alter the response of a neuron more slowly than neurotransmitters

Neuromuscular junction (NMJ) The synapse of a somatic motor neuron and a skeletal muscle fiber

Neurons A nerve cell, capable of generating and transmitting electrical signals

Neuropeptide Y Brain neurotransmitter that stimulates food intake

Neurotoxins Chemicals that adversely alter neuronal function

Neurotransmitter A chemical signal released by a neuron that influences the neuron's target cell

Neurotrophic factors Chemicals secreted by Schwann cells that keep damaged neurons alive

Neutropenias Diseases with abnormally low numbers of neutrophils

Neutrophils White blood cells that ingest pathogens and release cytokines

Nicotine An agonist of cholinergic nicotinic receptors and a chemical found in tobacco

Nicotinic receptors A subtype of acetylcholine receptor that responds to the agonist nicotine

Nitric oxide (NO) A short-acting paracrine that relaxes smooth muscle; also acts as a neurotransmitter and neuromodulator

Nitric oxide synthase (NOS) Enzyme that synthesizes NO from arginine and oxygen

Nitrogenous bases Carbon-nitrogen molecules with a ring structure; essential components of a nucleotide

NMDA receptors Glutamate receptor that opens only when the cell is depolarized

Nocebo effect Adverse effect that occurs because the patient expects it to

Nociceptors A sensory receptor associated with pain

Nocturnal enuresis Involuntary urination at night (bedwetting)

Nodes of Ranvier Unmyelinated regions on myelinated axons

Nonadrenergic – noncholinergic neurons Neurons that secrete a neurotransmitter other than ACh or norepinephrine

Nongenomic responses Actions of steroid hormones that do not require altered gene activity

Nonmembranous organelles Cell organelle that is not surrounded by a phospholipid membrane

Nonpenetrating solutes A solute that cannot cross the cell membrane

Nonpolar molecule A molecule whose electrons are distributed so evenly that there are no regions of partial positive or negative charge

Norepinephrine (NE) Primary neurotransmitter of the sympathetic division of the nervous system

Nuclear pore complexes Protein complexes in the nuclear envelope with a central pore

Nucleotides Molecules that carry energy and are the structural components of genetic material

Nucleus (Nervous system) A collection of nerve cell bodies in the central nervous system

Obesity Excess body fat

Occluding junctions Cell-cell junctions that prevent movement of material between cells

Occludins Proteins in tight junctions

Olfaction Pertaining to the sense of smell

Olfactory bulb Part of the brain that receives input from primary olfactory neurons

Oligodendrocytes CNS glial cell that forms myelin around several axons

Oocytes Developing female germ cells that have begun meiosis

Oögonia Germ cells of the ovary

Open-loop control system Ends with the response and has no feedback

Opsin Visual pigment forms from rhodopsin when light strikes it; opsin initiates a signal transduction cascade

Opsonins Proteins that coat pathogens to make them targets for immune cells

Optic chiasm Portion of the brain where some fibers from each eye cross to opposite sides of the brain

Optic disk Region of the retina where the optic nerve and blood vessels exit the eye

Optics The physical relationship between light and lenses

Orbit Bony cavity that protects the eye

Organ of Corti Portion of the cochlea that contains the hair cells

Organ systems Group of organs that work together to perform a certain task

Organelles Assorted intracellular structures that each take on one or more of the cell's functions

Organic molecules Molecules that contain carbon

Organoids Tiny 3D mini-organ that self assembles from stem cells

Organs Group of tissues that carries out related functions

Orgasm A series of involuntary muscular contractions during the sex act, accompanied by sensations of intense pleasure

Origin of a muscle The end of the muscle attached closest to the trunk or to the more stationary bone

Orphan receptors Receptors that have no known ligand

Orthostatic hypotension Low blood pressure that occurs when going from the supine position to standing up

Osmolarity Concentration expressed in osmoles per liter

Osmometer An instrument for measuring osmolarity of a fluid

Osmoreceptors Sensory receptor that monitors extracellular fluid osmolarity

Osmosis The movement of water across a membrane in response to a solute concentration gradient

Osmotic diuresis Water loss in the urine due to unreabsorbed solute in the tubule lumen

Osmotic pressure The pressure that exactly opposes a given concentration gradient

Osteoblasts Cells that produce bone

Osteoclasts Large, mobile, multinucleate cell that is responsible for bone resorption

Osteocytes A less active form of osteoblast

Otolith membrane Gelatinous mass within which otoliths are embedded

Otolith organs The utricle and saccule of the vestibular apparatus that sense linear acceleration and head position

Otoliths Small calcium carbonate crystals whose movement activates hair cells for equilibrium

Oval window Membrane between the middle ear and cochlea

Ovarian cycle The monthly cycle of egg development in the ovary

Ovaries The female gonad

Ovulation Release of a mature egg from its follicle in the ovary

Ovum The female gamete. Synonym: egg. Plural: ova

Oxidation-reduction reaction Involves the transfer of electrons or protons (H^+) between chemicals

Oxidation-reduction reactions Reactions that involve the transfer of electrons between chemicals

Oxygen consumption The disappearance of oxygen during oxidative phosphorylation, when oxygen combines with hydrogen

Oxyhemoglobin Hemoglobin bound to oxygen

Oxytocin Posterior pituitary hormone that causes uterine and breast smooth muscle contraction

P cells Parvocellular ganglion cells of the retina that transmit information about color, form, and texture. *See also* principal cell

P wave Wave of the ECG that represents atrial depolarization

Pacemaker potential Cyclic depolarizations of smooth and cardiac muscle that always reach threshold

Pacinian corpuscles (Lamellar corpuscles) Sensory receptors of skin that sense vibration

Pain The brain's perception of irritating or damaging stimuli

Paneth cells Gut cells that produce antimicrobial compounds

Papillary muscles Small muscle in the interior of the ventricles to which the chordae tendineae attach

Paracrine signal A chemical secreted by a cell that acts on cells in the immediate vicinity

Parallel processing One function is carried out by multiple brain circuits

Parameter One of the variables in a system

Parasympathetic branches Division of the autonomic nervous system that is responsible for day-to-day activities

Parathyroid hormone (PTH, parathormone) Hormone from the parathyroid glands that increases plasma Ca^{2+} concentration

Parietal cells Cells of the stomach that secrete hydrochloric acid

Partial pressure The pressure of a single gas in a mixture of gases

Parturition The birth process

Passive transport Movement across a membrane that does not depend on an outside source of energy

Pathogens Any substance capable of causing disease

Pathophysiology The study of body functions in a disease state

Penetrating solutes A solute that freely crosses the cell membrane

Pepsin Stomach enzyme that begins protein digestion

Pepsinogen The inactive form of pepsin

Peptidases Enzyme that breaks up peptides into smaller peptides or amino acids

Peptide bonds Bond formed between the carboxyl group of one amino acid and the amino group of another amino acid

Peptide hormones Any hormone made of amino acids, including peptides, proteins, and glycoproteins

Peptides A chain of 2-9 nine amino acid

Percent solution Solution concentration expressed as parts of solute per 100 parts of solution

Perceptual threshold The level of stimulus intensity necessary for awareness

Perforin Pore-forming protein secreted by immune cells

Perfusion Blood flow to tissues

Pericardium The connective tissue sac that encloses the heart

Pericytes Cells that form a mesh-like outer layer between the capillary endothelium and the interstitial fluid

Perilymph Fluid within the vestibular and tympanic ducts of the cochlea

Peripheral chemoreceptors Chemoreceptors not found in the CNS

Peripheral nervous system (PNS) All neurons that lie completely or partially outside the central nervous system

Peripheral proteins Proteins attached to membrane-spanning proteins or to the polar regions of membrane phospholipids

Peripheral receptors Sensory receptors that are not located in or close to the brain

Peripheral resistance Resistance to blood flow created primarily by the arterioles

Peristalsis Waves of contraction that move along the gastrointestinal tract

Peritoneal membrane Lines the inside of abdominal cavity

Peritoneum A membrane that lines the abdomen

Permissiveness One hormone cannot exert its effects fully unless a second hormone is present

Peroxisomes Storage vesicles that contain enzymes to degrade long-chain fatty acids and potentially toxic foreign molecules

Peyer's patches Bumps of lymphoid tissue visible in the mucosa of the GI tract. Synonym: lymphoid follicles

pH A measure of the concentration of H^+; $pH = -\log [H^+]$

Phagocytes Immune cell that ingests material by phagocytosis

Phagocytosis The process by which a cell engulfs a particle into a vesicle by using the cytoskeleton to push the membrane around the particle

Phagosome The vesicle formed around ingested material during phagocytosis; site of digestion

Pharmacomechanical coupling Contraction that occurs in smooth muscle as a result of a ligand binding; not accompanied by a change in membrane potential

Phasic receptors Rapidly adapting receptors that are attuned to changing conditions

Pheromones External hormones secreted to influence others of the same species

Phosphocreatine (PCr) Muscle molecule that stores energy in high-energy phosphate bonds

Phospholamban Regulatory protein in contractile myocardium that alters Ca^{2+}- ATPase activity in the sarcoplasmic reticulum

Phospholipase A2 (PLA2) Enzyme that converts membrane phospholipids to arachidonic acid

Phospholipase C Enzyme that converts a membrane phospholipid into two different second messenger molecules, DAG and IP_3

Phospholipids Diglycerides with phosphate attached to the single carbon that lacks a fatty acid

Phosphorylation Addition of a phosphate group to a molecule

Photoreceptors Sensory receptors in the eye that respond primarily to light energy

Phototransduction Conversion of light energy to action potentials

Physiology The study of the normal functioning of a living organism and its component parts, including all its chemical and physical processes

Pia mater Inner membrane of the meninges

Piezo2 ion channels Pressure-sensitive cation channel on cell membranes

Piloerection Hair standing on end

Pinna The outer ear

Pitch Physiological interpretation of sound wave frequency

Pituitary gland Endocrine and neuroendocrine gland that lies beneath the hypothalamus

Placebo An inactive substance used in medical treatment

Placebo effect Response to a placebo treatment

Plasma The fluid portion of the blood

Plasma cells Type of lymphocyte that secretes antibodies

Plasma membrane The cell membrane. Synonym: cell membrane

Plasmin Enzyme that breaks down fibrin. Synonym: fibrinolysin

Plasticity Ability of a structure or process to change

Plateau (CV) The flattening phase (phase 2) of the myocardial contractile cell action potential

Plateau phase Intermediate phase of the human sexual response

Platelet adhesion Platelets stick to exposed collagen in wall of damaged blood vessel

Platelets Cell fragments that participate in coagulation. Synonym: thrombocyte

Pleura The membranes that line the chest cavity and cover the outer surface of the lungs and form the pleural sacs

Plicae Large folds of the intestinal wall

Pneumothorax Air in the intrapleural space

Podocytes Specialized epithelial cells in Bowman's capsule that surround each capillary and form filtration slits

Polar body A structure containing unused chromosomes that is discarded from an egg as it undergoes meiosis

Polar molecules Molecules that develop regions of partial positive and negative charge when one or more atoms in the molecule have a strong attraction for electrons

Polarized distribution of transporters Cells restrict certain membrane transport proteins to particular regions, thereby creating cells with different functions in different areas

Polycythemia Elevated hematocrit

Polymers Large molecules made up of repeating units

Polypeptide A chain of 10-100 amino acids

Polyribosomes Free ribosomes forming groups of 10 to 20

Polysaccharide Complex carbohydrates composed of glucose polymers; used for energy storage and structure

Polyspermy Fertilization of an egg by more than one sperm

Pons Region of the brain stem that contains centers for respiration and serves as a relay station

Population coding The number of sensory receptors activated encodes the intensity of a stimulus

Portal system A specialized region of the circulation consisting of two capillary beds directly connected by a set of blood vessels

Positive feedback loop A feedback loop in which the response reinforces the stimulus, triggering a vicious cycle of ever-increasing response

Post-translational modification Alterations to a protein molecule made after translation

Posterior horns (Dorsal horns) Region of the spinal cord where sensory neurons synapse with interneurons

Posterior pituitary An extension of the brain that secretes neurosecretory hormones made in the hypothalamus

Postganglionic neuron Autonomic neuron that has its cell body in the ganglion and sends its axon to the target tissue

Postsynaptic cell The target cell at a synapse

Postsynaptic integration Multiple signals in a postsynaptic cell combine to create a single integrated signal

Potential energy Stored energy that has the ability to do work

Power stroke Movement of the myosin head that is the basis for muscle contraction

Precapillary sphincters Smooth muscle bands that alter capillary blood flow *only* in mesentery

Preganglionic neuron Autonomic neuron that originates in the central nervous system and terminates in an autonomic ganglion

Preload The degree of myocardial stretch created by venous return

Preprohormones Inactive molecule composed of one or more copies of a peptide hormone, a signal sequence, and other peptide sequences that may or may not have biological activity

Presbycusis Age-related hearing loss

Presbyopia Loss of the accommodation reflex with aging

Presynaptic cell The cell releasing neurotransmitter into a chemical synapse

Primary active transport The energy for transport comes from the high-energy phosphate bond of ATP

Primary bronchi The first two airways created by branching of the trachea

Primary follicles An undeveloped oocyte and its outer layer of granulosa cells

Primary immune response The immune response that occurs with first exposure to a pathogen

Primary motor cortex Regions of the frontal lobe that coordinate skeletal muscle movements

Primary oocytes Oocyte that has duplicated its DNA but not undergone a meiotic division

Primary sensory neuron The sensory neuron that takes information from the sensory receptor into the spinal cord

Primary sex characteristics The internal sexual organs and external genitalia that distinguish each sex

Primary spermatocytes Spermatocyte that has duplicated its DNA but not undergone a meiotic division

Primary structure of a protein The sequence of amino acids in the peptide chain

Primordial follicle A primary oocyte surrounded by a single layer of granulosa cells

Pro-opiomelanocortin (POMC) Anterior pituitary pro-hormone that is processed into ACTH and other active fragments

Products The end-result of a chemical reaction

Proenzymes An inactive enzyme. Synonym: zymogen

Progesterone Female sex hormone produced by the corpus luteum

Prohormone Inactive protein containing one or more copies of a hormone

Prolactin (PRL) A peptide hormone from the anterior pituitary that controls milk production in the breast

Prolactin-inhibiting hormone (PIH) Hypothalamic hormone that inhibits prolactin secretion by the anterior pituitary. *See also* dopamine

Proliferative phase Phase of the menstrual cycle when the endometrium grows and thickens

Promoter region Section of DNA near the starting end of a gene that must be activated to begin transcription

Proprioception Awareness of body position in space and of the relative location of body parts to each other

Propriospinal tracts Tracts of white matter that remain within the cord

Prostacyclin Eicosanoid in membrane of intact endothelial cells that prevents platelets from adhering

Prostaglandins Lipid-derived molecules that act as physiological regulators

Prostanoids Eicosanoid signal molecules that include prostaglandins and thromboxanes

Prostate gland Male accessory organ that contributes enzymes, nutrients, and other secretions to semen

Proteases Enzymes that break proteins up into smaller peptides

Proteasomes Protein complexes that break down proteins tagged for destruction

Protein kinases Enzymes that transfer a phosphate group from ATP to a protein

Protein kinase C (PKC) Associated membrane enzyme that is activated by DAG and Ca^{2+}

Proteins Molecules composed of amino acids

Proteoglycans Glycoproteins in extracellular matrix

Proximal tubule The initial segment of the kidney tubule where most reabsorption takes place

Psychoneuroimmunology The study of interactions between the nervous, endocrine, and immune systems

Puberty The period in the early teen years when the gonads mature and produce gametes

Pulmonary arteries Blood vessel that carries low-oxygen blood from the heart to the lungs

Pulmonary circulation That portion of the circulation that carries blood to and from the lungs

Pulmonary edema Excessive interstitial fluid volume in the lungs

Pulmonary trunk The single artery that receives blood from the right ventricle before splitting into left and right pulmonary arteries

Pulmonary valve The semilunar valve between the right ventricle and the pulmonary trunk

Pulmonary veins Vessel that carries well-oxygenated blood from the lung to the left heart

Pulse Pressure wave that is transmitted through the fluid of the cardiovascular system

Pulse pressure The strength of the pulse wave, defined as the systolic pressure minus the diastolic pressure

Pupillary reflexes Constriction of the pupil in response to light

Purinergic receptors Receptors that bind to purines, such as AMP or ATP

Purkinje fiber Specialized ventricular myocardial cells that rapidly conduct electrical signals to the apex of the heart

Pylorus The region of increased muscle tone separating the stomach and small intestine

Pyramidal tract Descending pathways for movement that pass through the pyramids

Pyramids Region of the medulla where neurons from one side of the body cross to the other

Pyrogens Fever-causing substances

Q wave First wave of ventricular depolarization

QRS complex Wave complex that represents ventricular depolarization and atrial repolarization

Quaternary structure (Of protein) Arrangement of a protein with multiple peptide chains

R wave The largest wave of the QRS complex

RANK Receptors for RANKL on osteoclasts that promote acid secretion and bone resorption

RANKL Signal molecule from osteoblasts that promotes osteoclast formation and bone resorption

Reabsorption Movement of filtered material from the lumen of the nephron to the blood

Reactants A reaction begins with one or more molecules

Reaction rate The speed with which a reaction takes place

Reactive hyperemia An increase in tissue blood flow following a period of low perfusion

Receptive aphasia Inability to understand spoken or visual information due to damage to Wernicke's area

Receptive field The region within which a sensory neuron can sense a stimulus

Receptor adaptation A repeated stimulus loses its ability to stimulate a receptor

Receptor potential Graded potential in a special senses receptor

Receptor-enzyme Membrane proteins that bind ligands on the extracellular side and activate enzymes on the intracellular side

Receptor-mediated endocytosis A ligand binds to a membrane protein, which triggers endocytosis of the membrane receptor complex

Receptors (1) A cellular protein that binds to a ligand; (2) A cell or group of cells that continually monitor changes in the internal or external environment

Recruitment Addition of motor units to increase the force of contraction in a muscle

Rectum The distal segment of the large intestine

Red blood cells (RBC) Hemoglobin-filled cells that transport oxygen. Synonym: erythrocyte

Red muscle Muscle that has lots of mitochondria and good blood supply so that it can carry out oxidative metabolism

Referred pain Pain that is felt in a location away from the actual site of the stimulus

Reflex control Any long-distance pathway that receives input about a change, integrates the information, and uses the nervous system, endocrine system, or both to react appropriately

Reflex control pathways Any long-distance pathway that uses the nervous system, endocrine system, or both

Reflexive memory (implicit) Automatic memory that is acquired slowly through repetition and does not require conscious processes for its creation or recall. Synonym: implicit memory

Regulated variables A variable that is monitored to maintain homeostasis

Relative refractory period A period of time immediately following an action potential during which a higher-than-normal graded potential is required to start another action potential

Renal corpuscle The combination of glomerulus and Bowman's capsule

Renal medulla Inner portion of the kidney whose interstitial osmolarity ranges from 300-1200 mOsM

Renin Peptide secreted by juxtaglomerular cells that converts angiotensinogen into angiotensin I

Replication An experiment repeated to ensure that the results were not an unusual one-time event

Repolarization A depolarized membrane returns to its resting potential

Residual volume (RV) The volume of air left in the lungs following a maximal exhalation

Resorption Process in which osteoclasts dissolve the calcium phosphate matrix of bone

Respiration Cellular use of oxygen and substrates to produce energy

Respiratory acidosis Acidosis due to retention of CO_2

Respiratory alkalosis Alkalosis due to hyperventilation that decreases arterial carbon dioxide

Respiratory central pattern generator (rCPG) Network of medullary and pontine neurons that control the spontaneous cycle of inspiration and expiration

Respiratory cycle An inspiration followed by an expiration

Respiratory system Those structures involved in ventilation and gas exchange

Response loop Control pathway that begins with the stimulus and ends with the response

Resting membrane potential difference The uneven distribution of ions across a living cell membrane

Reticular activating system Neurons that contribute to arousal

Reticular formation Diffuse groups of neurons that branch from the brain stem into the brain and spinal cord; involved in muscle tone, stretch reflexes, coordination of breathing, blood pressure regulation, and modulation of pain

Reticulocyte Immature red blood cell with no nucleus

Reticuloendothelial system Old term for tissue macrophages

Retina Sensory receptors lining the posterior cavity of the eye

Retinal The light-absorbing pigment of rhodopsin

Retinal pigment epithelium Cell layer behind the retina of the eye that absorbs light and creates a blood-retinal barrier

Retrospective studies These studies match groups of people who all have a particular disease to a similar but healthy control group

Reversible reaction A chemical reaction that can proceed in both directions

Rhodopsin Visual pigment of rods

Ribosomes Small dense granules of RNA and protein that assemble amino acids into proteins

Right atrium Chamber of the heart that receives systemic venous blood

Right ventricle Chamber of the heart that pumps blood to the lungs

Rigor state Tight binding between actin and myosin in the absence of ATP

RNA (Ribonucleic acid) Nucleotide that interprets the genetic information stored in DNA and uses it to direct protein synthesis

RNA polymerase Enzyme needed for synthesis of mRNA from DNA

Rods Receptors for monochromatic nighttime vision

Rough endoplasmic reticulum (RER) Organelle that is the primary site of protein synthesis

Round window Membrane between cochlea and middle ear

Rugae Surface folds in the interior of the stomach

Ryanodine receptor-channels (RyR) Calcium-release channel of sarcoplasmic reticulum in striated muscles

Saccule One of the otolith organs of the vestibular apparatus

Saliva Watery enzyme and mucous secretions of the mouth

Saltatory conduction The apparent leap-frogging of the action potential down myelinated axons

Sarcolemma The cell membrane of a muscle fiber

Sarcomere The contractile unit of a myofibril

Satiety A sensation of fullness

Satiety center Hypothalamic center that decreases food intake

Saturation All active sites on a given amount of protein are filled with substrate and reaction rate is maximal

Scalene muscles Respiratory muscles that lift the upper rib cage

Schwann cells Cell that forms myelin around a peripheral neuron axon

Scientific theory A model with substantial evidence from multiple investigators supporting it

Scrotum The external sac into which the testes descend so that they can stay cooler than body temperature

Second heart sound Vibrations created when the semilunar valves close

Second law of thermodynamics Natural spontaneous processes move from a state of order (nonrandomness) to a condition of randomness or disorder

Second messengers Intracellular molecules that translate the signal from a first messenger into an intracellular response

Secondary immune response The stronger and more rapid immune response that occurs with the second or subsequent exposure to a pathogen

Secondary oocyte An immature egg that has completed the first meiotic division and has 23 duplicated chromosomes

Secondary sex characteristics Features of the body, such as body shape, that distinguish males from females

Secondary spermatocytes Spermatocyte that has gone through the first meiotic division

Secondary structures (Of protein) Spatial arrangement of amino acids into a spiral helix or zigzag sheet

Secretin Intestinal hormone that stimulates bicarbonate secretion and pepsin release; inhibits gastric acid

Secretion (1) The movement of selected molecules from the blood into the nephron; (2) The process by which a cell releases a substance into the extracellular space, exocrine

Secretory epithelia Epithelia that secrete hormones or exocrine secretions

Secretory phase Postovulatory phase of the uterus when it develops into a secretory structure

Self-tolerance The lack of immune response to cells of the body

Semen Sperm plus secretions from accessory glands

Semilunar valves Heart valves between the ventricles and major arteries

Seminal vesicles Male accessory glands that contribute enzymes and other secretions to semen

Seminiferous tubules Region of the testes where sperm and hormones are produced

Sensitization Exposure to a noxious or intense stimulus creates an enhanced response upon subsequent exposure

Sensory neurons A neuron that transmits sensory information to the central nervous system

Septum A dividing wall, such as between the chambers of the heart

Series elastic elements Elastic fibers in the muscle that stretch during isometric contraction

Serosa Outer surface of the digestive tract created by a continuation of the peritoneum

Serotonin A CNS neurotransmitter. Synonym: 5-hydroxytryptamine (5-HTHT)

Serous secretions Watery exocrine solution that often contains enzymes

Sertoli cells Testicular cells that secrete anti-Mullerian hormone and support sperm production

Shock Generalized, severe circulatory failure

Signal amplification Process by which a single signal molecule can generate multiple intracellular effector molecules

Signal sequence Initial segment of a newly-made protein that directs the protein to the proper organelle for processing, packaging, and delivery

Signal transduction The transmission of information from one side of a membrane to the other using membrane proteins

Simple diffusion Diffusion across the phospholipid bilayer of a cell

Single-unit smooth muscle Smooth muscle fibers that are electrically coupled by numerous gap junctions

Sinoatrial node (SA node) Group of autorhythmic cells in the right atrium of the heart; the main pacemaker of the heart

Skeletal muscles Striated muscle usually attached to bones; responsible for positioning and movement of the skeleton

Sliding filament mechanism of contraction The current model for muscle contraction in which muscle proteins slide past each other to generate force

Slow synaptic potentials Slower onset and longer lasting response of postsynaptic cells to certain neurotransmitters and neuromodulators

Slow wave potentials Cyclic depolarization and repolarization of membrane potential in smooth muscle

Small intestine The segment of the gastrointestinal tract where most absorption and digestion take place

Smooth muscle Muscle that makes up internal organs and tubes; lacks visible striations

Sodium-iodide symporter (NIS) Transport protein for uptake of iodide into thyroid gland

Sodium-potassium pump (Na^+-K^+-ATPase; sodium-potassium ATPase) Active transporter that uses ATP to move Na^+ out of the cell and K^+ into the cell against their respective concentration gradients

Solubility The ease with which a molecule or gas dissolves in a solution: The more easily a substance dissolves, the higher its solubility

Solute Molecules that dissolve in liquid

Solutions A solute or combination of solutes dissolved in solvent

Solvent The liquid into which solutes dissolve. In biological solutions, water is the solvent

Somatic motor division Efferent branch of nervous system that controls skeletal muscles

Somatic motor neurons Efferent neurons that control skeletal muscles

Somatic senses Touch-pressure, temperature, pain, and proprioception

Somatomedins Old name for insulin-like growth factors

Somatosensory tracts Axons carrying sensory information from the body to the brain

Somatostatin Hypothalamic hormone that inhibits growth hormone release and gastric paracrine that inhibits gastrin secretion

Sound The brain's interpretation of the amplitude, frequency, and duration of sound waves

Spatial summation Summation of graded potentials from several sources

Special senses Vision, hearing, taste, smell, and equilibrium

Specific hunger A craving for a particular substance such as salt

Specificity The ability of an enzyme or receptor to bind to a particular molecule or a group of closely related molecules

Spinal reflexes A simple reflex that can be integrated within the spinal cord without input from the brain

SRY gene The sex-determining region on the Y chromosome

Stapes The third bone of the inner ear that connects the incus to the oval window

Starch Digestible storage polysaccharide made by plants

Stem cells Immature cells that have the ability to differentiate

Stereocilia Stiffened cilia of hair cells in the ear

Sternocleidomastoids Inspiratory muscles that help elevate the upper ribs

Steroid Lipid-related molecules derived from cholesterol

Steroid hormones Hormones made from cholesterol

Stimulus The disturbance or change that sets a reflex in motion

Store-operated Ca^{2+} channels Smooth muscle calcium channels that open to allow calcium into the cell when SR calcium stores run low.

Streptokinase An enzyme that dissolves blood clots

Stressors An event that causes a stress reaction

Stretch reflexes A reflex pathway in which muscle stretch initiates a contraction response

Striated muscles Muscles that appear to have alternating light and dark bands; includes skeletal and cardiac muscle

Stroke Blockage or rupture of a blood vessel in the brain

Stroke volume (SV) The amount of blood pumped by one ventricle during one contraction

Stroma Supporting connective tissue

Subarachnoid space Fluid-filled space beneath the arachnoid membrane of the skull

Substrates The ligand that binds to an enzyme or a membrane transporter

Subthreshold graded potential A graded potential that is not strong enough to trigger an action potential

Subtraction reaction Reaction in which a functional group is removed from one or more of the substrates

Sucrose Disaccharide made from one glucose and one fructose. Synonym: table sugar

Suprachiasmatic nucleus (SCN) Region of the hypothalamus believed to be the center for the biological clock

Suprathreshold graded potential A graded potential that is strong enough to trigger an action potential

Surfactant Chemical that decreases the surface tension of water

Sympathetic Division of the autonomic nervous system that is responsible for fight-or-flight response

Sympathetic cholinergic neurons Sympathetic neuron that uses ACh as a neurotransmitter

Symport carriers A membrane transport protein that moves two or more molecules in the same direction across a membrane

Synapse Region where a neuron meets its target cell

Synaptic cleft The space between the pre- and postsynaptic cells

Synaptic vesicles Small secretory vesicles that release neurotransmitter into the synapse

Synergism Interaction of two or more hormones or drugs that yields a result that is more than additive

Systemic circulation Portion of the circulation that carries blood to and from most tissues of the body

Systole The time when the heart is contracting

Systolic pressure The highest pressures in the circulatory system that reflect the pressures created by contraction of the ventricles

T lymphocytes (T cells) Immune cells that bind to and kill their target cells

T wave ECG wave that represents ventricular repolarization

Tachycardia Rapid heart rate

Tamoxifen Drug that is a selective estrogen receptor antagonist

Tectorial membrane Membrane in the cochlea whose movement moves cilia of hair cells

Teleological approach Describing physiological processes by their purpose rather than their mechanism

Temporal summation Summation of two stimuli that follow one another in time

Tendons Connective tissue that attaches skeletal muscle to bone

Tenia coli Muscle bands of the large intestine that pull the wall into haustra

Terminal cisternae The ends of sarcoplasmic reticulum that abut the t-tubules

Tertiary structure (Of protein) The three-dimensional shape of the protein

Testes The male gonads

Testosterone Steroid sex hormone, dominant in males

Tetanus Sustained muscle contraction

Tetramers Molecule with four subunits

Thalamus Portion of the brain that serves as a relay station for information going to and from higher brain centers

Theca Layer of cells in the follicle that secrete steroid hormones

Thick filament An aggregation of myosin in muscle

Thin filaments An actin-containing filament of the myofibril

Thoracic cage The ribs, sternum, spine, and attached muscles

Thorax The body cavity above the diaphragm

Threshold (1) The minimum depolarization that will initiate an action potential in the trigger zone; (2) The minimum stimulus required to set a reflex response in motion

Thrombin Plasma protein that converts fibrinogen into fibrin

Thrombocytes Alternate name for platelets

Thrombopoietin (TPO) Cytokine that promotes platelet formation

Thrombus A blood clot that adheres to the wall of a blood vessel

Thymus gland Immune tissue that produces lymphocytes

Thyroglobulin Large protein on which thyroid hormones are formed

Thyroid gland Endocrine gland in the neck that produces thyroid hormones

Thyroid-binding globulin (TBG) Plasma protein that serves as carrier for thyroid hormones

Tidal volume The volume of air that moves in a single normal inspiration or expiration

Tight junctions Cell-to-cell junction in epithelia that does not allow much movement of material between the cells

Tissue factor A protein-phospholipid mixture released by damaged blood vessel walls

Tissue plasminogen activator (TPA) A molecule that promotes dissolution of blood clots

Tissues A collection of cells, usually held together by cell junctions, that works together to achieve a common purpose

Titin Elastic giant protein that maintains spatial structure of myofibrils

Tonic control Ongoing control that is adjusted up and down

Tonic receptors Slowly adapting receptors

Total lung capacity (TLC) Vital capacity plus residual volume

Total pulmonary ventilation The volume of air moved in and out of the lungs each minute

Totipotent A stem cell that can develop into a functioning organism

Trabecular bone Spongy bone with many open spaces

Trace elements Essential elements required in very small amounts

Trachea Main airway of the respiratory system

Tracts Bundles of axons in the CNS, generally with a common origin and destination

Transamination Transfer of an amino group from one molecule to another

Transcellular compartments Fluid-filled compartments that are distinct from the extracellular fluid. Examples: cerebrospinal fluid, pleural fluid

Transcription Transfer of information coded in DNA to mRNA

Transcription factors Regulatory proteins that bind to DNA and alter gene expression

Transcytosis A combination of endocytosis, vesicular transport across the cell, and exocytosis; used to move macromolecules across an epithelium

Transducin G protein that mediates bitter taste and photoreceptor transduction

Transduction Conversion of a signal from one modality to another

Transferrin Plasma protein that binds and transports iron

Transient receptor vanilloid 1 channel (TRPV1) Temperature-sensitive cation channel

Translation Conversion of the message carried by mRNA into a peptide chain

Translational research Applies basic biomedical research findings to treatment and prevention of human diseases

Transmembrane proteins Membrane proteins whose chains extend all the way across the cell membrane

Transport maximum (T_m) The maximum transport rate that occurs when all carriers are saturated

Transport work This enables cells to move ions, molecules, and larger particles through the cell membrane and through the membranes of organelles in the cell

Transporting epithelia Epithelium whose primary function is the selective movement of solutes and water between two compartments

Transverse tubules (T-tubules) Invaginations of the muscle fiber membrane, associated with the sarcoplasmic reticulum

Triad One t-tubule with its flanking terminal cisternae

Tricuspid valve The right AV valve of the heart

Trigger zone The region of the axon where graded potentials are integrated and an action potential begins if the signal is above threshold

Triglyceride Lipid composed of one glycerol and three fatty acids. Synonym: triacylglycerol

Triiodothyronine (T3) Most active form of thyroid hormone; produced mostly in peripheral tissues from T4

Trophic hormones Any hormone that controls the secretion of another hormone

Tropomyosin A regulatory protein that blocks the myosin binding site on actin

Troponin (TN) Complex of three proteins associated with tropomyosin

Trypsin Enzyme that digests proteins

Trypsinogen Inactive form of the proteolytic enzyme trypsin

Tryptophan Amino acid from which the hormone melatonin is made

Tubuloglomerular feedback The process by which changes in fluid flow through the distal tubule influence glomerular filtration rate

Twitch A single contraction/relaxation cycle in a muscle fiber

Type I alveolar cells Thin alveolar cells for gas exchange

Type II alveolar cells Alveolar cells that synthesize and secrete surfactant

Tyrosine Amino acid that is the basis for thyroid hormones and the catecholamines

Tyrosine kinase (TK) Membrane enzyme that adds a phosphate group to the tyrosine residue of a cytoplasmic protein, enhancing or inhibiting its activity

Ubiquitin Protein tag that marks proteins for destruction

Umami The taste sensation triggered by glutamate and associated with nutritious food

Uniport carriers A membrane transport protein that moves only one kind of molecule

Unsaturated Fatty acid with one or more double bonds between carbons

Up-regulation Increase in protein number or binding affinity that increases the response of the target cell

Urea Nitrogenous waste product produced from amino groups

Ureter Tube that links a kidney to the urinary bladder

Urethra Single tube that drains urine from the bladder to the external environment

Uric acid Nitrogenous waste product

Urinary system The kidneys, bladder, and accessory structures

Urine Fluid waste product produced by the kidneys

Utricle One of the otolith organs of the vestibular apparatus

Vagotomy Operation that severs the vagus nerve

Vagus nerve Cranial nerve that carries sensory information and efferent signals to many internal organs including the heart and GI tract

Valsalva maneuver Abdominal contraction and forced expiratory movement against a closed glottis

Van der Waals forces Weak attractive force that occurs between two polar molecules or a polar molecule and an ion

Varicosity Swollen regions along autonomic axons that store and release neurotransmitter

Vas deferens Tube that carries sperm from the epididymis to the urethra. Synonym: ductus deferens

Vasa recta Peritubular capillaries in the kidney that dip into the medulla and then go back up to the cortex, forming hairpin loops

Vascular endothelial growth factor (VEGF) Growth factors that regulate angiogenesis

Vascular smooth muscle The smooth muscle of blood vessels

Vasculature The blood vessels

Vasoconstriction Contraction of circular vascular smooth muscle that narrows the lumen of a blood vessel

Vasodilation Relaxation of circular vascular smooth muscle that widens the lumen of a blood vessel

Vasopressin (Arginine vasopressin, AVP) Posterior pituitary hormone that regulates water reabsorption in the kidney. Alternate name: antidiuretic hormone, ADH

Vasovagal syncope Fainting due to a sudden decrease in blood pressure, often as a result of an emotional stimulus

Veins Blood vessels that return blood to the heart

Velocity of flow The distance a fixed volume will travel in a given period of time

Venous return The amount of blood that enters the heart from the venous circulation

Ventilation The movement of air between the atmosphere and the lungs

Ventral root Section of a spinal nerve that carries information from the central nervous system to the muscles and glands

Vesicles A sac-like, membrane-bound organelle used for storage and transport

Vestibular apparatus Portion of the inner ear that contains sensory receptors for balance and equilibrium

Villi Fingerlike projections of the cell surface

Viscosity Thickness or resistance to flow of a solution

Visual cortex Region of the cerebral cortex that processes visual information

Visual pigments Retinal pigment that converts light energy to a change in membrane potential

Vital capacity (VC) The maximum amount of air that can be voluntarily moved in and out of the respiratory system

Vitamins Nutrient needed in small amounts to serve as a cofactor or coenzyme

Vitreous body Gelatinous matrix that fills the eye chamber behind the lens. Synonym: vitreous humor

Voltage-gated Ca^{2+} channel A gated channel that opens or closes in response to a change in membrane potential

Vomeronasal organ (VNO) An olfactory structure linked to pheromone reception in rodents

Vulva The external female genitalia

Walter B. Cannon The father of American physiology

Wernicke's area One of the speech centers of the brain

White fat Adipose cells that typically contain a single enormous lipid droplet that occupies most of the volume of the cell

White matter Central nervous system tissue composed primarily of myelinated axons

White muscle Muscle with fewer mitochondria that uses primarily anaerobic glycolysis

Wolffian ducts Embryonic structures that develop into male reproductive structures

Working memory A form of short-term memory

X chromosome Sex chromosome found in both sexes that contains essential genes

Y chromosome Sex chromosome required for development of male reproductive organs

Z disks Sarcomere proteins to which actin filaments attach

Zona fasciculata Middle zone of adrenal cortex that synthesizes glucocorticoids

Zona glomerulosa Outer zone of adrenal cortex that synthesizes aldosterone

Zona pellucida Protective glycoprotein coat around an ovum

Zona reticularis Inner zone of adrenal cortex that synthesizes sex steroids

Zonules Fibers that attach the lens of the eye and change its shape

Zygote Fertilized egg

Zymogens Inactive proenzymes in the digestive system

Index

Symbols

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

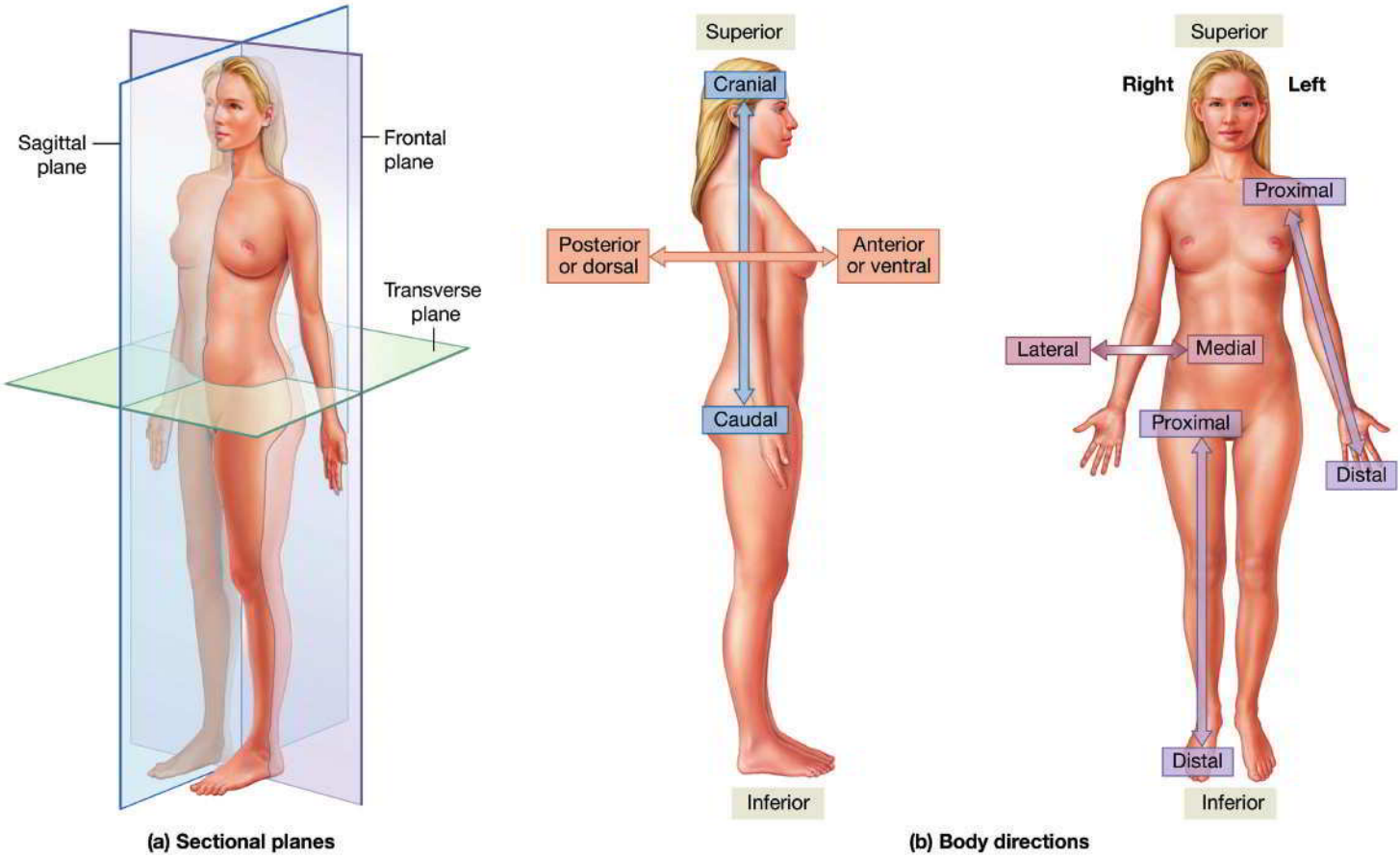
W

X

Y

Z

Anatomical Positions of the Body



Anterior	(situated in front of): in humans, toward the front of the body (see VENTRAL).
Posterior	(situated behind): in humans, toward the back of the body (see DORSAL).
Medial	(middle, as in *median strip*): located nearer to the midline of the body (the line that divides the body into mirror-image halves)
Lateral	(side, as in a *football lateral*): located toward the sides of the body
Distal	(distant): farther away from the point of reference or from the center of the body
Proximal	(closer, as in *proximity*): closer to the center of the body
Superior	(higher): located toward the head or the upper part of the body
Inferior	(lower): located away from the head or from the upper part of the body
Prone:	lying on the stomach, face downward
Supine:	lying on the back, face up
Dorsal:	refers to the back of the body
Ventral:	refers to the front of the body
Ipsilateral:	on the same side as
Contralateral:	on the opposite side from

Measurements and Conversions

PREFIXES				
deci-	(d)	1/10	0.1	1×10^{-1}
centi-	(c)	1/100	0.01	1×10^{-2}
milli-	(m)	1/1000	0.001	1×10^{-3}
micro-	(μ)	1/1,000,000	0.000001	1×10^{-6}
nano-	(n)	1/1,000,000,000	0.000000001	1×10^{-9}
pico-	(p)	1/1,000,000,000,000	0.000000000001	1×10^{-12}
kilo-	(k)		1000.	1×10^{3}

METRIC SYSTEM				
1 meter (m)	=	100 centimeters (cm)	=	1000 millimeters (mm)
1 centimeter (cm)	=	10 millimeters (mm)	=	0.01 meter (m)
1 millimeter (mm)	=	1000 micrometers (μm; also called micron, μ)		
1 angstrom (Å)	=	1/10,000 micrometer	=	1×10^{-7} millimeters
1 liter (L)	=	1000 milliliters (mL)		
1 deciliter (dL)	=	100 milliliters (mL)	=	0.1 liter (L)
1 cubic centimeter (cc)	=	1 milliliter (mL)		
1 milliliter (mL)	=	1000 microliters (μL)		
1 kilogram (kg)	=	1000 grams (g)		
1 gram (g)	=	1000 milligrams (mg)		
1 milligram (mg)	=	1000 micrograms (μg)		

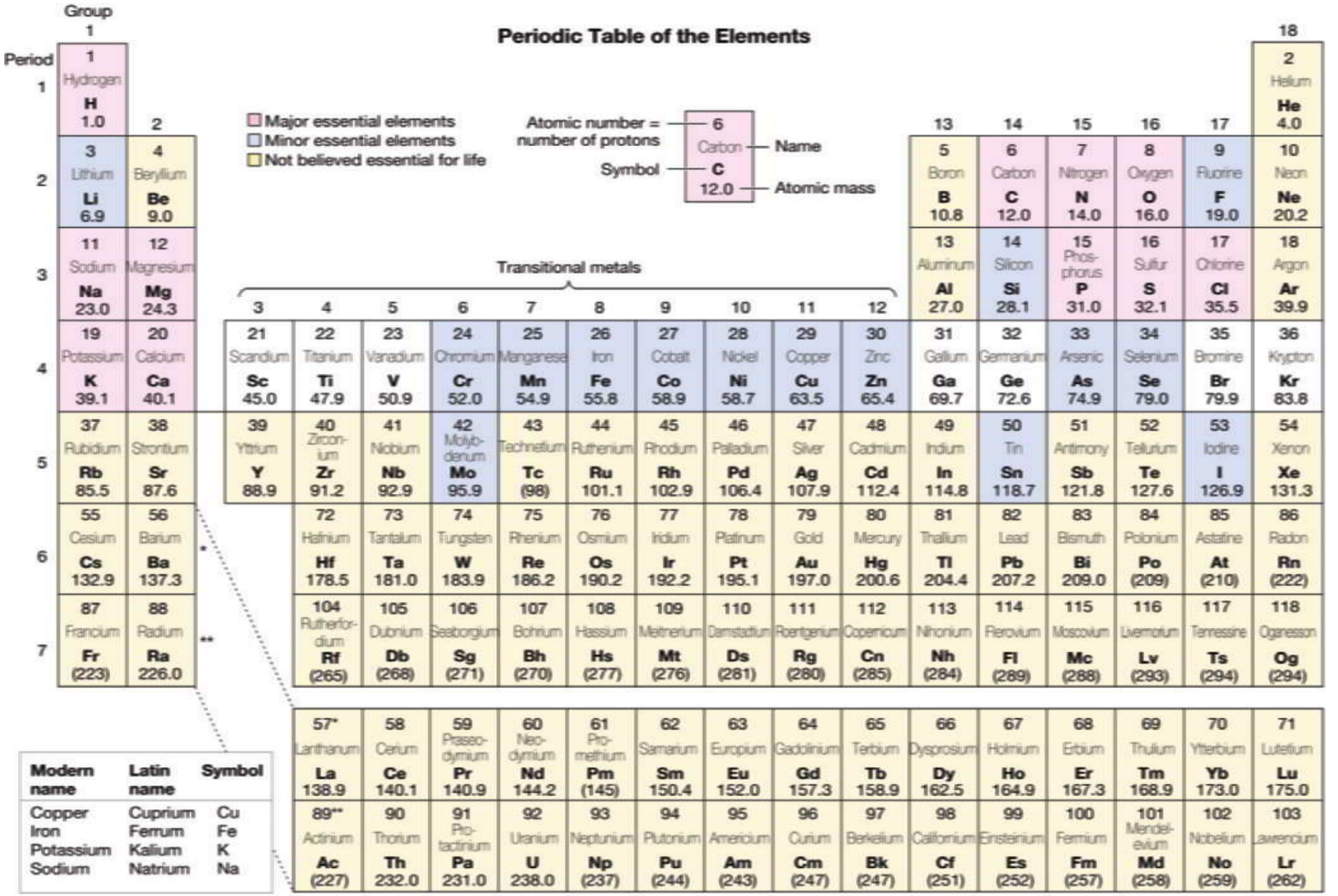
CONVERSIONS	
1 yard (yd)	= 0.92 meter
1 inch (in)	= 2.54 centimeters
1 meter	= 1.09 yards
1 centimeter	= 0.39 inch
1 liquid quart (qt)	= 946 milliliters
1 fluid ounce (oz)	= 8 fluid drams = 29.57 milliliters (mL)
1 liter	= 1.05 liquid quarts
1 pound (lb)	= 453.6 grams
1 kilogram	= 2.2 pounds

TEMPERATURE				
FREEZING				
0 degrees Celsius (°C)	=	32 degrees Fahrenheit (°F)	=	273 Kelvin (K)
To convert degrees Celsius (°C) to degrees Fahrenheit (°F): $(°C \times 9/5) + 32$				
To convert degrees Fahrenheit (°F) to degrees Celsius (°C): $(°F - 32) \times 5/9$				

NORMAL VALUES OF BLOOD COMPONENTS		
SUBSTANCE OR PARAMETER	NORMAL RANGE	MEASURED
Bicarbonate (HCO_3^-)	23–29 meq/L	Serum
Calcium (Ca^{2+})	4.3–5.3 meq/L	Serum
Chloride (Cl^-)	100–108 meq/L	Serum
Potassium (K^+)	3.5–5.0 meq/L	Serum
Sodium (Na^+)	135–145 meq/L	Serum
pH	7.35–7.45	Whole blood
P_{O_2}	75–100 mm Hg	Arterial blood
P_{CO_2}	34–45 mm Hg	Arterial blood
Osmolality	280–296 mosmol/kg water	Serum
Glucose, fasting	70–110 mg/dL	Plasma
Creatinine	0.6–1.5 mg/dL	Serum
Protein, total	6.0–8.0 g/dL	Serum

Modified from W. R Ganong, *Review of Medical Physiology* (Norwalk: Appleton & Lange). 1995.

Periodic Table of the Elements



Modern name	Latin name	Symbol
Copper	Cuprium	Cu
Iron	Ferrum	Fe
Potassium	Kalium	K
Sodium	Natrium	Na

Note: Numbers in parentheses are mass numbers (the total number of protons and neutrons in the nucleus) of the most stable or best-known isotope of radioactive elements.