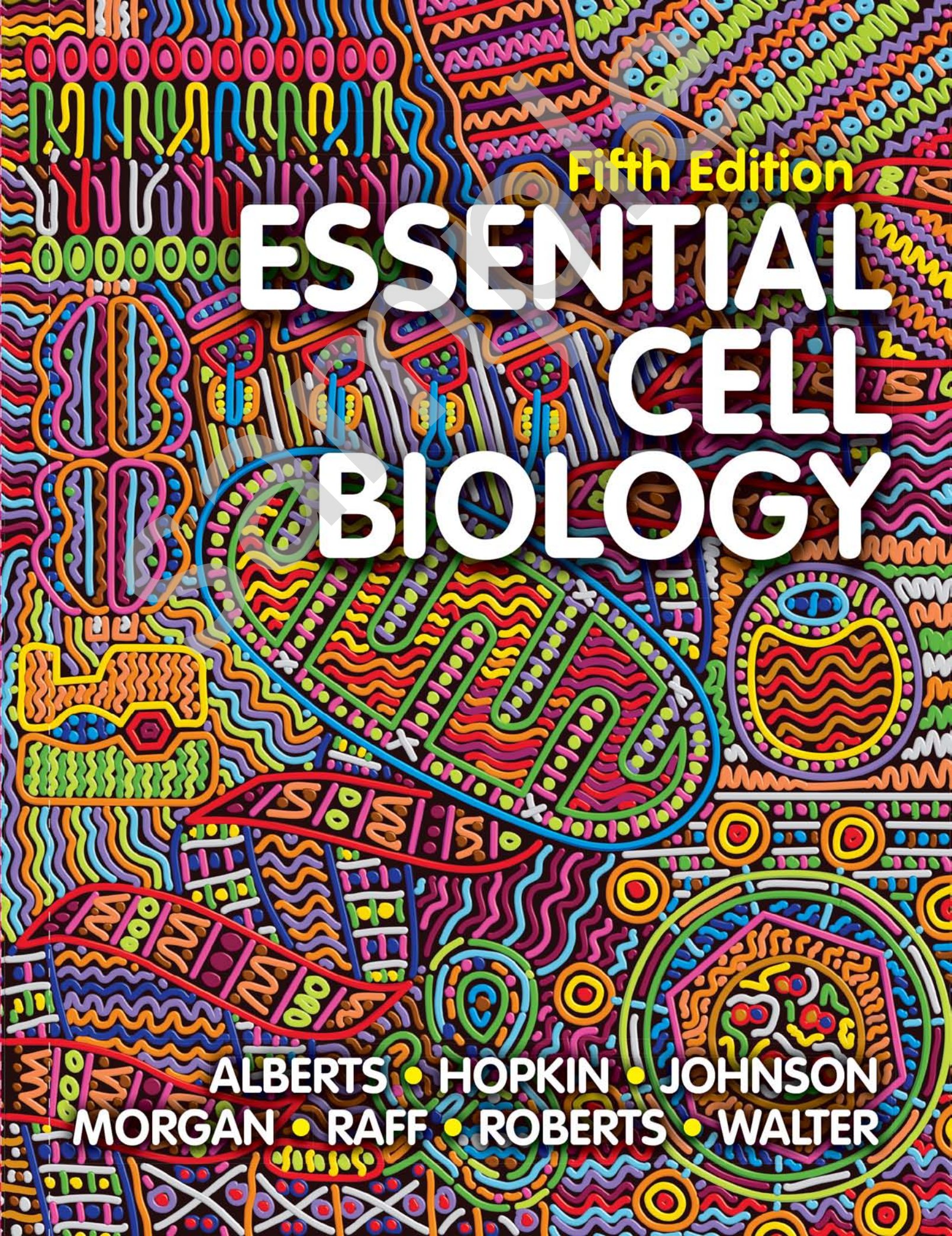

Fifth Edition
ESSENTIAL CELL BIOLOGY
ALBERTS • HOPKIN • JOHNSON
MORGAN • RAFF • ROBERTS • WALTER

ESSENTIAL
CELL BIOLOGY

FIFTH EDITION

FIFTH EDITION

ESSENTIAL CELL BIOLOGY

Bruce Alberts
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Karen Hopkin
SCIENCE WRITER

Alexander Johnson
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

David Morgan
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Martin Raff
UNIVERSITY COLLEGE LONDON (EMERITUS)

Keith Roberts
UNIVERSITY OF EAST ANGLIA (EMERITUS)

Peter Walter
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

W. W. NORTON & COMPANY
NEW YORK • LONDON

W. W. Norton & Company has been independent since its founding in 1923, when William Warder Norton and Mary D. Herter Norton first published lectures delivered at the People's Institute, the adult education division of New York City's Cooper Union. The firm soon expanded its program beyond the Institute, publishing books by celebrated academics from America and abroad. By midcentury, the two major pillars of Norton's publishing program—trade books and college texts—were firmly established. In the 1950s, the Norton family transferred control of the company to its employees, and today—with a staff of four hundred and a comparable number of trade, college, and professional titles published each year—W. W. Norton & Company stands as the largest and oldest publishing house owned wholly by its employees.

Printed in Canada

Editors: Betsy Twitchell and Michael Morales
Associate Editor: Katie Callahan
Editorial Consultant: Denise Schanck
Senior Associate Managing Editor, College: Carla L. Talmadge
Editorial Assistants: Taylere Peterson and Danny Vargo
Director of Production, College: Jane Searle
Managing Editor, College: Marian Johnson
Managing Editor, College Digital Media: Kim Yi
Media Editor: Kate Brayton
Associate Media Editor: Gina Forsythe
Media Project Editor: Jesse Newkirk
Media Editorial Assistant: Katie Daloia
Ebook Production Manager: Michael Hicks
Content Development Specialist: Todd Pearson
Marketing Manager, Biology: Stacy Loyal
Director of College Permissions: Megan Schindel
Permissions Clearer: Sheri Gilbert
Composition: Emma Jeffcock of EJ Publishing Services
Illustrations: Nigel Orme
Design Director: Hope Miller Goodell
Designer: Matthew McClements, Blink Studio, Ltd.
Indexer: Bill Johncocks
Manufacturing: Transcontinental Interglobe—Beauceville, Quebec

Permission to use copyrighted material is included alongside the appropriate content.

Library of Congress Cataloging-in-Publication Data

Names: Alberts, Bruce, author.
Title: Essential cell biology / Bruce Alberts, Karen Hopkin, Alexander Johnson, David Morgan, Martin Raff, Keith Roberts, Peter Walter.
Description: Fifth edition. | New York : W.W. Norton & Company, [2019] | Includes index.
Identifiers: LCCN 2018036121 | **ISBN 9780393679533 (hardcover)**
Subjects: LCSH: Cytology. | Molecular biology. | Biochemistry.
Classification: LCC QH581.2 .E78 2019 | DDC 571.6—dc23 LC record available at https://lccn.loc.gov/2018036121

W. W. Norton & Company, Inc., 500 Fifth Avenue, New York, NY 10110
wwnorton.com
W. W. Norton & Company Ltd., 15 Carlisle Street, London W1D 3BS

1 2 3 4 5 6 7 8 9 0

PREFACE

Nobel Prize–winning physicist Richard Feynman once noted that nature has a far, far better imagination than our own. Few things in the universe illustrate this observation better than the cell. A tiny sac of molecules capable of self-replication, this marvelous structure constitutes the fundamental building block of life. We are made of cells. Cells provide all the nutrients we consume. And the continuous activity of cells makes our planet habitable. To understand ourselves—and the world of which we are a part—we need to know something of the life of cells. Armed with such knowledge, we—as citizens and stewards of the global community—will be better equipped to make well-informed decisions about increasingly sophisticated issues, from climate change and food security to biomedical technologies and emerging epidemics.

In *Essential Cell Biology* we introduce readers to the fundamentals of cell biology. The Fifth Edition introduces powerful new techniques that allow us to examine cells and their components with unprecedented precision—such as super-resolution fluorescence microsocopy and cryoelectron microscopy—as well as the latest methods for DNA sequencing and gene editing. We discuss new thinking about how cells organize and encourage the chemical reactions that make life possible, and we review recent insights into human origins and genetics.

With each edition of *Essential Cell Biology*, its authors re-experience the joy of learning something new and surprising about cells. We are also reminded of how much we still don't know. Many of the most fascinating questions in cell biology remain unanswered. How did cells arise on the early Earth, multiplying and diversifying through billions of years of evolution to fill every possible niche—from steaming vents on the ocean floor to frozen mountaintops—and, in doing so, transform our planet's entire environment? How is it possible for billions of cells to seamlessly cooperate and form large, multicellular organisms like ourselves? These are among the many challenges that remain for the next generation of cell biologists, some of whom will begin a wonderful, lifelong journey with this textbook.

Readers interested in learning how scientific inquisitiveness can fuel breakthroughs in our understanding of cell biology will enjoy the stories of discovery presented in each chapter's "How We Know" feature. Packed with experimental data and design, these narratives illustrate how biologists tackle important questions and how experimental results shape future ideas. In this edition, a new "How We Know" recounts the discoveries that first revealed how cells transform the energy locked in food molecules into the forms used to power the metabolic reactions on which life depends.

As in previous editions, the questions in the margins and at the end of each chapter not only test comprehension but also encourage careful thought and the application of newly acquired information to a broader biological context. Some of these questions have more than one valid

answer and others invite speculation. Answers to all of the questions are included at the back of the book, and many provide additional information or an alternative perspective on material presented in the main text.

More than 160 video clips, animations, atomic structures, and high-resolution micrographs complement the book and are available online. The movies are correlated with each chapter and callouts are highlighted in color. This supplemental material, created to clarify complex and critical concepts, highlights the intrinsic beauty of living cells.

For those who wish to probe even more deeply, *Molecular Biology of the Cell*, now in its sixth edition, offers a detailed account of the life of the cell. In addition, *Molecular Biology of the Cell, Sixth Edition: A Problems Approach*, by John Wilson and Tim Hunt, provides a gold mine of thought-provoking questions at all levels of difficulty. We have drawn upon this tour-de-force of experimental reasoning for some of the questions in *Essential Cell Biology*, and we are very grateful to its authors.

Every chapter of *Essential Cell Biology* is the product of a communal effort: both text and figures were revised and refined as drafts circulated from one author to another—many times over and back again! The numerous other individuals who have helped bring this project to fruition are credited in the Acknowledgments that follow. Despite our best efforts, it is inevitable that errors will have crept into the book, and we encourage eagle-eyed readers who find mistakes to let us know, so that we can correct them in the next printing.

Acknowledgments

The authors acknowledge the many contributions of professors and students from around the world in the creation of this Fifth Edition. In particular, we received detailed reviews from the following instructors who had used the fourth edition, and we would like to thank them for their important contributions to our revision:

Delbert Abi Abdallah, Thiel College, Pennsylvania
Ann Aguanno, Marymount Manhattan College
David W. Barnes, Georgia Gwinnett College
Manfred Beilharz, The University of Western Australia
Christopher Brandl, Western University, Ontario
Marion Brodhagen, Western Washington University
David Casso, San Francisco State University
Shazia S. Chaudhry, The University of Manchester, United Kingdom
Ron Dubreuil, The University of Illinois at Chicago
Heidi Engelhardt, University of Waterloo, Canada
Sarah Ennis, University of Southampton, United Kingdom
David Featherstone, The University of Illinois at Chicago
Yen Kang France, Georgia College
Barbara Frank, Idaho State University
Daniel E. Frigo, University of Houston
Marcos Garcia-Ojeda, University of California, Merced
David L. Gard, The University of Utah
Adam Gromley, Lincoln Memorial University, Tennessee
Elly Holthuizen, University Medical Center Utrecht, The Netherlands
Harold Hoops, The State University of New York, Geneseo
Bruce Jensen, University of Jamestown, North Dakota
Andor Kiss, Miami University, Ohio
Annette Koenders, Edith Cowan University, Australia
Arthur W. Lambert, Whitehead Institute for Biomedical Research
Denis Larochelle, Clark University, Massachusetts
David Leaf, Western Washington University
Esther Leise, The University of North Carolina at Greensboro
Bernhard Lieb, University of Mainz, Germany

Julie Lively, Louisiana State University
Caroline Mackintosh, University of Saint Mary, Kansas
John Mason, The University of Edinburgh, Scotland
Craig Milgrim, Grossmont College, California
Arkadeep Mitra, City College, Kolkata, India
Niels Erik Møllegaard, University of Copenhagen
Javier Naval, University of Zaragoza, Spain
Marianna Patrauchan, Oklahoma State University
Amanda Polson-Zeigler, University of South Carolina
George Risinger, Oklahoma City Community College
Laura Romberg, Oberlin College, Ohio
Sandra Schulze, Western Washington University
Isaac Skromne, University of Richmond, Virginia
Anna Slusarz, Stephens College, Missouri
Richard Smith, University of Tennessee Health Science Center
Alison Snape, King's College London
Shannon Stevenson, University of Minnesota Duluth
Marla Tipping, Providence College, Rhode Island
Jim Tokuhisa, Virginia Polytechnic Institute and State University
Guillaume van Eys, Maastricht University, The Netherlands
Barbara Vertel, Rosalind Franklin University of Medicine and Science, Illinois
Jennifer Waby, University of Bradford, United Kingdom
Dianne Watters, Griffith University, Australia
Allison Wiedemeier, University of Louisiana at Monroe
Elizabeth Wurdak, St. John's University, Minnesota
Kwok-Ming Yao, The University of Hong Kong
Foong May Yeong, National University of Singapore

We are also grateful to those readers who alerted us to errors that they found in the previous edition.

Working on this book has been a pleasure, in part due to the many people who contributed to its creation. Nigel Orme again worked closely with author Keith Roberts to generate the entire illustration program with his usual skill and care. He also produced all of the artwork for both cover and chapter openers as a respectful digital tribute to the "squeeze-bottle" paintings of the American artist Alden Mason (1919–2013). As in previous editions, Emma Jeffcock did a brilliant job in laying out the whole book and meticulously incorporated our endless corrections. We owe a special debt to Michael Morales, our editor at Garland Science, who coordinated the whole enterprise. He oversaw the initial reviewing, worked closely with the authors on their chapters, took great care of us at numerous writing meetings, and kept us organized and on schedule. He also orchestrated the wealth of online materials, including all video clips and animations. Our copyeditor, Jo Clayton, ensured that the text was stylistically consistent and error-free. At Garland, we also thank Jasmine Ribeaux, Georgina Lucas, and Adam Sendroff.

For welcoming our book to W. W. Norton and bringing this edition to print, we thank our editor Betsy Twitchell, as well as Roby Harrington, Drake McFeely, Julia Reidhead, and Ann Shin for their support. Taylere Peterson and Danny Vargo deserve thanks for their assistance as the book moved from Garland to Norton and through production. We are grateful to media editor Kate Brayton and content development specialist Todd Pearson, associate editors Gina Forsythe and Katie Callahan, and media editorial assistant Katie Daloia whose coordination of electronic media development has resulted in an unmatched suite of resources for cell biology students and instructors alike. We are grateful for marketing manager Stacy Loyal's tireless enthusiasm and advocacy for our book. Megan Schindel, Ted Szczepanski, and Stacey Stambaugh are all owed thanks for navigating the permissions for this edition. And Jane Searle's able management of production, Carla Talmadge's incredible attention to detail, and their shared knack for troubleshooting made the book you hold in your hands a reality.

Denise Schanck deserves extra special thanks for providing continuity as she helped shepherd this edition from Garland to Norton. As always, she attended all of our writing retreats and displayed great wisdom in orchestrating everything she touched.

Last but not least, we are grateful, yet again, to our colleagues and our families for their unflagging tolerance and support. We give our thanks to everyone in this long list.

Resources for Instructors and Students

INSTRUCTOR RESOURCES

wwnorton.com/instructors

Smartwork5

Smartwork5 is an easy-to-use online assessment tool that helps students become better problem solvers through a variety of interactive question types and extensive answer-specific feedback. All Smartwork5 questions are written specifically for the book, are tagged to Bloom's levels and learning objectives, and many include art and animations. Get started quickly with our premade assignments or take advantage of Smartwork5's flexibility by customizing questions and adding your own content. Integration with your campus LMS saves you time by allowing Smartwork5 grades to report right to your LMS gradebook, while individual and class-wide performance reports help you see students' progress.

Interactive Instructor's Guide

An all-in-one resource for instructors who want to integrate active learning into their course. Searchable by chapter, phrase, topic, or learning objective, the Interactive Instructor's Guide compiles the many valuable teaching resources available with *Essential Cell Biology*. This website includes activities, discussion questions, animations and videos, lecture outlines, learning objectives, primary literature suggestions, medical topics guide, and more.

Coursepacks

Easily add high-quality Norton digital media to your online, hybrid, or lecture course. Norton Coursepacks work within your existing learning management system. Content is customizable and includes chapter-based, multiple-choice reading quizzes, text-based learning objectives, access to the full suite of animations, flashcards, and a glossary.

Test Bank

Written by Linda Huang, University of Massachusetts Boston, and Cheryl D. Vaughan, Harvard University Division of Continuing Education, the revised and expanded Test Bank for *Essential Cell Biology* includes 65–80 questions per chapter. Questions are available in multiple-choice, matching, fill-in-the-blank, and short-answer formats, with many using art from the textbook. All questions are tagged to Bloom's taxonomy level, learning objective, book section, and difficulty level, allowing instructors to easily create meaningful exams. The Test Bank is available in ExamView and as downloadable PDFs from wwnorton.com/instructors.

Animations and Videos

Streaming links give access to more than 130 videos and animations, bringing the concepts of cell biology to life. The movies are correlated with each chapter and callouts are highlighted in color.

Figure-integrated Lecture Outlines

All of the figures are integrated in PowerPoint, along with the section and concept headings from the text, to give instructors a head start creating lectures for their course.

Image Files

Every figure and photograph in the book is available for download in PowerPoint and JPG formats from wwnorton.com/instructors.

STUDENT RESOURCES

digital.wwnorton.com/ecb5

Animations and Videos

Streaming links give access to more than 130 videos and animations, bringing the concepts of cell biology to life. Animations can also be accessed via the ebook and in select Smartwork5 questions. The movies are correlated with each chapter and callouts are highlighted in color.

Student Site

Resources for self-study are available on the student site, including multiple-choice quizzes, cell explorer slides, challenge and concept questions, flashcards, and a glossary.

ABOUT THE AUTHORS

BRUCE ALBERTS received his PhD from Harvard University and is a professor in the Department of Biochemistry and Biophysics at the University of California, San Francisco. He was the editor in chief of *Science* from 2008 to 2013 and served as president of the U.S. National Academy of Sciences from 1993 to 2005.

KAREN HOPKIN received her PhD from the Albert Einstein College of Medicine and is a science writer. Her work has appeared in various scientific publications, including *Science*, *Proceedings of the National Academy of Sciences*, and *The Scientist*, and she is a regular contributor to *Scientific American*'s daily podcast, "60-Second Science."

ALEXANDER JOHNSON received his PhD from Harvard University and is a professor in the Department of Microbiology and Immunology at the University of California, San Francisco.

DAVID MORGAN received his PhD from the University of California, San Francisco, where he is a professor in the Department of Physiology and vice dean for research in the School of Medicine.

MARTIN RAFF received his MD from McGill University and is emeritus professor of biology at the Medical Research Council Laboratory for Molecular Cell Biology at University College London.

KEITH ROBERTS received his PhD from the University of Cambridge and was deputy director of the John Innes Centre. He is emeritus professor at the University of East Anglia.

PETER WALTER received his PhD from The Rockefeller University in New York and is a professor in the Department of Biochemistry and Biophysics at the University of California, San Francisco, and an investigator of the Howard Hughes Medical Institute.

LIST OF CHAPTERS and SPECIAL FEATURES

CHAPTER 1 **Cells: The Fundamental Units of Life 1**
PANEL 1–1 Microscopy 12
TABLE 1–1 Historical Landmarks in Determining Cell Structure 24
PANEL 1–2 Cell Architecture 25
How We Know: Life's Common Mechanisms 30
TABLE 1–2 Some Model Organisms and Their Genomes 35

CHAPTER 2 **Chemical Components of Cells 39**
TABLE 2–1 Length and Strength of Some Chemical Bonds 48
TABLE 2–2 The Chemical Composition of a Bacterial Cell 52
How We Know: The Discovery of Macromolecules 60
PANEL 2–1 Chemical Bonds and Groups 66
PANEL 2–2 The Chemical Properties of Water 68
PANEL 2–3 The Principal Types of Weak Noncovalent Bonds 70
PANEL 2–4 An Outline of Some of the Types of Sugars 72
PANEL 2–5 Fatty Acids and Other Lipids 74
PANEL 2–6 The 20 Amino Acids Found in Proteins 76
PANEL 2–7 A Survey of the Nucleotides 78

CHAPTER 3 **Energy, Catalysis, and Biosynthesis 81**
PANEL 3–1 Free Energy and Biological Reactions 94
TABLE 3–1 Relationship Between the Standard Free-Energy Change, $\triangle G°$, and the Equilibrium Constant 96
How We Know: "High-Energy" Phosphate Bonds Power Cell Processes 102
TABLE 3–2 Some Activated Carriers Widely Used in Metabolism 109

CHAPTER 4 **Protein Structure and Function 117**
PANEL 4–1 A Few Examples of Some General Protein Functions 118
PANEL 4–2 Making and Using Antibodies 140
TABLE 4–1 Some Common Functional Classes of Enzymes 142
How We Know: Measuring Enzyme Performance 144
TABLE 4–2 Historical Landmarks in Our Understanding of Proteins 160
PANEL 4–3 Cell Breakage and Initial Fractionation of Cell Extracts 164
PANEL 4–4 Protein Separation by Chromatography 166
PANEL 4–5 Protein Separation by Electrophoresis 167
PANEL 4–6 Protein Structure Determination 168

CHAPTER 5 **DNA and Chromosomes 173**
How We Know: Genes Are Made of DNA 193

CHAPTER 6 DNA Replication and Repair 199

How We Know: The Nature of Replication 202

TABLE 6–1 Proteins Involved in DNA Replication 213

TABLE 6–2 Error Rates 218

CHAPTER 7 From DNA to Protein: How Cells Read the Genome 227

TABLE 7–1 Types of RNA Produced in Cells 232

TABLE 7–2 The Three RNA Polymerases in Eukaryotic Cells 235

How We Know: Cracking the Genetic Code 246

TABLE 7–3 Antibiotics That Inhibit Bacterial Protein or RNA Synthesis 256

TABLE 7–4 Biochemical Reactions That Can Be Catalyzed by Ribozymes 261

CHAPTER 8 Control of Gene Expression 267

How We Know: Gene Regulation—The Story of *Eve* 280

CHAPTER 9 How Genes and Genomes Evolve 297

TABLE 9–1 Viruses That Cause Human Disease 318

TABLE 9–2 Some Vital Statistics for the Human Genome 322

How We Know: Counting Genes 324

CHAPTER 10 Analyzing the Structure and Function of Genes 333

How We Know: Sequencing the Human Genome 348

CHAPTER 11 Membrane Structure 365

TABLE 11–1 Some Examples of Plasma Membrane Proteins and Their Functions 375

How We Know: Measuring Membrane Flow 384

CHAPTER 12 Transport Across Cell Membranes 389

TABLE 12–1 A Comparison of Ion Concentrations Inside and Outside a Typical Mammalian Cell 391

TABLE 12–2 Some Examples of Transmembrane Pumps 403

How We Know: Squid Reveal Secrets of Membrane Excitability 412

TABLE 12–3 Some Examples of Ion Channels 419

CHAPTER 13 How Cells Obtain Energy from Food 427

TABLE 13–1 Some Types of Enzymes Involved in Glycolysis 431

PANEL 13–1 Details of the 10 Steps of Glycolysis 436

PANEL 13–2 The Complete Citric Acid Cycle 442

How We Know: Unraveling the Citric Acid Cycle 444

CHAPTER 14 Energy Generation in Mitochondria and Chloroplasts 455

TABLE 14–1 Product Yields from Glucose Oxidation 469

PANEL 14–1 Redox Potentials 472

How We Know: How Chemiosmotic Coupling Drives ATP Synthesis 476

CHAPTER 15 Intracellular Compartments and Protein Transport 495

TABLE 15–1 The Main Functions of Membrane-enclosed Organelles of a Eukaryotic Cell 497

TABLE 15–2 The Relative Volumes and Numbers of the Major Membrane-enclosed Organelles in a Liver Cell (Hepatocyte) 498

TABLE 15–3 Some Typical Signal Sequences 502
TABLE 15–4 Some Types of Coated Vesicles 513
How We Know: Tracking Protein and Vesicle Transport 520

CHAPTER 16 Cell Signaling 533
TABLE 16–1 Some Examples of Signal Molecules 536
TABLE 16–2 Some Foreign Substances That Act on Cell-Surface Receptors 544
TABLE 16–3 Some Cell Responses Mediated by Cyclic AMP 550
TABLE 16–4 Some Cell Responses Mediated by Phospholipase C Activation 552
How We Know: Untangling Cell Signaling Pathways 563

CHAPTER 17 Cytoskeleton 573
TABLE 17–1 Drugs That Affect Microtubules 584
How We Know: Pursuing Microtubule-associated Motor Proteins 588
TABLE 17–2 Drugs That Affect Filaments 594

CHAPTER 18 The Cell-Division Cycle 609
TABLE 18–1 Some Eukaryotic Cell-Cycle Durations 611
How We Know: Discovery of Cyclins and Cdks 615
TABLE 18–2 The Major Cyclins and Cdks of Vertebrates 617
PANEL 18–1 The Principal Stages of M Phase in an Animal Cell 628

CHAPTER 19 Sexual Reproduction and Genetics 651
PANEL 19–1 Some Essentials of Classical Genetics 675
How We Know: Using SNPs to Get a Handle on Human Disease 684

CHAPTER 20 Cell Communities: Tissues, Stem Cells, and Cancer 691
TABLE 20–1 A Variety of Factors Can Contribute to Genetic Instability 721
TABLE 20–2 Examples of Cancer-critical Genes 728
How We Know: Making Sense of the Genes That Are Critical for Cancer 730

CONTENTS

Preface v
About the Authors x

CHAPTER 1

Cells: The Fundamental Units of Life 1

UNITY AND DIVERSITY OF CELLS 2
Cells Vary Enormously in Appearance and Function 2
Living Cells All Have a Similar Basic Chemistry 3
Living Cells Are Self-Replicating Collections of Catalysts 4
All Living Cells Have Apparently Evolved from the Same Ancestral Cell 5
Genes Provide Instructions for the Form, Function, and Behavior of Cells and Organisms 6
CELLS UNDER THE MICROSCOPE 6
The Invention of the Light Microscope Led to the Discovery of Cells 7
Light Microscopes Reveal Some of a Cell's Components 8
The Fine Structure of a Cell Is Revealed by Electron Microscopy 9
THE PROKARYOTIC CELL 11
Prokaryotes Are the Most Diverse and Numerous Cells on Earth 14
The World of Prokaryotes Is Divided into Two Domains: Bacteria and Archaea 15
THE EUKARYOTIC CELL 16
The Nucleus Is the Information Store of the Cell 16
Mitochondria Generate Usable Energy from Food Molecules 17
Chloroplasts Capture Energy from Sunlight 18
Internal Membranes Create Intracellular Compartments with Different Functions 19
The Cytosol Is a Concentrated Aqueous Gel of Large and Small Molecules 21
The Cytoskeleton Is Responsible for Directed Cell Movements 22
The Cytosol Is Far from Static 23
Eukaryotic Cells May Have Originated as Predators 24
MODEL ORGANISMS 27
Molecular Biologists Have Focused on *E. coli* 27
Brewer's Yeast Is a Simple Eukaryote 28
Arabidopsis Has Been Chosen as a Model Plant 28
Model Animals Include Flies, Worms, Fish, and Mice 29
Biologists Also Directly Study Humans and Their Cells 32
Comparing Genome Sequences Reveals Life's Common Heritage 33
Genomes Contain More Than Just Genes 35
ESSENTIAL CONCEPTS 36
QUESTIONS 37

CHAPTER 2

Chemical Components of Cells 39

CHEMICAL BONDS 40

Cells Are Made of Relatively Few Types of Atoms 40
The Outermost Electrons Determine How Atoms Interact 41
Covalent Bonds Form by the Sharing of Electrons 43
Some Covalent Bonds Involve More Than One Electron Pair 44
Electrons in Covalent Bonds Are Often Shared Unequally 45
Covalent Bonds Are Strong Enough to Survive the Conditions Inside Cells 45
Ionic Bonds Form by the Gain and Loss of Electrons 46
Hydrogen Bonds Are Important Noncovalent Bonds for Many Biological Molecules 47
Four Types of Weak Interactions Help Bring Molecules Together in Cells 47
Some Polar Molecules Form Acids and Bases in Water 49

SMALL MOLECULES IN CELLS 50

A Cell Is Formed from Carbon Compounds 50
Cells Contain Four Major Families of Small Organic Molecules 51
Sugars Are both Energy Sources and Subunits of Polysaccharides 52
Fatty Acid Chains Are Components of Cell Membranes 54
Amino Acids Are the Subunits of Proteins 56
Nucleotides Are the Subunits of DNA and RNA 56

MACROMOLECULES IN CELLS 58

Each Macromolecule Contains a Specific Sequence of Subunits 59
Noncovalent Bonds Specify the Precise Shape of a Macromolecule 62
Noncovalent Bonds Allow a Macromolecule to Bind Other Selected Molecules 62

ESSENTIAL CONCEPTS 64

QUESTIONS 65

CHAPTER 3

Energy, Catalysis, and Biosynthesis 81

THE USE OF ENERGY BY CELLS 82

Biological Order Is Made Possible by the Release of Heat Energy from Cells 83
Cells Can Convert Energy from One Form to Another 84
Photosynthetic Organisms Use Sunlight to Synthesize Organic Molecules 85
Cells Obtain Energy by the Oxidation of Organic Molecules 86
Oxidation and Reduction Involve Electron Transfers 87

FREE ENERGY AND CATALYSIS 88

Chemical Reactions Proceed in the Direction That Causes a Loss of Free Energy 89
Enzymes Reduce the Energy Needed to Initiate Spontaneous Reactions 89
The Free-Energy Change for a Reaction Determines Whether It Can Occur 90
$\triangle G$ Changes as a Reaction Proceeds Toward Equilibrium 92
The Standard Free-Energy Change, $\triangle G°$, Makes It Possible to Compare the Energetics of Different Reactions 92
The Equilibrium Constant Is Directly Proportional to $\triangle G°$ 96
In Complex Reactions, the Equilibrium Constant Includes the Concentrations of All Reactants and Products 96

The Equilibrium Constant Also Indicates the Strength of Noncovalent Binding Interactions 97
For Sequential Reactions, the Changes in Free Energy Are Additive 98
Enzyme-catalyzed Reactions Depend on Rapid Molecular Collisions 99
Noncovalent Interactions Allow Enzymes to Bind Specific Molecules 100

ACTIVATED CARRIERS AND BIOSYNTHESIS 101

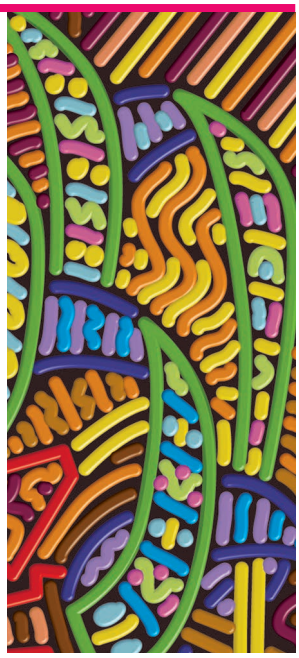
The Formation of an Activated Carrier Is Coupled to an Energetically Favorable Reaction 101
ATP Is the Most Widely Used Activated Carrier 104
Energy Stored in ATP Is Often Harnessed to Join Two Molecules Together 106
NADH and NADPH Are Both Activated Carriers of Electrons 106
NADPH and NADH Have Different Roles in Cells 108
Cells Make Use of Many Other Activated Carriers 108
The Synthesis of Biological Polymers Requires an Energy Input 110

ESSENTIAL CONCEPTS 113

QUESTIONS 114

CHAPTER 4

Protein Structure and Function 117



THE SHAPE AND STRUCTURE OF PROTEINS 119

The Shape of a Protein Is Specified by Its Amino Acid Sequence 119
Proteins Fold into a Conformation of Lowest Energy 122
Proteins Come in a Wide Variety of Complicated Shapes 124
The α Helix and the β Sheet Are Common Folding Patterns 126
Helices Form Readily in Biological Structures 127
β Sheets Form Rigid Structures at the Core of Many Proteins 129
Misfolded Proteins Can Form Amyloid Structures That Cause Disease 129
Proteins Have Several Levels of Organization 129
Proteins Also Contain Unstructured Regions 130
Few of the Many Possible Polypeptide Chains Will Be Useful 131
Proteins Can Be Classified into Families 132
Large Protein Molecules Often Contain More than One Polypeptide Chain 132
Proteins Can Assemble into Filaments, Sheets, or Spheres 134
Some Types of Proteins Have Elongated Fibrous Shapes 134
Extracellular Proteins Are Often Stabilized by Covalent Cross-Linkages 135

HOW PROTEINS WORK 137

All Proteins Bind to Other Molecules 137
Humans Produce Billions of Different Antibodies, Each with a Different Binding Site 138
Enzymes Are Powerful and Highly Specific Catalysts 139
Enzymes Greatly Accelerate the Speed of Chemical Reactions 142
Lysozyme Illustrates How an Enzyme Works 143
Many Drugs Inhibit Enzymes 147
Tightly Bound Small Molecules Add Extra Functions to Proteins 148

HOW PROTEINS ARE CONTROLLED 149

The Catalytic Activities of Enzymes Are Often Regulated by Other Molecules 150
Allosteric Enzymes Have Two or More Binding Sites That Influence One Another 151
Phosphorylation Can Control Protein Activity by Causing a Conformational Change 152
Covalent Modifications Also Control the Location and Interaction of Proteins 153
Regulatory GTP-Binding Proteins Are Switched On and Off by the Gain and Loss of a Phosphate Group 154

ATP Hydrolysis Allows Motor Proteins to Produce Directed Movements in Cells 154
Proteins Often Form Large Complexes That Function as Machines 155
Many Interacting Proteins Are Brought Together by Scaffolds 156
Weak Interactions Between Macromolecules Can Produce Large Biochemical Subcompartments in Cells 157

HOW PROTEINS ARE STUDIED 158
Proteins Can Be Purified from Cells or Tissues 158
Determining a Protein's Structure Begins with Determining Its Amino Acid Sequence 159
Genetic Engineering Techniques Permit the Large-Scale Production, Design, and Analysis of Almost Any Protein 161
The Relatedness of Proteins Aids the Prediction of Protein Structure and Function 162

ESSENTIAL CONCEPTS 162
QUESTIONS 170

CHAPTER 5
DNA and Chromosomes 173

THE STRUCTURE OF DNA 174
A DNA Molecule Consists of Two Complementary Chains of Nucleotides 175
The Structure of DNA Provides a Mechanism for Heredity 176

THE STRUCTURE OF EUKARYOTIC CHROMOSOMES 178
Eukaryotic DNA Is Packaged into Multiple Chromosomes 179
Chromosomes Organize and Carry Genetic Information 180
Specialized DNA Sequences Are Required for DNA Replication and Chromosome Segregation 181
Interphase Chromosomes Are Not Randomly Distributed Within the Nucleus 182
The DNA in Chromosomes Is Always Highly Condensed 183
Nucleosomes Are the Basic Units of Eukaryotic Chromosome Structure 184
Chromosome Packing Occurs on Multiple Levels 186

THE REGULATION OF CHROMOSOME STRUCTURE 188
Changes in Nucleosome Structure Allow Access to DNA 188
Interphase Chromosomes Contain both Highly Condensed and More Extended Forms of Chromatin 189

ESSENTIAL CONCEPTS 192
QUESTIONS 196

CHAPTER 6

DNA Replication and Repair 199

DNA REPLICATION 200
Base-Pairing Enables DNA Replication 200
DNA Synthesis Begins at Replication Origins 201
Two Replication Forks Form at Each Replication Origin 201
DNA Polymerase Synthesizes DNA Using a Parental Strand as a Template 205
The Replication Fork Is Asymmetrical 206
DNA Polymerase Is Self-correcting 207
Short Lengths of RNA Act as Primers for DNA Synthesis 208
Proteins at a Replication Fork Cooperate to Form a Replication Machine 210
Telomerase Replicates the Ends of Eukaryotic Chromosomes 213
Telomere Length Varies by Cell Type and with Age 214
DNA REPAIR 215
DNA Damage Occurs Continually in Cells 215
Cells Possess a Variety of Mechanisms for Repairing DNA 217
A DNA Mismatch Repair System Removes Replication Errors That Escape Proofreading 218
Double-Strand DNA Breaks Require a Different Strategy for Repair 219
Homologous Recombination Can Flawlessly Repair DNA Double-Strand Breaks 220
Failure to Repair DNA Damage Can Have Severe Consequences for a Cell or Organism 222
A Record of the Fidelity of DNA Replication and Repair Is Preserved in Genome Sequences 223
ESSENTIAL CONCEPTS 224
QUESTIONS 225

CHAPTER 7

From DNA to Protein: How Cells Read the Genome 227

FROM DNA TO RNA 228
Portions of DNA Sequence Are Transcribed into RNA 229
Transcription Produces RNA That Is Complementary to One Strand of DNA 230
Cells Produce Various Types of RNA 232
Signals in the DNA Tell RNA Polymerase Where to Start and Stop Transcription 233
Initiation of Eukaryotic Gene Transcription Is a Complex Process 235
Eukaryotic RNA Polymerase Requires General Transcription Factors 235
Eukaryotic mRNAs Are Processed in the Nucleus 237
In Eukaryotes, Protein-Coding Genes Are Interrupted by Noncoding Sequences Called Introns 239
Introns Are Removed from Pre-mRNAs by RNA Splicing 239
RNA Synthesis and Processing Takes Place in "Factories" Within the Nucleus 242
Mature Eukaryotic mRNAs Are Exported from the Nucleus 242
mRNA Molecules Are Eventually Degraded in the Cytosol 242
FROM RNA TO PROTEIN 243
An mRNA Sequence Is Decoded in Sets of Three Nucleotides 244
tRNA Molecules Match Amino Acids to Codons in mRNA 245

Specific Enzymes Couple tRNAs to the Correct Amino Acid 249
The mRNA Message Is Decoded on Ribosomes 249
The Ribosome Is a Ribozyme 252
Specific Codons in an mRNA Signal the Ribosome Where to Start and to Stop Protein Synthesis 253
Proteins Are Produced on Polyribosomes 255
Inhibitors of Prokaryotic Protein Synthesis Are Used as Antibiotics 255
Controlled Protein Breakdown Helps Regulate the Amount of Each Protein in a Cell 256
There Are Many Steps Between DNA and Protein 257

RNA AND THE ORIGINS OF LIFE 259
Life Requires Autocatalysis 259
RNA Can Store Information and Catalyze Chemical Reactions 260
RNA Is Thought to Predate DNA in Evolution 261

ESSENTIAL CONCEPTS 262

QUESTIONS 264

CHAPTER 8

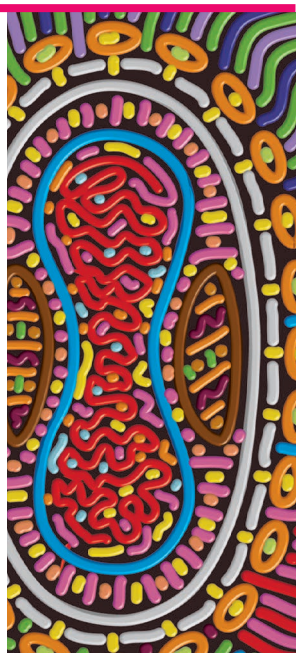
Control of Gene Expression 267

AN OVERVIEW OF GENE EXPRESSION 268
The Different Cell Types of a Multicellular Organism Contain the Same DNA 268
Different Cell Types Produce Different Sets of Proteins 269
A Cell Can Change the Expression of Its Genes in Response to External Signals 270
Gene Expression Can Be Regulated at Various Steps from DNA to RNA to Protein 270

HOW TRANSCRIPTION IS REGULATED 271
Transcription Regulators Bind to Regulatory DNA Sequences 271
Transcription Switches Allow Cells to Respond to Changes in Their Environment 273
Repressors Turn Genes Off and Activators Turn Them On 274
The Lac Operon Is Controlled by an Activator and a Repressor 275
Eukaryotic Transcription Regulators Control Gene Expression from a Distance 276
Eukaryotic Transcription Regulators Help Initiate Transcription by Recruiting Chromatin-Modifying Proteins 276
The Arrangement of Chromosomes into Looped Domains Keeps Enhancers in Check 278

GENERATING SPECIALIZED CELL TYPES 278
Eukaryotic Genes Are Controlled by Combinations of Transcription Regulators 279
The Expression of Different Genes Can Be Coordinated by a Single Protein 279
Combinatorial Control Can Also Generate Different Cell Types 282
The Formation of an Entire Organ Can Be Triggered by a Single Transcription Regulator 284
Transcription Regulators Can Be Used to Experimentally Direct the Formation of Specific Cell Types in Culture 285
Differentiated Cells Maintain Their Identity 286

POST-TRANSCRIPTIONAL CONTROLS 287
mRNAs Contain Sequences That Control Their Translation 288
Regulatory RNAs Control the Expression of Thousands of Genes 288
MicroRNAs Direct the Destruction of Target mRNAs 289
Small Interfering RNAs Protect Cells From Infections 290
Thousands of Long Noncoding RNAs May Also Regulate Mammalian Gene Activity 291
ESSENTIAL CONCEPTS 292
QUESTIONS 293



CHAPTER 9
How Genes and Genomes Evolve 297
GENERATING GENETIC VARIATION 298
In Sexually Reproducing Organisms, Only Changes to the Germ Line Are Passed On to Progeny 299
Point Mutations Are Caused by Failures of the Normal Mechanisms for Copying and Repairing DNA 300
Mutations Can Also Change the Regulation of a Gene 302
DNA Duplications Give Rise to Families of Related Genes 302
Duplication and Divergence Produced the Globin Gene Family 304
Whole-Genome Duplications Have Shaped the Evolutionary History of Many Species 306
Novel Genes Can Be Created by Exon Shuffling 306
The Evolution of Genomes Has Been Profoundly Influenced by Mobile Genetic Elements 307
Genes Can Be Exchanged Between Organisms by Horizontal Gene Transfer 308
RECONSTRUCTING LIFE'S FAMILY TREE 309
Genetic Changes That Provide a Selective Advantage Are Likely to Be Preserved 309
Closely Related Organisms Have Genomes That Are Similar in Organization as Well as Sequence 310
Functionally Important Genome Regions Show Up as Islands of Conserved DNA Sequence 310
Genome Comparisons Show That Vertebrate Genomes Gain and Lose DNA Rapidly 313
Sequence Conservation Allows Us to Trace Even the Most Distant Evolutionary Relationships 313
MOBILE GENETIC ELEMENTS AND VIRUSES 315
Mobile Genetic Elements Encode the Components They Need for Movement 315
The Human Genome Contains Two Major Families of Transposable Sequences 316
Viruses Can Move Between Cells and Organisms 317
Retroviruses Reverse the Normal Flow of Genetic Information 318
EXAMINING THE HUMAN GENOME 320
The Nucleotide Sequences of Human Genomes Show How Our Genes Are Arranged 321
Differences in Gene Regulation May Help Explain How Animals with Similar Genomes Can Be So Different 323
The Genome of Extinct Neanderthals Reveals Much about What Makes Us Human 326
Genome Variation Contributes to Our Individuality—But How? 327
ESSENTIAL CONCEPTS 328
QUESTIONS 329

CHAPTER 10

Analyzing the Structure and Function of Genes 333

ISOLATING AND CLONING DNA MOLECULES 334

Restriction Enzymes Cut DNA Molecules at Specific Sites 335
Gel Electrophoresis Separates DNA Fragments of Different Sizes 335
DNA Cloning Begins with the Production of Recombinant DNA 337
Recombinant DNA Can Be Copied Inside Bacterial Cells 337
An Entire Genome Can Be Represented in a DNA Library 339
Hybridization Provides a Sensitive Way to Detect Specific Nucleotide Sequences 340

DNA CLONING BY PCR 341

PCR Uses DNA Polymerase and Specific DNA Primers to Amplify DNA Sequences in a Test Tube 342
PCR Can Be Used for Diagnostic and Forensic Applications 343

SEQUENCING DNA 346

Dideoxy Sequencing Depends on the Analysis of DNA Chains Terminated at Every Position 346
Next-Generation Sequencing Techniques Make Genome Sequencing Faster and Cheaper 347
Comparative Genome Analyses Can Identify Genes and Predict Their Function 350

EXPLORING GENE FUNCTION 350

Analysis of mRNAs Provides a Snapshot of Gene Expression 351
In Situ Hybridization Can Reveal When and Where a Gene Is Expressed 352
Reporter Genes Allow Specific Proteins to Be Tracked in Living Cells 352
The Study of Mutants Can Help Reveal the Function of a Gene 354
RNA Interference (RNAi) Inhibits the Activity of Specific Genes 354
A Known Gene Can Be Deleted or Replaced with an Altered Version 355
Genes Can Be Edited with Great Precision Using the Bacterial CRISPR System 358
Mutant Organisms Provide Useful Models of Human Disease 359
Transgenic Plants Are Important for both Cell Biology and Agriculture 359
Even Rare Proteins Can Be Made in Large Amounts Using Cloned DNA 361

ESSENTIAL CONCEPTS 362

QUESTIONS 363

CHAPTER 11

Membrane Structure 365

THE LIPID BILAYER 367

Membrane Lipids Form Bilayers in Water 367

The Lipid Bilayer Is a Flexible Two-dimensional Fluid 370

The Fluidity of a Lipid Bilayer Depends on Its Composition 371

Membrane Assembly Begins in the ER 373

Certain Phospholipids Are Confined to One Side of the Membrane 373

MEMBRANE PROTEINS 375

Membrane Proteins Associate with the Lipid Bilayer in Different Ways 376

A Polypeptide Chain Usually Crosses the Lipid Bilayer as an α Helix 377

Membrane Proteins Can Be Solubilized in Detergents 378

We Know the Complete Structure of Relatively Few Membrane Proteins 379

The Plasma Membrane Is Reinforced by the Underlying Cell Cortex 380

A Cell Can Restrict the Movement of Its Membrane Proteins 381

The Cell Surface Is Coated with Carbohydrate 382

ESSENTIAL CONCEPTS 386

QUESTIONS 387

CHAPTER 12

Transport Across Cell Membranes 389

PRINCIPLES OF TRANSMEMBRANE TRANSPORT 390

Lipid Bilayers Are Impermeable to Ions and Most Uncharged Polar Molecules 390

The Ion Concentrations Inside a Cell Are Very Different from Those Outside 391

Differences in the Concentration of Inorganic Ions Across a Cell Membrane Create a Membrane Potential 391

Cells Contain Two Classes of Membrane Transport Proteins: Transporters and Channels 392

Solutes Cross Membranes by Either Passive or Active Transport 392

Both the Concentration Gradient and Membrane Potential Influence the Passive Transport of Charged Solutes 393

Water Moves Across Cell Membranes Down Its Concentration Gradient—a Process Called Osmosis 394

TRANSPORTERS AND THEIR FUNCTIONS 395

Passive Transporters Move a Solute Along Its Electrochemical Gradient 396

Pumps Actively Transport a Solute Against Its Electrochemical Gradient 396

The Na^+ Pump in Animal Cells Uses Energy Supplied by ATP to Expel Na^+ and Bring in K^+ 397

The Na^+ Pump Generates a Steep Concentration Gradient of Na^+ Across the Plasma Membrane 398

Ca^{2+} Pumps Keep the Cytosolic Ca^{2+} Concentration Low 399

Gradient-driven Pumps Exploit Solute Gradients to Mediate Active Transport 399

The Electrochemical Na^+ Gradient Drives the Transport of Glucose Across the Plasma Membrane of Animal Cells 400

Electrochemical H^+ Gradients Drive the Transport of Solutes in Plants, Fungi, and Bacteria 402

ION CHANNELS AND THE MEMBRANE POTENTIAL 403

Ion Channels Are Ion-selective and Gated 404

Membrane Potential Is Governed by the Permeability of a Membrane to Specific Ions 405

Ion Channels Randomly Snap Between Open and Closed States 407
Different Types of Stimuli Influence the Opening and Closing of Ion Channels 408
Voltage-gated Ion Channels Respond to the Membrane Potential 409
ION CHANNELS AND NERVE CELL SIGNALING 410
Action Potentials Allow Rapid Long-Distance Communication Along Axons 411
Action Potentials Are Mediated by Voltage-gated Cation Channels 411
Voltage-gated Ca^{2+} Channels in Nerve Terminals Convert an Electrical Signal into a Chemical Signal 416
Transmitter-gated Ion Channels in the Postsynaptic Membrane Convert the Chemical Signal Back into an Electrical Signal 417
Neurotransmitters Can Be Excitatory or Inhibitory 418
Most Psychoactive Drugs Affect Synaptic Signaling by Binding to Neurotransmitter Receptors 419
The Complexity of Synaptic Signaling Enables Us to Think, Act, Learn, and Remember 420
Light-gated Ion Channels Can Be Used to Transiently Activate or Inactivate Neurons in Living Animals 421
ESSENTIAL CONCEPTS 422
QUESTIONS 424

CHAPTER 13
How Cells Obtain Energy from Food 427
THE BREAKDOWN AND UTILIZATION OF SUGARS AND FATS 428
Food Molecules Are Broken Down in Three Stages 428
Glycolysis Extracts Energy from the Splitting of Sugar 430
Glycolysis Produces both ATP and NADH 431
Fermentations Can Produce ATP in the Absence of Oxygen 433
Glycolytic Enzymes Couple Oxidation to Energy Storage in Activated Carriers 434
Several Types of Organic Molecules Are Converted to Acetyl CoA in the Mitochondrial Matrix 438
The Citric Acid Cycle Generates NADH by Oxidizing Acetyl Groups to CO_2 438
Many Biosynthetic Pathways Begin with Glycolysis or the Citric Acid Cycle 441
Electron Transport Drives the Synthesis of the Majority of the ATP in Most Cells 446
REGULATION OF METABOLISM 447
Catabolic and Anabolic Reactions Are Organized and Regulated 447
Feedback Regulation Allows Cells to Switch from Glucose Breakdown to Glucose Synthesis 447
Cells Store Food Molecules in Special Reservoirs to Prepare for Periods of Need 449
ESSENTIAL CONCEPTS 451
QUESTIONS 452

CHAPTER 14

Energy Generation in Mitochondria and Chloroplasts 455

Cells Obtain Most of Their Energy by a Membrane-based Mechanism 456
Chemiosmotic Coupling Is an Ancient Process, Preserved in Present-Day Cells 457

MITOCHONDRIA AND OXIDATIVE PHOSPHORYLATION 459

Mitochondria Are Dynamic in Structure, Location, and Number 459
A Mitochondrion Contains an Outer Membrane, an Inner Membrane, and Two Internal Compartments 460
The Citric Acid Cycle Generates High-Energy Electrons Required for ATP Production 461
The Movement of Electrons Is Coupled to the Pumping of Protons 462
Electrons Pass Through Three Large Enzyme Complexes in the Inner Mitochondrial Membrane 464
Proton Pumping Produces a Steep Electrochemical Proton Gradient Across the Inner Mitochondrial Membrane 464
ATP Synthase Uses the Energy Stored in the Electrochemical Proton Gradient to Produce ATP 465
The Electrochemical Proton Gradient Also Drives Transport Across the Inner Mitochondrial Membrane 466
The Rapid Conversion of ADP to ATP in Mitochondria Maintains a High ATP/ADP Ratio in Cells 467
Cell Respiration Is Amazingly Efficient 468

MOLECULAR MECHANISMS OF ELECTRON TRANSPORT AND PROTON PUMPING 469

Protons Are Readily Moved by the Transfer of Electrons 469
The Redox Potential Is a Measure of Electron Affinities 470
Electron Transfers Release Large Amounts of Energy 471
Metals Tightly Bound to Proteins Form Versatile Electron Carriers 471
Cytochrome *c* Oxidase Catalyzes the Reduction of Molecular Oxygen 474

CHLOROPLASTS AND PHOTOSYNTHESIS 478

Chloroplasts Resemble Mitochondria but Have an Extra Compartment—the Thylakoid 478
Photosynthesis Generates—and Then Consumes—ATP and NADPH 479
Chlorophyll Molecules Absorb the Energy of Sunlight 480
Excited Chlorophyll Molecules Funnel Energy into a Reaction Center 481
A Pair of Photosystems Cooperate to Generate both ATP and NADPH 482
Oxygen Is Generated by a Water-Splitting Complex Associated with Photosystem II 483
The Special Pair in Photosystem I Receives its Electrons from Photosystem II 484
Carbon Fixation Uses ATP and NADPH to Convert CO_2 into Sugars 484
Sugars Generated by Carbon Fixation Can Be Stored as Starch or Consumed to Produce ATP 487

THE EVOLUTION OF ENERGY-GENERATING SYSTEMS 488

Oxidative Phosphorylation Evolved in Stages 488
Photosynthetic Bacteria Made Even Fewer Demands on Their Environment 489
The Lifestyle of *Methanococcus* Suggests That Chemiosmotic Coupling Is an Ancient Process 490

ESSENTIAL CONCEPTS 491

QUESTIONS 492

CHAPTER 15

Intracellular Compartments and Protein Transport 495

MEMBRANE-ENCLOSED ORGANELLES 496

Eukaryotic Cells Contain a Basic Set of Membrane-enclosed Organelles 496

Membrane-enclosed Organelles Evolved in Different Ways 499

PROTEIN SORTING 500

Proteins Are Transported into Organelles by Three Mechanisms 500

Signal Sequences Direct Proteins to the Correct Compartment 502

Proteins Enter the Nucleus Through Nuclear Pores 503

Proteins Unfold to Enter Mitochondria and Chloroplasts 505

Proteins Enter Peroxisomes from both the Cytosol and the Endoplasmic Reticulum 506

Proteins Enter the Endoplasmic Reticulum While Being Synthesized 507

Soluble Proteins Made on the ER Are Released into the ER Lumen 508

Start and Stop Signals Determine the Arrangement of a Transmembrane Protein in the Lipid Bilayer 509

VESICULAR TRANSPORT 511

Transport Vesicles Carry Soluble Proteins and Membrane Between Compartments 511

Vesicle Budding Is Driven by the Assembly of a Protein Coat 512

Vesicle Docking Depends on Tethers and SNAREs 514

SECRETORY PATHWAYS 515

Most Proteins Are Covalently Modified in the ER 516

Exit from the ER Is Controlled to Ensure Protein Quality 517

The Size of the ER Is Controlled by the Demand for Protein Folding 518

Proteins Are Further Modified and Sorted in the Golgi Apparatus 518

Secretory Proteins Are Released from the Cell by Exocytosis 519

ENDOCYTIC PATHWAYS 523

Specialized Phagocytic Cells Ingest Large Particles 523

Fluid and Macromolecules Are Taken Up by Pinocytosis 524

Receptor-mediated Endocytosis Provides a Specific Route into Animal Cells 525

Endocytosed Macromolecules Are Sorted in Endosomes 526

Lysosomes Are the Principal Sites of Intracellular Digestion 527

ESSENTIAL CONCEPTS 528

QUESTIONS 530

CHAPTER 16

Cell Signaling 533

GENERAL PRINCIPLES OF CELL SIGNALING 534

Signals Can Act over a Long or Short Range 534
A Limited Set of Extracellular Signals Can Produce a Huge Variety of Cell Behaviors 537
A Cell's Response to a Signal Can Be Fast or Slow 538
Cell-Surface Receptors Relay Extracellular Signals via Intracellular Signaling Pathways 539
Some Intracellular Signaling Proteins Act as Molecular Switches 541
Cell-Surface Receptors Fall into Three Main Classes 543
Ion-Channel-Coupled Receptors Convert Chemical Signals into Electrical Ones 544

G-PROTEIN-COUPLED RECEPTORS 545

Stimulation of GPCRs Activates G-Protein Subunits 545
Some Bacterial Toxins Cause Disease by Altering the Activity of G Proteins 547
Some G Proteins Directly Regulate Ion Channels 548
Many G Proteins Activate Membrane-bound Enzymes That Produce Small Messenger Molecules 549
The Cyclic AMP Signaling Pathway Can Activate Enzymes and Turn On Genes 549
The Inositol Phospholipid Pathway Triggers a Rise in Intracellular Ca^{2+} 552
A Ca^{2+} Signal Triggers Many Biological Processes 553
A GPCR Signaling Pathway Generates a Dissolved Gas That Carries a Signal to Adjacent Cells 554
GPCR-Triggered Intracellular Signaling Cascades Can Achieve Astonishing Speed, Sensitivity, and Adaptability 555

ENZYME-COUPLED RECEPTORS 557

Activated RTKs Recruit a Complex of Intracellular Signaling Proteins 558
Most RTKs Activate the Monomeric GTPase Ras 559
RTKs Activate PI 3-Kinase to Produce Lipid Docking Sites in the Plasma Membrane 560
Some Receptors Activate a Fast Track to the Nucleus 565
Some Extracellular Signal Molecules Cross the Plasma Membrane and Bind to Intracellular Receptors 565
Plants Make Use of Receptors and Signaling Strategies That Differ from Those Used by Animals 567
Protein Kinase Networks Integrate Information to Control Complex Cell Behaviors 567

ESSENTIAL CONCEPTS 569

QUESTIONS 571

CHAPTER 17

Cytoskeleton 573

INTERMEDIATE FILAMENTS 575

Intermediate Filaments Are Strong and Ropelike 575
Intermediate Filaments Strengthen Cells Against Mechanical Stress 577
The Nuclear Envelope Is Supported by a Meshwork of Intermediate Filaments 578
Linker Proteins Connect Cytoskeletal Filaments and Bridge the Nuclear Envelope 579

MICROTUBULES 580

Microtubules Are Hollow Tubes with Structurally Distinct Ends 581
The Centrosome Is the Major Microtubule-organizing Center in Animal Cells 581
Microtubules Display Dynamic Instability 582
Dynamic Instability Is Driven by GTP Hydrolysis 583
Microtubule Dynamics Can Be Modified by Drugs 584
Microtubules Organize the Cell Interior 584
Motor Proteins Drive Intracellular Transport 586
Microtubules and Motor Proteins Position Organelles in the Cytoplasm 587
Cilia and Flagella Contain Stable Microtubules Moved by Dynein 590

ACTIN FILAMENTS 592

Actin Filaments Are Thin and Flexible 593
Actin and Tubulin Polymerize by Similar Mechanisms 593
Many Proteins Bind to Actin and Modify Its Properties 594
A Cortex Rich in Actin Filaments Underlies the Plasma Membrane of Most Eukaryotic Cells 596
Cell Crawling Depends on Cortical Actin 596
Actin-binding Proteins Influence the Type of Protrusions Formed at the Leading Edge 598
Extracellular Signals Can Alter the Arrangement of Actin Filaments 598
Actin Associates with Myosin to Form Contractile Structures 599

MUSCLE CONTRACTION 600

Muscle Contraction Depends on Interacting Filaments of Actin and Myosin 600
Actin Filaments Slide Against Myosin Filaments During Muscle Contraction 601
Muscle Contraction Is Triggered by a Sudden Rise in Cytosolic Ca^{2+} 604
Different Types of Muscle Cells Perform Different Functions 605

ESSENTIAL CONCEPTS 606

QUESTIONS 607

CHAPTER 18

The Cell-Division Cycle 609

OVERVIEW OF THE CELL CYCLE 610

The Eukaryotic Cell Cycle Usually Includes Four Phases 611
A Cell-Cycle Control System Triggers the Major Processes of the Cell Cycle 612
Cell-Cycle Control Is Similar in All Eukaryotes 613

THE CELL-CYCLE CONTROL SYSTEM 613

The Cell-Cycle Control System Depends on Cyclically Activated Protein Kinases Called Cdks 613
Different Cyclin–Cdk Complexes Trigger Different Steps in the Cell Cycle 614
Cyclin Concentrations Are Regulated by Transcription and by Proteolysis 617
The Activity of Cyclin–Cdk Complexes Depends on Phosphorylation and Dephosphorylation 618
Cdk Activity Can Be Blocked by Cdk Inhibitor Proteins 618
The Cell-Cycle Control System Can Pause the Cycle in Various Ways 618

G_1 PHASE 620

Cdks Are Stably Inactivated in G_1 620
Mitogens Promote the Production of the Cyclins That Stimulate Cell Division 620
DNA Damage Can Temporarily Halt Progression Through G_1 621
Cells Can Delay Division for Prolonged Periods by Entering Specialized Nondividing States 621

S PHASE 623

S-Cdk Initiates DNA Replication and Blocks Re-Replication 623
Incomplete Replication Can Arrest the Cell Cycle in G_2 623

M PHASE 624

M-Cdk Drives Entry into Mitosis 625
Cohesins and Condensins Help Configure Duplicated Chromosomes for Separation 625
Different Cytoskeletal Assemblies Carry Out Mitosis and Cytokinesis 626
M Phase Occurs in Stages 627

MITOSIS 627

Centrosomes Duplicate to Help Form the Two Poles of the Mitotic Spindle 627
The Mitotic Spindle Starts to Assemble in Prophase 630
Chromosomes Attach to the Mitotic Spindle at Prometaphase 630
Chromosomes Assist in the Assembly of the Mitotic Spindle 632
Chromosomes Line Up at the Spindle Equator at Metaphase 632
Proteolysis Triggers Sister-Chromatid Separation at Anaphase 633
Chromosomes Segregate During Anaphase 634
An Unattached Chromosome Will Prevent Sister-Chromatid Separation 634
The Nuclear Envelope Re-forms at Telophase 635

CYTOKINESIS 636

The Mitotic Spindle Determines the Plane of Cytoplasmic Cleavage 636
The Contractile Ring of Animal Cells Is Made of Actin and Myosin Filaments 637
Cytokinesis in Plant Cells Involves the Formation of a New Cell Wall 638
Membrane-enclosed Organelles Must Be Distributed to Daughter Cells When a Cell Divides 638

CONTROL OF CELL NUMBERS AND CELL SIZE 639
Apoptosis Helps Regulate Animal Cell Numbers 640
Apoptosis Is Mediated by an Intracellular Proteolytic Cascade 640
The Intrinsic Apoptotic Death Program Is Regulated by the Bcl2 Family of Intracellular Proteins 642
Apoptotic Signals Can Also Come from Other Cells 642
Animal Cells Require Extracellular Signals to Survive, Grow, and Divide 642
Survival Factors Suppress Apoptosis 643
Mitogens Stimulate Cell Division by Promoting Entry into S Phase 644
Growth Factors Stimulate Cells to Grow 644
Some Extracellular Signal Proteins Inhibit Cell Survival, Division, or Growth 645
ESSENTIAL CONCEPTS 646
QUESTIONS 648

CHAPTER 19
Sexual Reproduction and Genetics 651
THE BENEFITS OF SEX 652
Sexual Reproduction Involves both Diploid and Haploid Cells 652
Sexual Reproduction Generates Genetic Diversity 653
Sexual Reproduction Gives Organisms a Competitive Advantage in a Changing Environment 654
MEIOSIS AND FERTILIZATION 654
Meiosis Involves One Round of DNA Replication Followed by Two Rounds of Nuclear Division 655
Duplicated Homologous Chromosomes Pair During Meiotic Prophase 657
Crossing-Over Occurs Between the Duplicated Maternal and Paternal Chromosomes in Each Bivalent 657
Chromosome Pairing and Crossing-Over Ensure the Proper Segregation of Homologs 659
The Second Meiotic Division Produces Haploid Daughter Nuclei 660
Haploid Gametes Contain Reassorted Genetic Information 660
Meiosis Is Not Flawless 662
Fertilization Reconstitutes a Complete Diploid Genome 663
MENDEL AND THE LAWS OF INHERITANCE 664
Mendel Studied Traits That Are Inherited in a Discrete Fashion 664
Mendel Disproved the Alternative Theories of Inheritance 664
Mendel's Experiments Revealed the Existence of Dominant and Recessive Alleles 665
Each Gamete Carries a Single Allele for Each Character 666
Mendel's Law of Segregation Applies to All Sexually Reproducing Organisms 667
Alleles for Different Traits Segregate Independently 668
The Behavior of Chromosomes During Meiosis Underlies Mendel's Laws of Inheritance 669
Genes That Lie on the Same Chromosome Can Segregate Independently by Crossing-Over 671
Mutations in Genes Can Cause a Loss of Function or a Gain of Function 672
Each of Us Carries Many Potentially Harmful Recessive Mutations 673

GENETICS AS AN EXPERIMENTAL TOOL 674
The Classical Genetic Approach Begins with Random Mutagenesis 674
Genetic Screens Identify Mutants Deficient in Specific Cell Processes 676
Conditional Mutants Permit the Study of Lethal Mutations 676
A Complementation Test Reveals Whether Two Mutations Are in the Same Gene 678
EXPLORING HUMAN GENETICS 678
Linked Blocks of Polymorphisms Have Been Passed Down from Our Ancestors 679
Polymorphisms Provide Clues to Our Evolutionary History 679
Genetic Studies Aid in the Search for the Causes of Human Diseases 680
Many Severe, Rare Human Diseases Are Caused by Mutations in Single Genes 681
Common Human Diseases Are Often Influenced by Multiple Mutations and Environmental Factors 682
Genome-wide Association Studies Can Aid the Search for Mutations Associated with Disease 683
We Still Have Much to Learn about the Genetic Basis of Human Variation and Disease 686
ESSENTIAL CONCEPTS 687
QUESTIONS 688

CHAPTER 20

Cell Communities: Tissues, Stem Cells, and Cancer 691

EXTRACELLULAR MATRIX AND CONNECTIVE TISSUES 692
Plant Cells Have Tough External Walls 693
Cellulose Microfibrils Give the Plant Cell Wall Its Tensile Strength 694
Animal Connective Tissues Consist Largely of Extracellular Matrix 695
Collagen Provides Tensile Strength in Animal Connective Tissues 696
Cells Organize the Collagen They Secrete 697
Integrins Couple the Matrix Outside a Cell to the Cytoskeleton Inside It 698
Gels of Polysaccharides and Proteins Fill Spaces and Resist Compression 700
EPITHELIAL SHEETS AND CELL JUNCTIONS 701
Epithelial Sheets Are Polarized and Rest on a Basal Lamina 702
Tight Junctions Make an Epithelium Leakproof and Separate Its Apical and Basolateral Surfaces 703
Cytoskeleton-linked Junctions Bind Epithelial Cells Robustly to One Another and to the Basal Lamina 704
Gap Junctions Allow Cytosolic Inorganic Ions and Small Molecules to Pass from Cell to Cell 707
STEM CELLS AND TISSUE RENEWAL 709
Tissues Are Organized Mixtures of Many Cell Types 710
Different Tissues Are Renewed at Different Rates 711
Stem Cells and Proliferating Precursor Cells Generate a Continuous Supply of Terminally Differentiated Cells 712
Specific Signals Maintain Stem-Cell Populations 714
Stem Cells Can Be Used to Repair Lost or Damaged Tissues 715
Induced Pluripotent Stem Cells Provide a Convenient Source of Human ES-like Cells 716
Mouse and Human Pluripotent Stem Cells Can Form Organoids in Culture 717

CANCER 718
Cancer Cells Proliferate Excessively and Migrate Inappropriately 718
Epidemiological Studies Identify Preventable Causes of Cancer 719
Cancers Develop by an Accumulation of Somatic Mutations 720
Cancer Cells Evolve, Acquiring an Increasing Competitive Advantage 721
Two Main Classes of Genes Are Critical for Cancer: Oncogenes and Tumor Suppressor Genes 723
Cancer-critical Mutations Cluster in a Few Fundamental Pathways 725
Colorectal Cancer Illustrates How Loss of a Tumor Suppressor Gene Can Lead to Cancer 726
An Understanding of Cancer Cell Biology Opens the Way to New Treatments 727
ESSENTIAL CONCEPTS 729
QUESTIONS 733

ANSWERS A:1
GLOSSARY G:1
INDEX I:1

CHAPTER **ONE** 1

Cells: The Fundamental Units of Life

What does it mean to be living? Petunias, people, and pond scum are all alive; stones, sand, and summer breezes are not. But what are the fundamental properties that characterize living things and distinguish them from nonliving matter?

The answer hinges on a basic fact that is taken for granted now but marked a revolution in thinking when first established more than 175 years ago. All living things (or *organisms*) are built from **cells**: small, membrane-enclosed units filled with a concentrated aqueous solution of chemicals and endowed with the extraordinary ability to create copies of themselves by growing and then dividing in two. The simplest forms of life are solitary cells. Higher organisms, including ourselves, are communities of cells derived by growth and division from a single founder cell. Every animal or plant is a vast colony of individual cells, each of which performs a specialized function that is integrated by intricate systems of cell-to-cell communication.

Cells, therefore, are the fundamental units of life. Thus it is to *cell biology*—the study of cells and their structure, function, and behavior—that we look for an answer to the question of what life is and how it works. With a deeper understanding of cells, we can begin to tackle the grand historical problems of life on Earth: its mysterious origins, its stunning diversity produced by billions of years of evolution, and its invasion of every conceivable habitat on the planet. At the same time, cell biology can provide us with answers to the questions we have about ourselves: Where did we come from? How do we develop from a single fertilized egg cell? How is each of us similar to—yet different from—everyone else on Earth? Why do we get sick, grow old, and die?

UNITY AND DIVERSITY OF CELLS

CELLS UNDER THE MICROSCOPE

THE PROKARYOTIC CELL

THE EUKARYOTIC CELL

MODEL ORGANISMS

In this chapter, we introduce the concept of cells: what they are, where they come from, and how we have learned so much about them. We begin by looking at the great variety of forms that cells can adopt, and we take a preliminary glimpse at the chemical machinery that all cells have in common. We then consider how cells are made visible under the microscope and what we see when we peer inside them. Finally, we discuss how we can exploit the similarities of living things to achieve a coherent understanding of all forms of life on Earth—from the tiniest bacterium to the mightiest oak.

UNITY AND DIVERSITY OF CELLS

Biologists estimate that there may be up to 100 million distinct species of living things on our planet—organisms as different as a dolphin and a rose or a bacterium and a butterfly. Cells, too, differ vastly in form and function. Animal cells differ from those in a plant, and even cells within a single multicellular organism can differ wildly in appearance and activity. Yet despite these differences, all cells share a fundamental chemistry and other common features.

In this section, we take stock of some of the similarities and differences among cells, and we discuss how all present-day cells appear to have evolved from a common ancestor.

Cells Vary Enormously in Appearance and Function

When comparing one cell and another, one of the most obvious places to start is with size. A bacterial cell—say a *Lactobacillus* in a piece of cheese—is a few **micrometers**, or μm, in length. That's about 25 times smaller than the width of a human hair. At the other extreme, a frog egg—which is also a single cell—has a diameter of about 1 millimeter (mm). If we scaled them up to make the *Lactobacillus* the size of a person, the frog egg would be half a mile high.

Cells vary just as widely in their shape (**Figure 1–1**). A typical nerve cell in your brain, for example, is enormously extended: it sends out its electrical signals along a single, fine protrusion (an axon) that is 10,000 times longer than it is thick, and the cell receives signals from other nerve cells through a collection of shorter extensions that sprout from its body like the branches of a tree (see Figure 1–1A). A pond-dwelling *Paramecium*, on the other hand, is shaped like a submarine and is covered with thousands of *cilia*—hairlike projections whose sinuous, coordinated beating sweeps the cell forward, rotating as it goes (Figure 1–1B). A cell in the surface layer of a plant is squat and immobile, surrounded by a rigid box of cellulose with an outer waterproof coating of wax (Figure 1–1C). A macrophage in the body of an animal, by contrast, crawls through tissues, constantly pouring itself into new shapes, as it searches for and engulfs debris, foreign microorganisms, and dead or dying cells (Figure 1–1D). A fission yeast is shaped like a rod (Figure 1–1E), whereas a budding yeast is delightfully spherical (see Figure 1–14). And so on.

Cells are also enormously diverse in their chemical requirements. Some require oxygen to live; for others the gas is deadly. Some cells consume little more than carbon dioxide (CO_2), sunlight, and water as their raw materials; others need a complex mixture of molecules produced by other cells.

These differences in size, shape, and chemical requirements often reflect differences in cell function. Some cells are specialized factories for the production of particular substances, such as hormones, starch, fat, latex, or pigments. Others, like muscle cells, are engines that burn fuel to do

mechanical work. Still others are electricity generators, like the modified muscle cells in the electric eel.

Some modifications specialize a cell so much that the cell ceases to proliferate, thus producing no descendants. Such specialization would be senseless for a cell that lived a solitary life. In a multicellular organism, however, there is a division of labor among cells, allowing some cells to become specialized to an extreme degree for particular tasks and leaving them dependent on their fellow cells for many basic requirements. Even the most basic need of all, that of passing on the genetic instructions of the organism to the next generation, is delegated to specialists—the egg and the sperm.

Living Cells All Have a Similar Basic Chemistry

Despite the extraordinary diversity of plants and animals, people have recognized from time immemorial that these organisms have something in common, something that entitles them all to be called living things. But while it seemed easy enough to recognize life, it was remarkably difficult to say in what sense all living things were alike. Textbooks had to settle for defining life in abstract general terms related to growth, reproduction, and an ability to actively alter their behavior in response to the environment.

The discoveries of biochemists and molecular biologists have provided an elegant solution to this awkward situation. Although the cells of all living things are enormously varied when viewed from the outside, they are fundamentally similar inside. We now know that cells resemble one another to an astonishing degree in the details of their chemistry. They are composed of the same sorts of molecules, which participate in the same types of chemical reactions (discussed in Chapter 2). In all organisms, genetic information—in the form of *genes*—is carried in DNA molecules. This information is written in the same chemical code, constructed out of the same chemical building blocks, interpreted by essentially the same chemical machinery, and replicated in the same way when a cell or

QUESTION 1–1

"Life" is easy to recognize but difficult to define. According to one popular biology text, living things:
1. Are highly organized compared to natural inanimate objects.
2. Display homeostasis, maintaining a relatively constant internal environment.
3. Reproduce themselves.
4. Grow and develop from simple beginnings.
5. Take energy and matter from the environment and transform it.
6. Respond to stimuli.
7. Show adaptation to their environment.

Score a person, a vacuum cleaner, and a potato with respect to these characteristics.

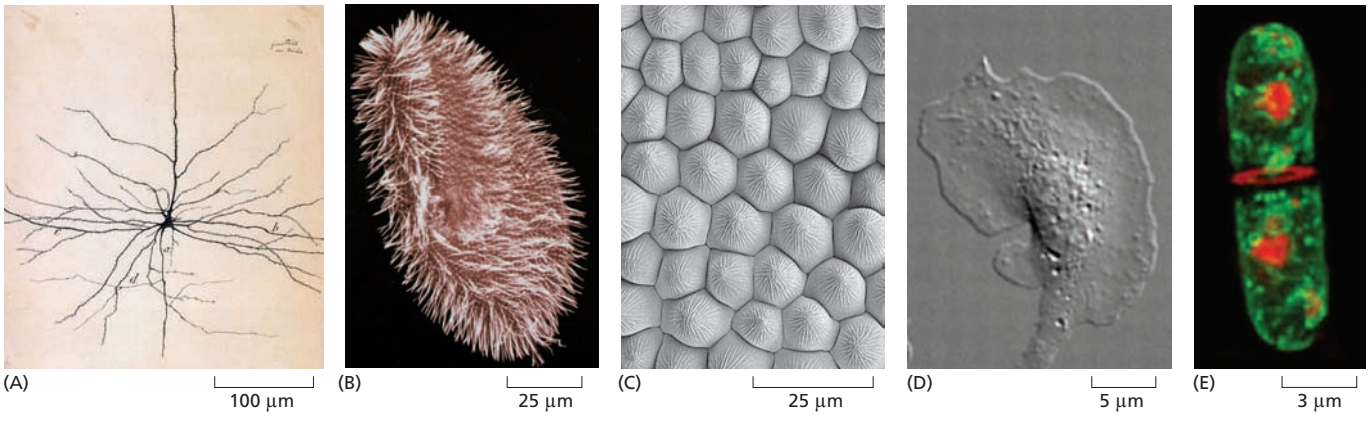


Figure 1–1 Cells come in a variety of shapes and sizes. Note the very different scales of these micrographs. (A) Drawing of a single nerve cell from a mammalian brain. This cell has a single, unbranched extension (axon), projecting toward the top of the image, through which it sends electrical signals to other nerve cells, and it possesses a huge branching tree of projections (dendrites) through which it receives signals from as many as 100,000 other nerve cells. (B) *Paramecium.* This protozoan—a single giant cell—swims by means of the beating cilia that cover its surface. (C) The surface of a snapdragon flower petal displays an orderly array of tightly packed cells. (D) A macrophage spreads itself out as it patrols animal tissues in search of invading microorganisms. (E) A fission yeast is caught in the act of dividing in two. The medial septum (stained *red* with a fluorescent dye) is forming a wall between the two nuclei (also stained *red*) that have been separated into the two daughter cells; in this image, the cells' membranes are stained with a *green* fluorescent dye. (A, Herederos de Santiago Ramón y Cajal, 1899; B, courtesy of Anne Aubusson Fleury, Michel Laurent, and André Adoutte; C, courtesy of Kim Findlay; D, from P.J. Hanley et al., *Proc. Natl Acad. Sci. USA* 107:12145–12150, 2010. With permission from National Academy of Sciences; E, courtesy of Janos Demeter and Shelley Sazer.)

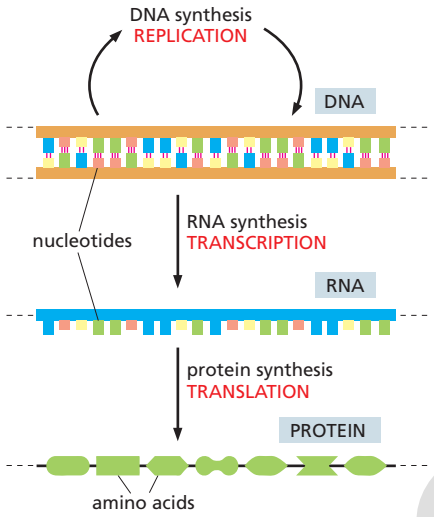


Figure 1–2 In all living cells, genetic information flows from DNA to RNA (transcription) and from RNA to protein (translation)—an arrangement known as the central dogma. The sequence of nucleotides in a particular segment of DNA (a gene) is transcribed into an RNA molecule, which can then be translated into the linear sequence of amino acids of a protein. Only a small part of the gene, RNA, and protein is shown.

organism reproduces. Thus, in every cell, long polymer chains of **DNA** are made from the same set of four monomers, called *nucleotides*, strung together in different sequences like the letters of an alphabet. The information encoded in these DNA molecules is read out, or *transcribed*, into a related set of polynucleotides called **RNA**. Although some of these RNA molecules have their own regulatory, structural, or chemical activities, most are *translated* into a different type of polymer called a **protein**. This flow of information—from DNA to RNA to protein—is so fundamental to life that it is referred to as the *central dogma* (**Figure 1–2**).

The appearance and behavior of a cell are dictated largely by its protein molecules, which serve as structural supports, chemical catalysts, molecular motors, and much more. Proteins are built from *amino acids*, and all organisms use the same set of 20 amino acids to make their proteins. But the amino acids are linked in different sequences, giving each type of protein molecule a different three-dimensional shape, or *conformation*, just as different sequences of letters spell different words. In this way, the same basic biochemical machinery has served to generate the whole gamut of life on Earth (**Figure 1–3**).

Living Cells Are Self-Replicating Collections of Catalysts

One of the most commonly cited properties of living things is their ability to reproduce. For cells, the process involves duplicating their genetic material and other components and then dividing in two—producing a pair of daughter cells that are themselves capable of undergoing the same cycle of replication.

It is the special relationship between DNA, RNA, and proteins—as outlined in the central dogma (see Figure 1–2)—that makes this self-replication possible. DNA encodes information that ultimately directs the assembly of proteins: the sequence of nucleotides in a molecule of DNA dictates the sequence of amino acids in a protein. Proteins, in turn, catalyze the replication of DNA and the transcription of RNA, and they participate in the translation of RNA into proteins. This feedback loop between proteins and polynucleotides underlies the self-reproducing behavior of living things (**Figure 1–4**). We discuss this complex interdependence between DNA, RNA, and proteins in detail in Chapters 5 through 8.

In addition to their roles in polynucleotide and protein synthesis, proteins also catalyze the many other chemical reactions that keep the self-replicating system shown in Figure 1–4 running. A living cell can break down

Figure 1–3 All living organisms are constructed from cells. (A) A colony of bacteria, (B) a butterfly, (C) a rose, and (D) a dolphin are all made of cells that have a fundamentally similar chemistry and operate according to the same basic principles. (A, courtesy of Janice Carr; D, courtesy of Jonathan Gordon, IFAW.)

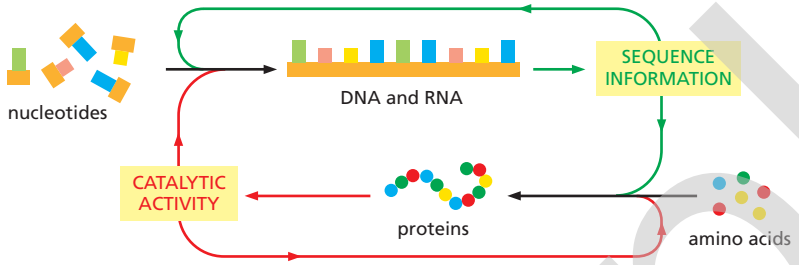


Figure 1–4 Life is an autocatalytic process. DNA and RNA provide the sequence information (*green* arrows) that is used to produce proteins and to copy themselves. Proteins, in turn, provide the catalytic activity (*red* arrows) needed to synthesize DNA, RNA, and themselves. Together, these feedback loops create the self-replicating system that endows living cells with their ability to reproduce.

nutrients and use the products to both make the building blocks needed to produce polynucleotides, proteins, and other cell constituents and to generate the energy needed to power these biosynthetic processes. We discuss these vital metabolic reactions in detail in Chapters 3 and 13.

Only living cells can perform these astonishing feats of self-replication. Viruses also contain information in the form of DNA or RNA, but they do not have the ability to reproduce by their own efforts. Instead, they parasitize the reproductive machinery of the cells that they invade to make copies of themselves. Thus, viruses are not truly considered living. They are merely chemical zombies: inert and inactive outside their host cells but able to exert a malign control once they gain entry. We review the life cycle of viruses in Chapter 9.

All Living Cells Have Apparently Evolved from the Same Ancestral Cell

When a cell replicates its DNA in preparation for cell division, the copying is not always perfect. On occasion, the instructions are corrupted by *mutations* that change the sequence of nucleotides in the DNA. For this reason, daughter cells are not necessarily exact replicas of their parent.

Mutations can create offspring that are changed for the worse (in that they are less able to survive and reproduce), changed for the better (in that they are better able to survive and reproduce), or changed in a neutral way (in that they are genetically different but equally viable). The struggle for survival eliminates the first, favors the second, and tolerates the third. The genes of the next generation will be the genes of the survivors.

For many organisms, the pattern of heredity may be complicated by sexual reproduction, in which two cells of the same species fuse, pooling their DNA. The genetic cards are then shuffled, re-dealt, and distributed in new combinations to the next generation, to be tested again for their ability to promote survival and reproduction.

These simple principles of genetic change and selection, applied repeatedly over billions of cell generations, are the basis of **evolution**—the process by which living species become gradually modified and adapted to their environment in more and more sophisticated ways. Evolution offers a startling but compelling explanation of why present-day cells are so similar in their fundamentals: they have all inherited their genetic instructions from the same common ancestral cell. It is estimated that this cell existed between 3.5 and 3.8 billion years ago, and we must suppose that it contained a prototype of the universal machinery of all life on Earth today. Through a very long process of mutation and natural selection, the descendants of this ancestral cell have gradually diverged to fill every habitat on Earth with organisms that exploit the potential of the machinery in a seemingly endless variety of ways.

QUESTION 1–2

Mutations are mistakes in the DNA that change the genetic plan from that of the previous generation. Imagine a shoe factory. Would you expect mistakes (i.e., unintentional changes) in copying the shoe design to lead to improvements in the shoes produced? Explain your answer.

Genes Provide Instructions for the Form, Function, and Behavior of Cells and Organisms

A cell's **genome**—that is, the entire sequence of nucleotides in an organism's DNA—provides a genetic program that instructs a cell how to behave. For the cells of plant and animal embryos, the genome directs the growth and development of an adult organism with hundreds of different cell types. Within an individual plant or animal, these cells can be extraordinarily varied, as we discuss in detail in Chapter 20. Fat cells, skin cells, bone cells, and nerve cells seem as dissimilar as any cells could be. Yet all these *differentiated cell types* are generated during embryonic development from a single fertilized egg cell, and they contain identical copies of the DNA of the species. Their varied characters stem from the way that individual cells use their genetic instructions. Different cells *express* different genes: that is, they use their genes to produce some RNAs and proteins and not others, depending on their internal state and on cues that they and their ancestor cells have received from their surroundings—mainly signals from other cells in the organism.

The DNA, therefore, is not just a shopping list specifying the molecules that every cell must make, and a cell is not just an assembly of all the items on the list. Each cell is capable of carrying out a variety of biological tasks, depending on its environment and its history, and it selectively uses the information encoded in its DNA to guide its activities. Later in this book, we will see in detail how DNA defines both the parts list of the cell and the rules that decide when and where these parts are to be made.

CELLS UNDER THE MICROSCOPE

Today, we have access to many powerful technologies for deciphering the principles that govern the structure and activity of the cell. But cell biology started without these modern tools. The earliest cell biologists began by simply looking at tissues and cells, and later breaking them open or slicing them up, attempting to view their contents. What they saw was to them profoundly baffling—a collection of tiny objects whose relationship to the properties of living matter seemed an impenetrable mystery. Nevertheless, this type of visual investigation was the first step toward understanding tissues and cells, and it remains essential today in the study of cell biology.

Cells were not made visible until the seventeenth century, when the **microscope** was invented. For hundreds of years afterward, all that was known about cells was discovered using this instrument. *Light microscopes* use visible light to illuminate specimens, and they allowed biologists to see for the first time the intricate structure that underpins all living things.

Although these instruments now incorporate many sophisticated improvements, the properties of light—specifically its wavelength—limit the fineness of detail these microscopes reveal. *Electron microscopes*, invented in the 1930s, go beyond this limit by using beams of electrons instead of beams of light as the source of illumination; because electrons have a much shorter wavelength, these instruments greatly extend our ability to see the fine details of cells and even render some of the larger molecules visible individually.

In this section, we describe various forms of light and electron microscopy. These vital tools in the modern cell biology laboratory continue to improve, revealing new and sometimes surprising details about how cells are built and how they operate.

The Invention of the Light Microscope Led to the Discovery of Cells

By the seventeenth century, glass lenses were powerful enough to permit the detection of structures invisible to the naked eye. Using an instrument equipped with such a lens, Robert Hooke examined a piece of cork and in 1665 reported to the Royal Society of London that the cork was composed of a mass of minute chambers. He called these chambers "cells," based on their resemblance to the simple rooms occupied by monks in a monastery. The name stuck, even though the structures Hooke described were actually the cell walls that remained after the plant cells living inside them had died. Later, Hooke and his Dutch contemporary Antoni van Leeuwenhoek were able to observe living cells, seeing for the first time a world teeming with motile microscopic organisms.

For almost 200 years, such instruments—the first light microscopes—remained exotic devices, available only to a few wealthy individuals. It was not until the nineteenth century that microscopes began to be widely used to look at cells. The emergence of cell biology as a distinct science was a gradual process to which many individuals contributed, but its official birth is generally said to have been signaled by two publications: one by the botanist Matthias Schleiden in 1838 and the other by the zoologist Theodor Schwann in 1839. In these papers, Schleiden and Schwann documented the results of a systematic investigation of plant and animal tissues with the light microscope, showing that cells were the universal building blocks of all living tissues. Their work, and that of other nineteenth-century microscopists, slowly led to the realization that all living cells are formed by the growth and division of existing cells—a principle sometimes referred to as the *cell theory* (**Figure 1–5**). The implication that living organisms do not arise spontaneously but can be generated only from existing organisms was hotly contested, but it was finally confirmed

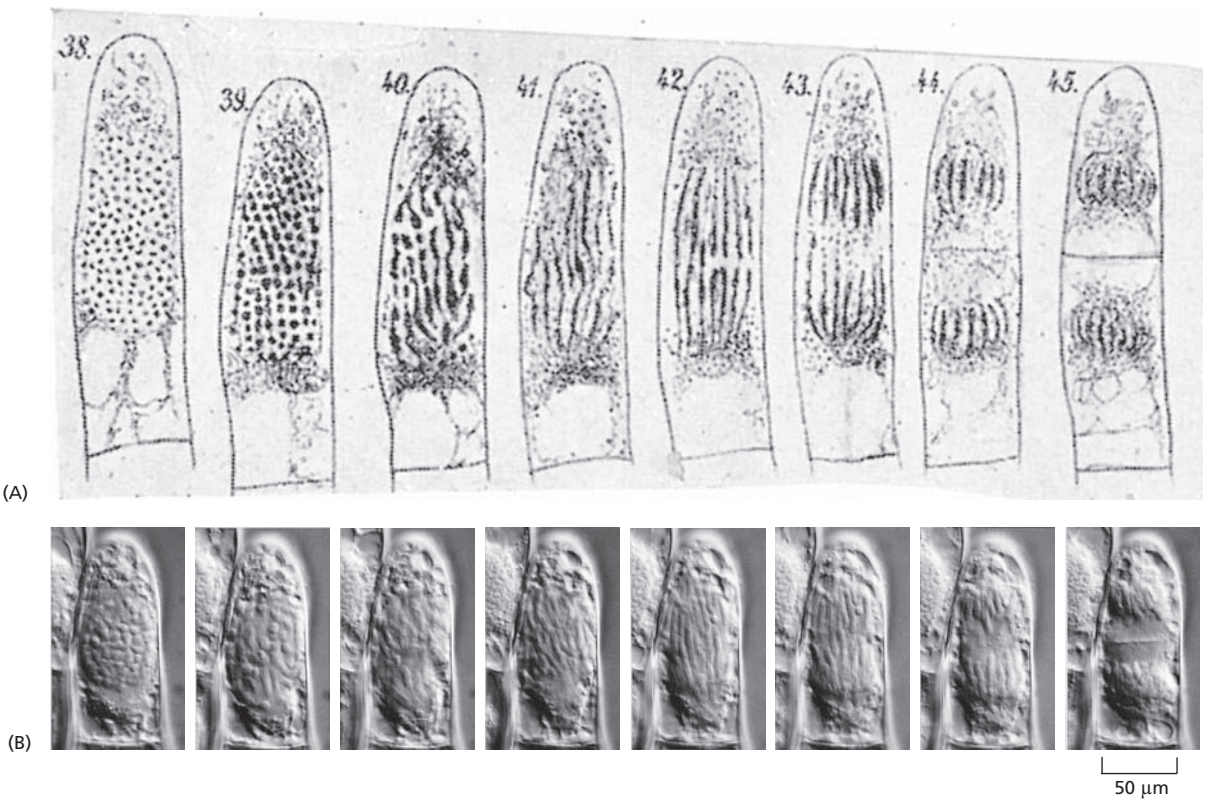


Figure 1–5 New cells form by growth and division of existing cells. (A) In 1880, Eduard Strasburger drew a living plant cell (a hair cell from a *Tradescantia* flower), which he observed dividing in two over a period of 2.5 hours. Inside the cell, DNA (*black*) can be seen condensing into chromosomes, which are then segregated into the two daughter cells. (B) A comparable living plant cell photographed through a modern light microscope. (B, from P.K. Hepler, *J. Cell Biol.* 100:1363–1368, 1985. With permission from Rockefeller University Press.)

in the 1860s by an elegant set of experiments performed by Louis Pasteur (see Question 1–3).

The principle that cells are generated only from preexisting cells and inherit their characteristics from them underlies all of biology and gives the subject a unique flavor: in biology, questions about the present are inescapably linked to conditions in the past. To understand why present-day cells and organisms behave as they do, we need to understand their history, all the way back to the misty origins of the first cells on Earth. Charles Darwin provided the key insight that makes this history comprehensible. His theory of evolution, published in 1859, explains how random variation and natural selection gave rise to diversity among organisms that share a common ancestry. When combined with the cell theory, the theory of evolution leads us to view all life, from its beginnings to the present day, as one vast family tree of individual cells. Although this book is primarily about how cells work today, we will encounter the theme of evolution again and again.

QUESTION 1–3

You have embarked on an ambitious research project: to create life in a test tube. You boil up a rich mixture of yeast extract and amino acids in a flask, along with a sprinkling of the inorganic salts known to be essential for life. You seal the flask and allow it to cool. After several months, the liquid is as clear as ever, and there are no signs of life. A friend suggests that excluding the air was a mistake, since most life as we know it requires oxygen. You repeat the experiment, but this time you leave the flask open to the atmosphere. To your great delight, the liquid becomes cloudy after a few days, and, under the microscope, you see beautiful small cells that are clearly growing and dividing. Does this experiment prove that you managed to generate a novel life-form? How might you redesign your experiment to allow air into the flask, yet eliminate the possibility that contamination by airborne microorganisms is the explanation for the results? (For a ready-made answer, look up the classic experiments of Louis Pasteur.)

Light Microscopes Reveal Some of a Cell's Components

If a very thin slice is cut from a suitable plant or animal tissue and viewed using a light microscope, it is immediately apparent that the tissue is divided into thousands of small cells. In some cases, the cells are closely packed; in others, they are separated from one another by an *extracellular matrix*—a dense material often made of protein fibers embedded in a gel of long sugar chains. Each cell is typically about 5–20 μm in diameter. If care has been taken to keep the specimen alive, particles will be seen moving around inside its individual cells. On occasion, a cell may even be seen slowly changing shape and dividing into two (see Figure 1–5 and **Movie 1.1**).

Distinguishing the internal structure of a cell is difficult, not only because the parts are small, but also because they are transparent and mostly colorless. One way around the problem is to stain cells with dyes that color particular components differently (**Figure 1–6**). Alternatively, one can exploit the fact that cell components differ slightly from one another in refractive index, just as glass differs in refractive index from water, causing light rays to be deflected as they pass from the one medium into

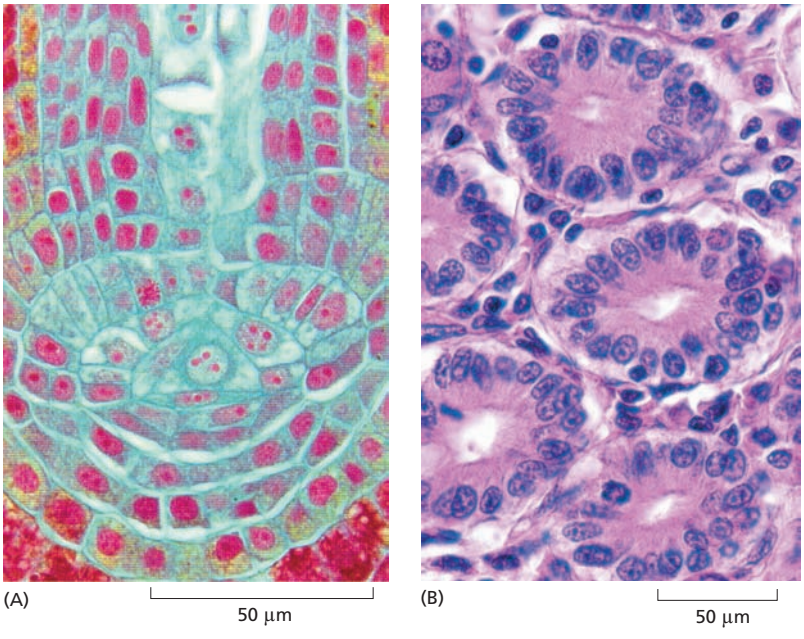


Figure 1–6 Cells form tissues in plants and animals. (A) Cells in the root tip of a fern. The DNA-containing nuclei are stained *red*, and each cell is surrounded by a thin cell wall (*light blue*). The *red* nuclei of densely packed cells are seen at the bottom corners of the preparation. (B) Cells in the crypts of the small intestine. Each crypt appears in this cross section as a ring of closely packed cells (with nuclei stained *blue*). The ring is surrounded by extracellular matrix, which contains the scattered cells that produced most of the matrix components. (A, courtesy of James Mauseth; B, Jose Luis Calvo/Shutterstock.)

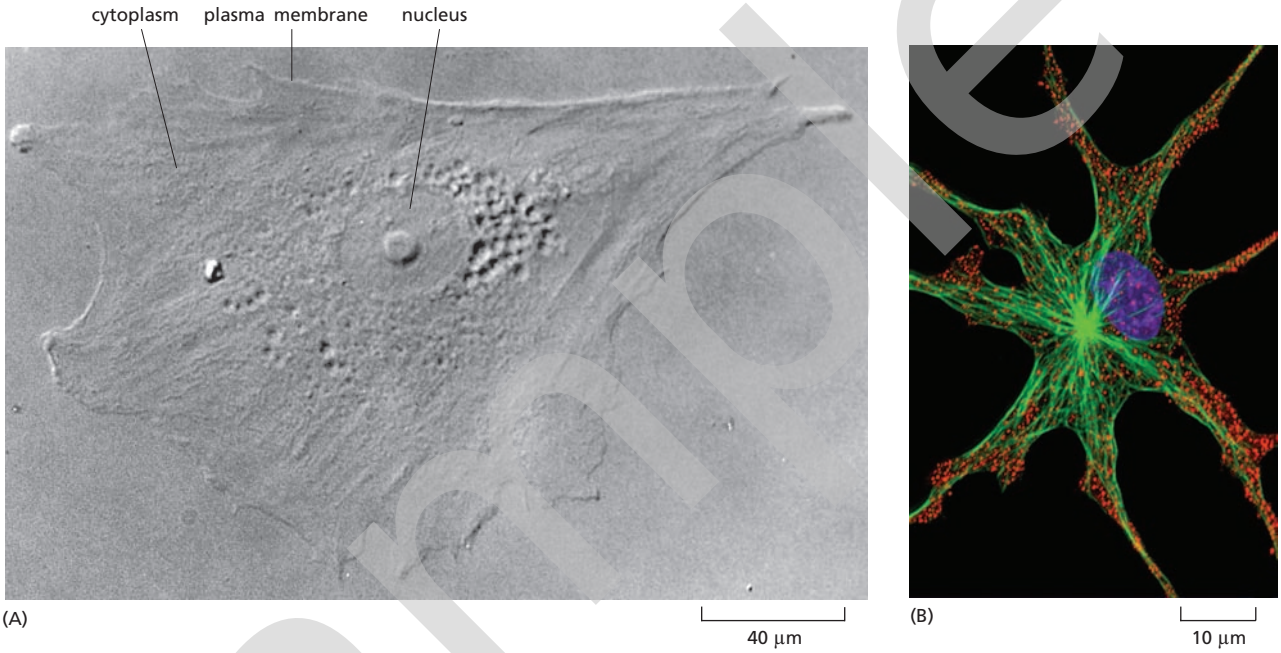


Figure 1–7 Some of the internal structures of a cell can be seen with a light microscope. (A) A cell taken from human skin and grown in culture was photographed through a light microscope using interference-contrast optics (described in Panel 1–1, pp. 12–13). The nucleus is especially prominent, as is the small, round nucleolus within it (discussed in Chapter 5 and see Panel 1–2, p. 25). (B) A pigment cell from a frog, stained with fluorescent dyes and viewed with a confocal fluorescence microscope (discussed in Panel 1–1). The nucleus is shown in *purple,* the pigment granules in *red,* and the microtubules—a class of protein filaments in the cytoplasm—in *green.* (A, courtesy of Casey Cunningham; B, courtesy of Stephen Rogers and the Imaging Technology Group of the Beckman Institute, University of Illinois, Urbana.)

the other. The small differences in refractive index can be made visible by specialized optical techniques, and the resulting images can be enhanced further by electronic processing (**Figure 1–7A**).

As shown in Figures 1–6B and 1–7A, typical animal cells visualized in these ways have a distinct anatomy. They have a sharply defined boundary, indicating the presence of an enclosing membrane, the **plasma membrane**. A large, round structure, the *nucleus*, is prominent near the middle of the cell. Around the nucleus and filling the cell's interior is the **cytoplasm**, a transparent substance crammed with what seems at first to be a jumble of miscellaneous objects. With a good light microscope, one can begin to distinguish and classify some of the specific components in the cytoplasm, but structures smaller than about 0.2 μm—about half the wavelength of visible light—cannot normally be resolved; points closer than this are not distinguishable and appear as a single blur.

In recent years, however, new types of light microscope called **fluorescence microscopes** have been developed that use sophisticated methods of illumination and electronic image processing to see fluorescently labeled cell components in much finer detail (**Figure 1–7B**). The most recent super-resolution fluorescence microscopes, for example, can push the limits of resolution down even further, to about 20 nanometers (nm). That is the size of a single **ribosome**, a large macromolecular complex in which RNAs are translated into proteins. These super-resolution techniques are described further in Panel 1–1 (pp. 12–13).

The Fine Structure of a Cell Is Revealed by Electron Microscopy

For the highest magnification and best resolution, one must turn to an **electron microscope**, which can reveal details down to a few nanometers. Preparing cell samples for the electron microscope is a painstaking process. Even for light microscopy, a tissue often has to be *fixed* (that is, preserved by pickling in a reactive chemical solution), supported by *embedding* in a solid wax or resin, cut, or *sectioned,* into thin slices, and *stained* before it is viewed. (The tissues in Figure 1–6 were prepared in

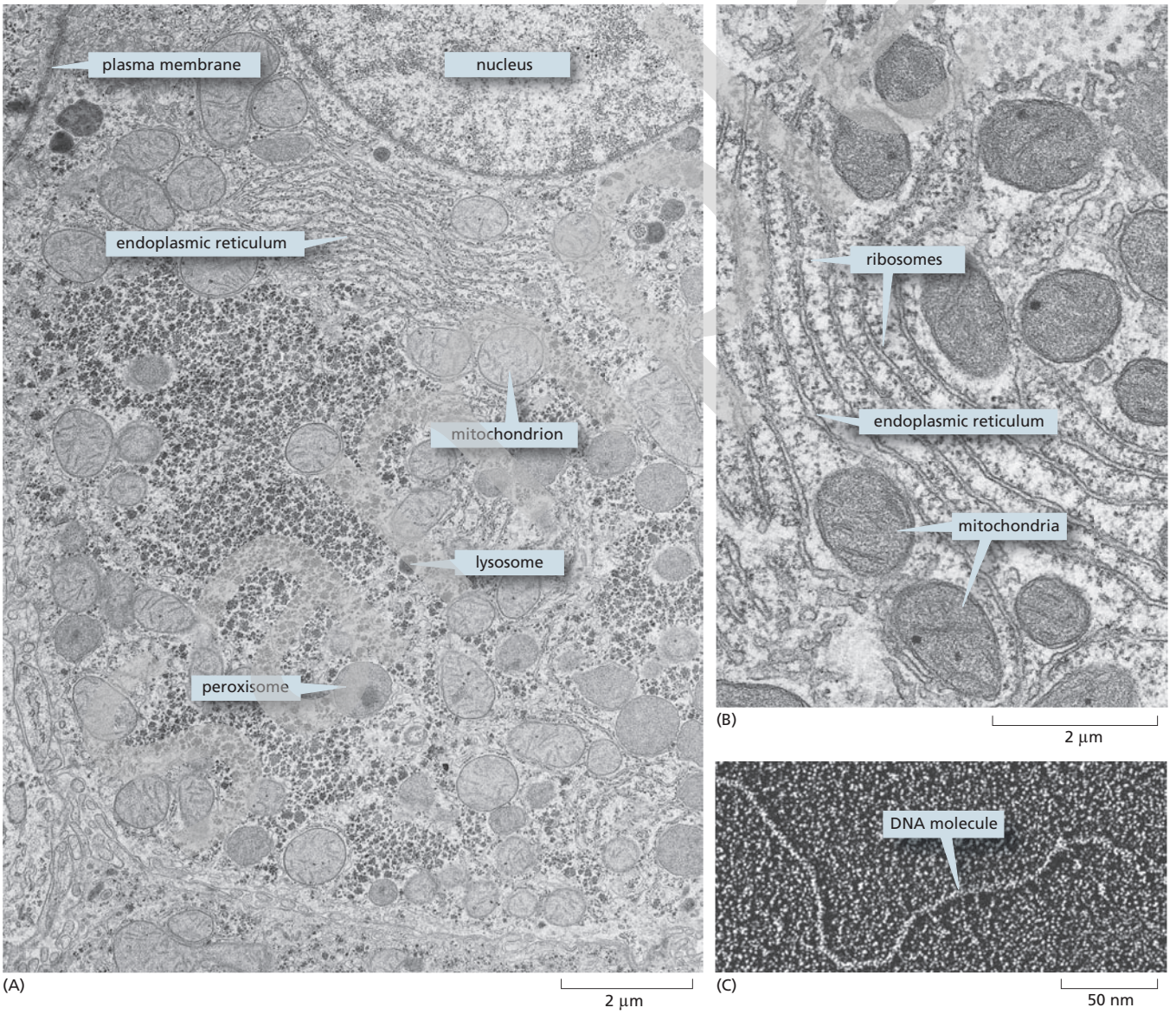


Figure 1–8 The fine structure of a cell can be seen in a transmission electron microscope. (A) Thin section of a liver cell showing the enormous amount of detail that is visible. Some of the components to be discussed later in the chapter are labeled; they are identifiable by their size, location, and shape. (B) A small region of the cytoplasm at higher magnification. The smallest structures that are clearly visible are the ribosomes, each of which is made of 80–90 or so individual protein and RNA molecules; some of the ribosomes are free in the cytoplasm, while others are bound to a membrane-enclosed organelle—the endoplasmic reticulum—discussed later (see Figure 1–22). (C) Portion of a long, threadlike DNA molecule isolated from a cell and viewed by electron microscopy. (A and B, by permission of E.L. Bearer and Daniel S. Friend; C, courtesy of Mei Lie Wong.)

this way.) For electron microscopy, similar procedures are required, but the sections have to be much thinner and there is no possibility of looking at living cells.

When thin sections are cut, stained with electron-dense heavy metals, and placed in the electron microscope, much of the jumble of cell components becomes sharply resolved into distinct **organelles**—separate, recognizable substructures with specialized functions that are often only hazily defined with a conventional light microscope. A delicate membrane, only about 5 nm thick, is visible enclosing the cell, and similar membranes form the boundary of many of the organelles inside (**Figure 1–8A and B**). The plasma membrane separates the interior of the cell from its external environment, while *internal membranes* surround most organelles. All of these membranes are only two molecules thick (as discussed in Chapter 11). With an electron microscope, even individual large molecules can be seen (**Figure 1–8C**).

The type of electron microscope used to look at thin sections of tissue is known as a *transmission electron microscope*. This instrument is, in principle, similar to a light microscope, except that it transmits a beam of

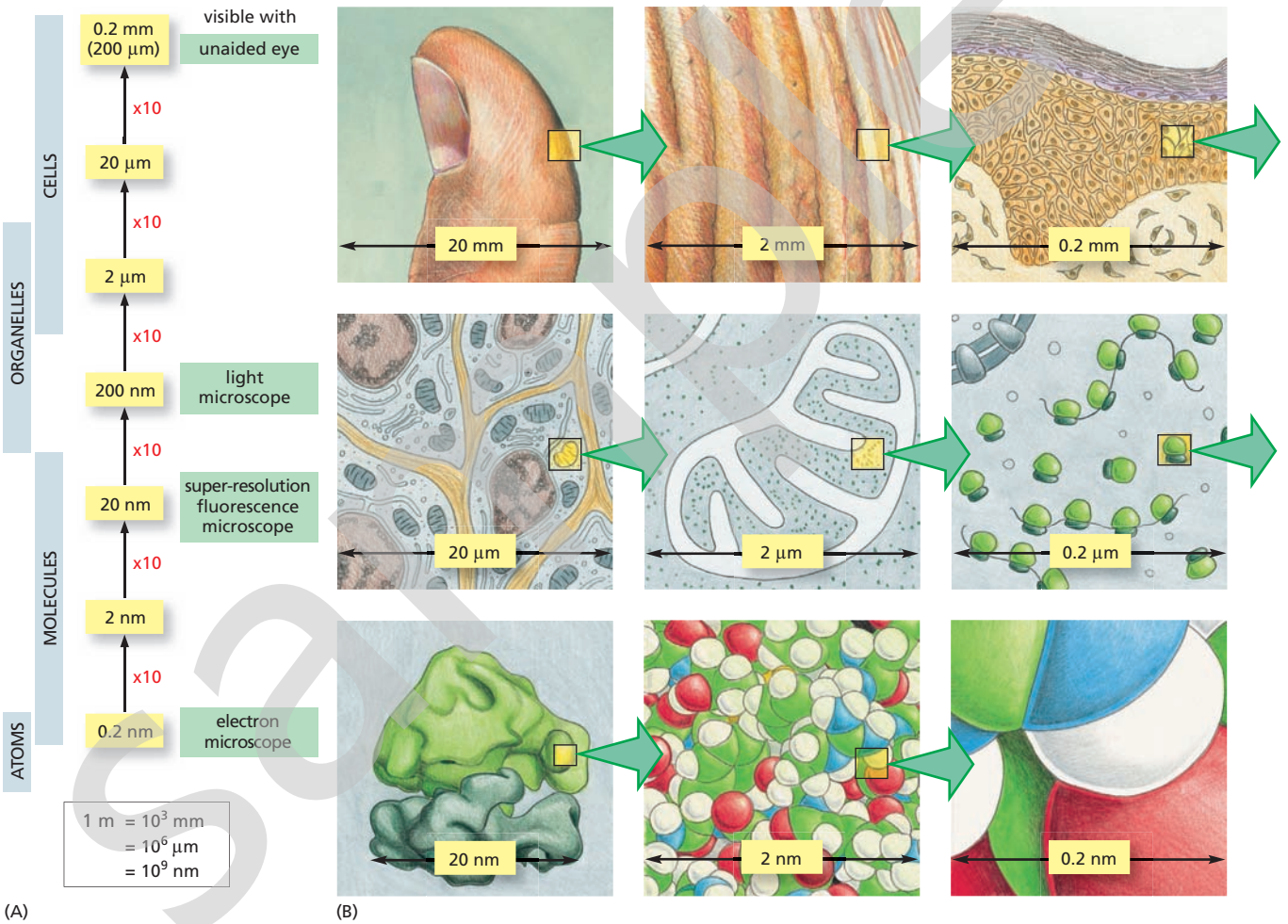


Figure 1–9 How big are cells and their components? (A) This chart lists sizes of cells and their component parts, the units in which they are measured, and the instruments needed to visualize them. (B) Drawings convey a sense of scale between living cells and atoms. Each panel shows an image that is magnified by a factor of 10 compared to its predecessor—producing an imaginary progression from a thumb, to skin, to skin cells, to a mitochondrion, to a ribosome, and ultimately to a cluster of atoms forming part of one of the many protein molecules in our bodies. Note that ribosomes are present inside mitochondria (as shown here), as well as in the cytoplasm. Details of molecular structure, as shown in the last two bottom panels, are beyond the power of the electron microscope.

electrons rather than a beam of light through the sample. Another type of electron microscope—the *scanning electron microscope*—scatters electrons off the surface of the sample and so is used to look at the surface detail of cells and other structures. These techniques, along with the different forms of light microscopy, are reviewed in **Panel 1–1** (pp. 12–13).

Even the most powerful electron microscopes, however, cannot visualize the individual atoms that make up biological molecules (**Figure 1–9**). To study the cell's key components in atomic detail, biologists have developed even more sophisticated tools. Techniques such as x-ray crystallography or cryoelectron microscopy, for example, can be used to determine the precise positioning of atoms within the three-dimensional structure of protein molecules and complexes (discussed in Chapter 4).

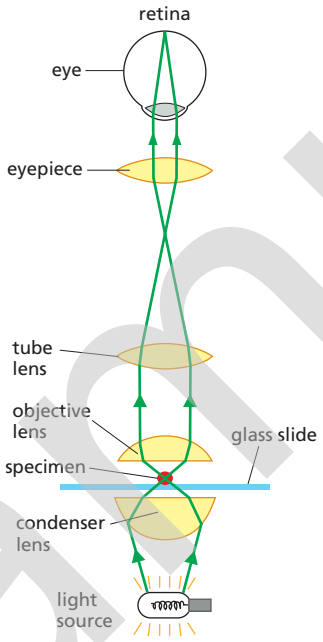
THE PROKARYOTIC CELL

Of all the types of cells that have been examined microscopically, *bacteria* have the simplest structure and come closest to showing us life stripped down to its essentials. Indeed, a bacterium contains no organelles other than ribosomes—not even a nucleus to hold its DNA. This property—the presence or absence of a nucleus—is used as the basis for a simple but fundamental classification of all living things. Organisms whose cells have a nucleus are called **eukaryotes** (from the Greek words *eu*, meaning "well" or "truly," and *karyon*, a "kernel" or "nucleus"). Organisms whose cells do not have a nucleus are called **prokaryotes** (from *pro*, meaning "before").

Courtesy of Andrew Davis.

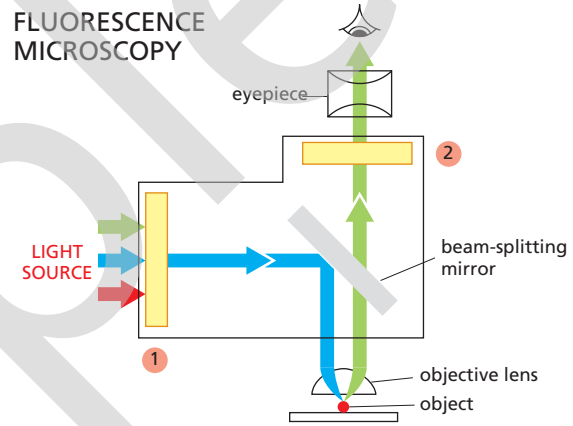
CONVENTIONAL LIGHT MICROSCOPY

A conventional light microscope allows us to magnify cells up to 1000 times and to resolve details as small as 0.2 μm (200 nm), a limitation imposed by the wavelike nature of light, not by the quality of the lenses. Three things are required for viewing cells in a light microscope. First, a bright light must be focused onto the specimen by lenses in the condenser. Second, the specimen must be carefully prepared to allow light to pass through it. Third, an appropriate set of lenses (objective, tube, and eyepiece) must be arranged to focus an image of the specimen in the eye.

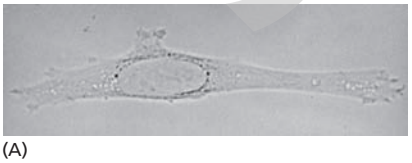


the light path in a light microscope

FLUORESCENCE MICROSCOPY

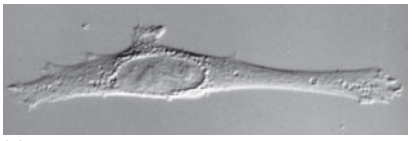


Fluorescent dyes used for staining cells are detected with the aid of a *fluorescence microscope*. This is similar to an ordinary light microscope, except that the illuminating light is passed through two sets of filters (*yellow*). The first (1) filters the light before it reaches the specimen, passing only those wavelengths that excite the particular fluorescent dye. The second (2) blocks out this light and passes only those wavelengths emitted when the dye fluoresces. Dyed objects show up in bright color on a dark background.



(A)

(B)



(C)

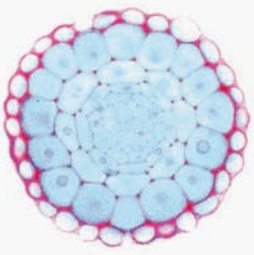
50 μm

LOOKING AT LIVING CELLS

The same unstained, living animal cell (fibroblast) in culture viewed with
(A) the simplest, bright-field optics;
(B) phase-contrast optics;
(C) interference-contrast optics.
The two latter systems exploit differences in the way light travels through regions of the cell with differing refractive indices. All three images can be obtained on the same microscope simply by interchanging optical components.

FIXED SAMPLES

Most tissues are neither small enough nor transparent enough to examine directly in the microscope. Typically, therefore, they are chemically fixed and cut into thin slices, or *sections*, that can be mounted on a glass microscope slide and subsequently stained to reveal different components of the cells. A stained section of a plant root tip is shown here (D).

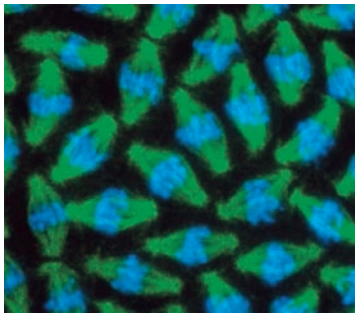


Courtesy of Catherine Kidner.

(D)

50 μm

FLUORESCENT PROBES

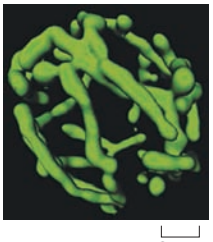


Courtesy of William Sullivan.

10 μm

Fluorescent molecules absorb light at one wavelength and emit it at another, longer wavelength. Some fluorescent dyes bind specifically to particular molecules in cells and can reveal their location when the cells are examined with a fluorescence microscope. In these dividing nuclei in a fly embryo, the stain for DNA fluoresces *blue*. Other dyes can be coupled to antibody molecules, which then serve as highly specific staining reagents that bind selectively to particular molecules, showing their distribution in the cell. Because fluorescent dyes emit light, they allow objects even smaller than 0.2 μm to be seen. Here, a microtubule protein in the mitotic spindle (see Figure 1–28) is stained *green* with a fluorescent antibody.

CONFOCAL FLUORESCENCE MICROSCOPY



Courtesy of Stefan Hell.

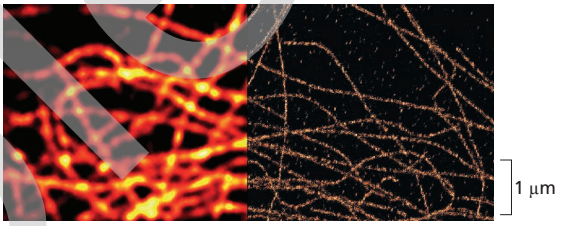
2 μm

A confocal microscope is a specialized type of fluorescence microscope that builds up an image by scanning the specimen with a laser beam. The beam is focused onto a single point at a specific depth in the specimen, and a pinhole aperture in the detector allows only fluorescence emitted from this same point to be included in the image. Scanning the beam across the specimen generates a sharp image of the plane of focus—an *optical* section. A series of optical sections at different depths allows a three-dimensional image to be constructed, such as this highly branched mitochondrion in a living yeast cell.

SUPER-RESOLUTION FLUORESCENCE MICROSCOPY

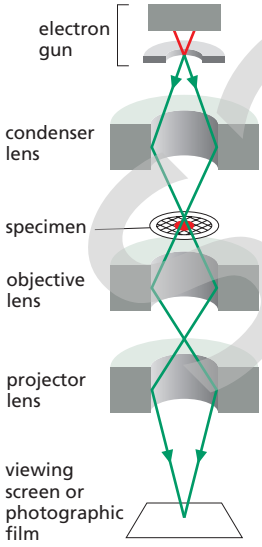
Several recent and ingenious techniques have allowed fluorescence microscopes to break the usual resolution limit of 200 nm. One such technique uses a sample that is labeled with molecules whose fluorescence can be reversibly switched on and off by different colored lasers. The specimen is scanned by a nested set of two laser beams, in which the central beam excites fluorescence in a very small spot of the sample, while a second beam—wrapped around the first—switches off fluorescence in the surrounding area. A related approach allows the positions of individual fluorescent molecules to be accurately mapped while others nearby are switched off. Both approaches slowly build up an image with a resolution as low as 20 nm. These new super-resolution methods are being extended into 3-D imaging and real-time live cell imaging.

Courtesy of Carl Zeiss Microscopy, LLC.



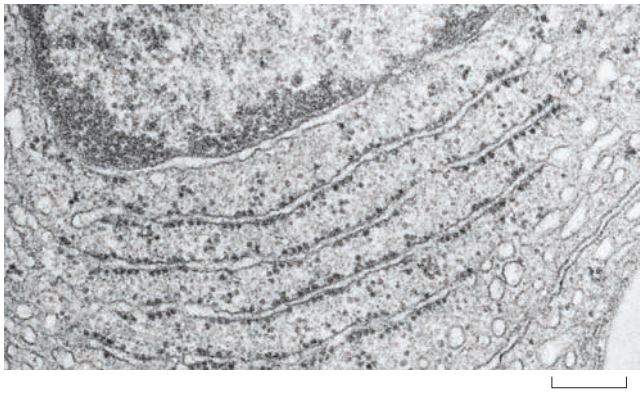
Microtubules viewed with conventional fluorescence microscope (*left*) and with super-resolution optics (*right*). In the super-resolution image, the microtubule can be clearly seen at the actual size, which is only 25 nm in diameter.

TRANSMISSION ELECTRON MICROSCOPY



Courtesy of Andrew Davis.

The electron micrograph below shows a small region of a cell in a thin section of testis. The tissue has been chemically fixed, embedded in plastic, and cut into very thin sections that have then been stained with salts of uranium and lead.



Courtesy of Daniel S. Friend.

0.5 μm

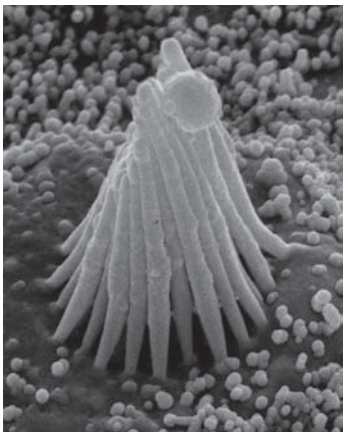
The transmission electron microscope (TEM) is in principle similar to a light microscope, but it uses a beam of electrons, whose wavelength is very short, instead of a beam of light, and magnetic coils to focus the beam instead of glass lenses. Because of the very small wavelength of electrons, the specimen must be very thin. Contrast is usually introduced by staining the specimen with electron-dense heavy metals. The specimen is then placed in a vacuum in the microscope. The TEM has a useful magnification of up to a million-fold and can resolve details as small as about 1 nm in biological specimens.

SCANNING ELECTRON MICROSCOPY

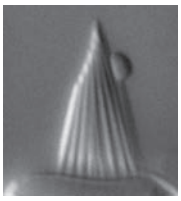
Courtesy of Andrew Davis.

In the scanning electron microscope (SEM), the specimen, which has been coated with a very thin film of a heavy metal, is scanned by a beam of electrons brought to a focus on the specimen by magnetic coils that act as lenses. The quantity of electrons scattered or emitted as the beam bombards each successive point on the surface of the specimen is measured by the detector, and is used to control the intensity of successive points in an image built up on a video screen. The microscope creates striking images of three-dimensional objects with great depth of focus and can resolve details down to somewhere between 3 nm and 20 nm, depending on the instrument.

Courtesy of Richard Jacobs and James Hudspeth.



1 μm



5 μm

Scanning electron micrograph of stereocilia projecting from a hair cell in the inner ear (*left*). For comparison, the same structure is shown by light microscopy, at the limit of its resolution (*above*).

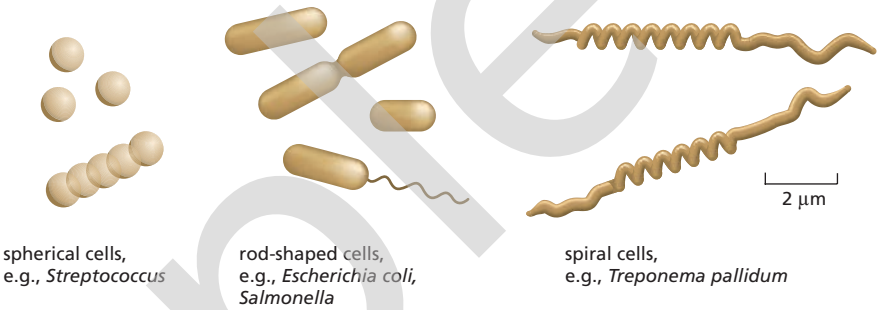


Figure 1–10 Bacteria come in different shapes and sizes. Typical spherical, rodlike, and spiral-shaped bacteria are drawn to scale. The spiral cells shown are the organisms that cause syphilis.

Prokaryotes are typically spherical, rodlike, or corkscrew-shaped (**Figure 1–10**). They are also small—generally just a few micrometers long, although some giant species are as much as 100 times longer than this. Prokaryotes often have a tough protective coat, or cell wall, surrounding the plasma membrane, which encloses a single compartment containing the cytoplasm and the DNA. In the electron microscope, the cell interior typically appears as a matrix of varying texture, without any obvious organized internal structure (**Figure 1–11**). The cells reproduce quickly by dividing in two. Under optimum conditions, when food is plentiful, many prokaryotic cells can duplicate themselves in as little as 20 minutes. In only 11 hours, a single prokaryote can therefore give rise to more than 8 billion progeny (which exceeds the total number of humans currently on Earth). Thanks to their large numbers, rapid proliferation, and ability to exchange bits of genetic material by a process akin to sex, populations of prokaryotic cells can evolve fast, rapidly acquiring the ability to use a new food source or to resist being killed by a new antibiotic.

In this section, we offer an overview of the world of prokaryotes. Despite their simple appearance, these organisms lead sophisticated lives—occupying a stunning variety of ecological niches. We will also introduce the two distinct classes into which prokaryotes are divided: bacteria and *archaea* (singular, archaeon). Although they are structurally indistinguishable, archaea and bacteria are only distantly related.

QUESTION 1–4

A bacterium weighs about 10^{-12} g and can divide every 20 minutes. If a single bacterial cell carried on dividing at this rate, how long would it take before the mass of bacteria would equal that of the Earth (6×10^{24} kg)? Contrast your result with the fact that bacteria originated at least 3.5 billion years ago and have been dividing ever since. Explain the apparent paradox. (The number of cells N in a culture at time t is described by the equation $N = N_0 \times 2^{t/G}$, where N_0 is the number of cells at zero time, and G is the population doubling time.)

Prokaryotes Are the Most Diverse and Numerous Cells on Earth

Most prokaryotes live as single-celled organisms, although some join together to form chains, clusters, or other organized, multicellular structures. In shape and structure, prokaryotes may seem simple and limited, but in terms of chemistry, they are the most diverse class of cells on the planet. Members of this class exploit an enormous range of habitats, from hot puddles of volcanic mud to the interiors of other living cells, and they vastly outnumber all eukaryotic organisms on Earth. Some are aerobic, using oxygen to oxidize food molecules; some are strictly anaerobic and are killed by the slightest exposure to oxygen. As we discuss later in this chapter, *mitochondria*—the organelles that generate energy in eukaryotic cells—are thought to have evolved from aerobic bacteria that took

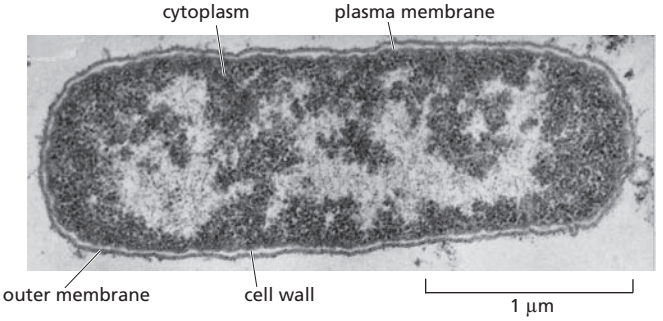


Figure 1–11 The bacterium *Escherichia coli* (*E. coli*) has served as an important model organism. An electron micrograph of a longitudinal section is shown here; the cell's DNA is concentrated in the lightly stained region. Note that *E. coli* has an outer membrane and an inner (plasma) membrane, with a thin cell wall in between. The many flagella distributed over its surface are not visible in this micrograph. (Courtesy of E. Kellenberger.)

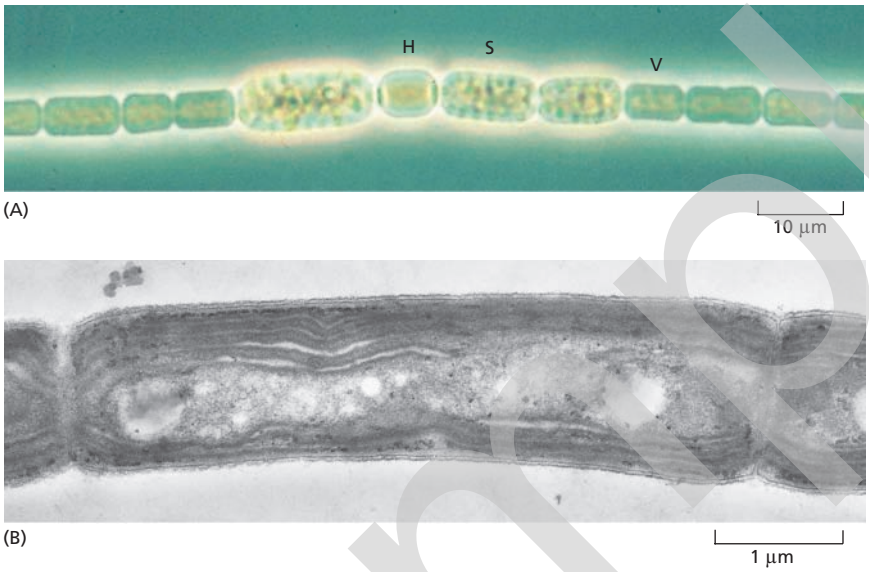


Figure 1–12 Some bacteria are photosynthetic. (A) *Anabaena cylindrica* forms long, multicellular chains. This light micrograph shows specialized cells that either fix nitrogen (that is, capture N_2 from the atmosphere and incorporate it into organic compounds; labeled H), fix CO_2 through photosynthesis (labeled V), or become resistant spores (labeled S) that can survive under unfavorable conditions. (B) An electron micrograph of a related species, *Phormidium laminosum*, shows the intracellular membranes where photosynthesis occurs. As shown in these micrographs, some prokaryotes can have intracellular membranes and form simple multicellular organisms. (A, courtesy of David Adams; B, courtesy of D.P. Hill and C.J. Howe.)

to living inside the anaerobic ancestors of today's eukaryotic cells. Thus our own oxygen-based metabolism can be regarded as a product of the activities of bacterial cells.

Virtually any organic, carbon-containing material—from wood to petroleum—can be used as food by one sort of bacterium or another. Even more remarkably, some prokaryotes can live entirely on inorganic substances: they can get their carbon from CO_2 in the atmosphere, their nitrogen from atmospheric N_2, and their oxygen, hydrogen, sulfur, and phosphorus from air, water, and inorganic minerals. Some of these prokaryotic cells, like plant cells, perform *photosynthesis*, using energy from sunlight to produce organic molecules from CO_2 (**Figure 1–12**); others derive energy from the chemical reactivity of inorganic substances in the environment (**Figure 1–13**). In either case, such prokaryotes play a unique and fundamental part in the economy of life on Earth, as other living organisms depend on the organic compounds that these cells generate from inorganic materials.

Plants, too, can capture energy from sunlight and carbon from atmospheric CO_2. But plants unaided by bacteria cannot capture N_2 from the atmosphere. In a sense, plants even depend on bacteria for photosynthesis: as we discuss later, it is almost certain that the organelles in the plant cell that perform photosynthesis—the *chloroplasts*—have evolved from photosynthetic bacteria that long ago found a home inside the cytoplasm of a plant-cell ancestor.

The World of Prokaryotes Is Divided into Two Domains: Bacteria and Archaea

Traditionally, all prokaryotes have been classified together in one large group. But molecular studies have determined that there is a gulf within the class of prokaryotes, dividing it into two distinct *domains*—the **bacteria** and the **archaea**—which are thought to have diverged from a common prokaryotic ancestor approximately 3.5 billion years ago. Remarkably, DNA sequencing reveals that, at a molecular level, the members of these two domains differ as much from one another as either does from the eukaryotes. Most of the prokaryotes familiar from everyday life—the species that live in the soil or make us ill—are bacteria. Archaea are found not only in these habitats but also in environments that are too hostile for most other cells: concentrated brine, the hot acid of volcanic springs,

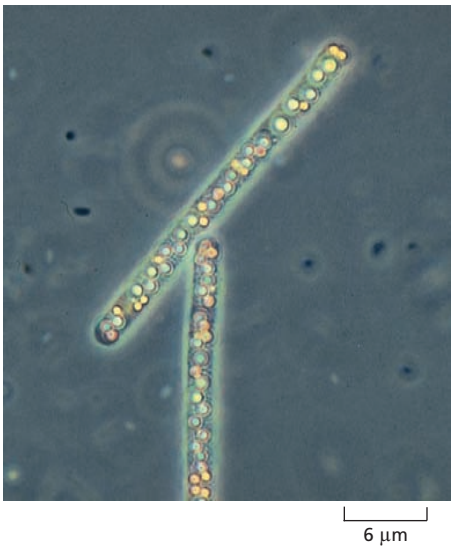


Figure 1–13 A sulfur bacterium gets its energy from H_2S. *Beggiatoa*, a prokaryote that lives in sulfurous environments, oxidizes H_2S to produce sulfur and can fix carbon even in the dark. In this light micrograph, yellow deposits of sulfur can be seen inside two of these bacterial cells. (Courtesy of Ralph S. Wolfe.)

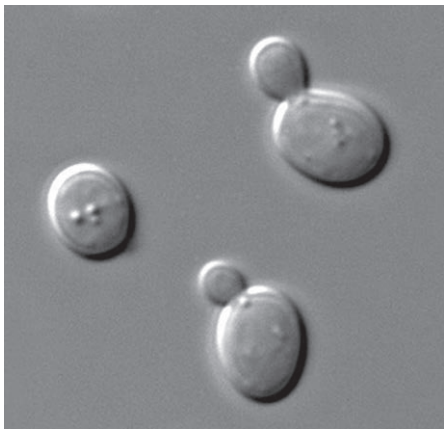


Figure 1–14 Yeasts are simple, free-living eukaryotes. The cells shown in this micrograph belong to the species of yeast, *Saccharomyces cerevisiae*, used to make dough rise and turn malted barley juice into beer. As can be seen in this image, the cells reproduce by growing a bud and then dividing asymmetrically into a large mother cell and a small daughter cell; for this reason, they are called budding yeast.

the airless depths of marine sediments, the sludge of sewage treatment plants, pools beneath the frozen surface of Antarctica, as well as in the acidic, oxygen-free environment of a cow's stomach, where they break down ingested cellulose and generate methane gas. Many of these extreme environments resemble the harsh conditions that must have existed on the primitive Earth, where living things first evolved before the atmosphere became rich in oxygen.

THE EUKARYOTIC CELL

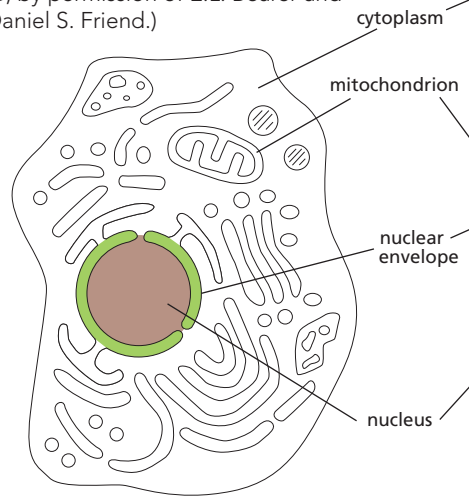
Eukaryotic cells, in general, are bigger and more elaborate than bacteria and archaea. Some live independent lives as single-celled organisms, such as amoebae and yeasts (**Figure 1–14**); others live in multicellular assemblies. All of the more complex multicellular organisms—including plants, animals, and fungi—are formed from eukaryotic cells.

By definition, all eukaryotic cells have a nucleus. But possession of a nucleus goes hand-in-hand with possession of a variety of other organelles, most of which are membrane-enclosed and common to all eukaryotic organisms. In this section, we take a look at the main organelles found in eukaryotic cells from the point of view of their functions, and we consider how they came to serve the roles they have in the life of the eukaryotic cell.

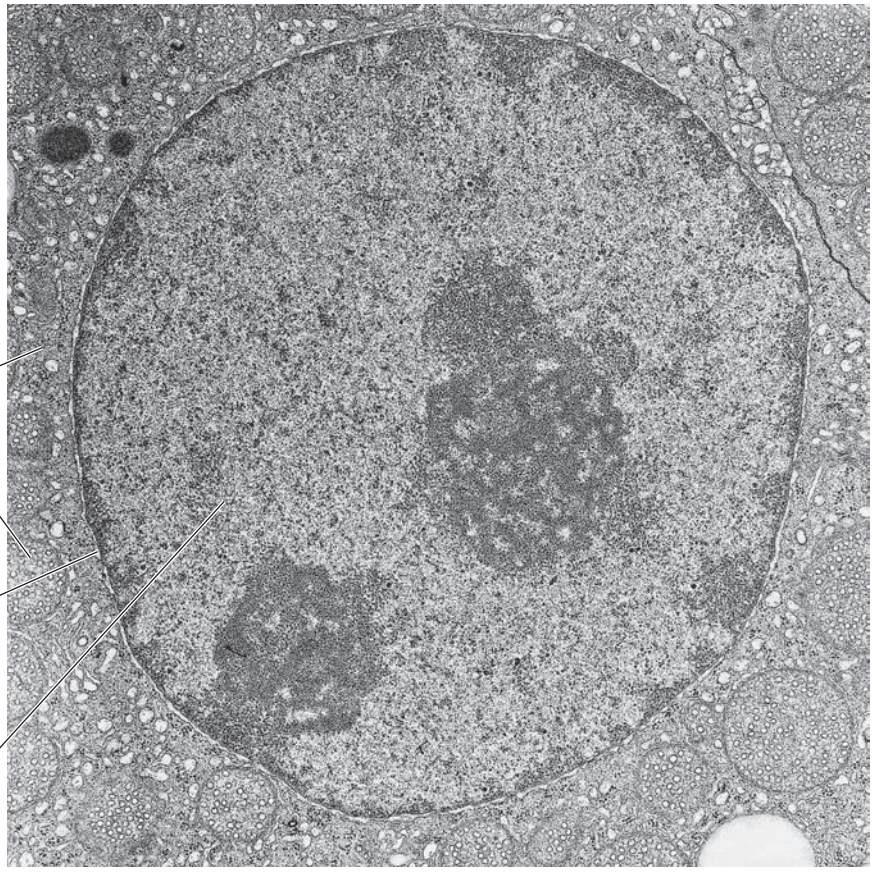
The Nucleus Is the Information Store of the Cell

The **nucleus** is usually the most prominent organelle in a eukaryotic cell (**Figure 1–15**). It is enclosed within two concentric membranes that form

Figure 1–15 The nucleus contains most of the DNA in a eukaryotic cell. (A) This drawing of a typical animal cell shows its extensive system of membrane-enclosed organelles. The nucleus is colored *brown*, the nuclear envelope is *green*, and the cytoplasm (the interior of the cell outside the nucleus) is *white*. (B) An electron micrograph of the nucleus in a mammalian cell. Individual chromosomes are not visible because at this stage of the cell-division cycle the DNA molecules are dispersed as fine threads throughout the nucleus. (B, by permission of E.L. Bearer and Daniel S. Friend.)



(A)



(B)

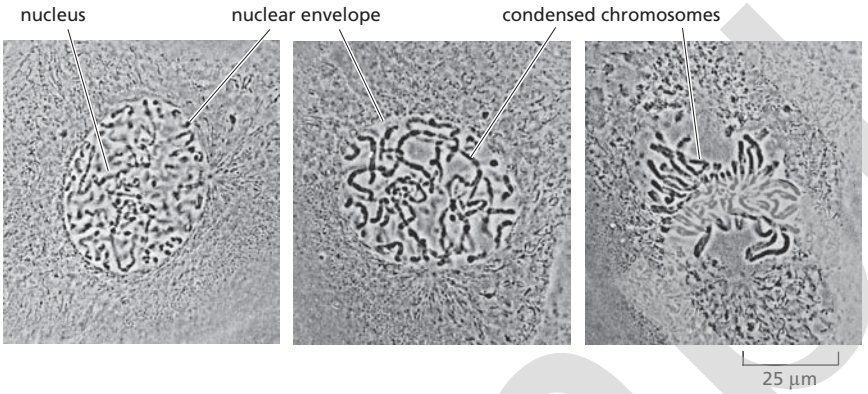


Figure 1–16 Chromosomes become visible when a cell is about to divide. As a eukaryotic cell prepares to divide, its DNA molecules become progressively more compacted (condensed), forming wormlike chromosomes that can be distinguished in the light microscope (see also Figure 1–5). The photographs here show three successive steps in this chromosome condensation process in a cultured cell from a newt's lung; note that in the last micrograph on the right, the nuclear envelope has broken down. (Courtesy of Conly L. Rieder, Albany, New York.)

the *nuclear envelope*, and it contains molecules of DNA—extremely long polymers that encode the genetic information of the organism. In the light microscope, these giant DNA molecules become visible as individual **chromosomes** when they become more compact before a cell divides into two daughter cells (**Figure 1–16**). DNA also carries the genetic information in prokaryotic cells; these cells lack a distinct nucleus not because they lack DNA, but because they do not keep their DNA inside a nuclear envelope, segregated from the rest of the cell contents.

Mitochondria Generate Usable Energy from Food Molecules

Mitochondria are present in essentially all eukaryotic cells, and they are among the most conspicuous organelles in the cytoplasm (see Figure 1–8B). In a fluorescence microscope, they appear as worm-shaped structures that often form branching networks (**Figure 1–17**). When seen with an electron microscope, individual mitochondria are found to be enclosed in two separate membranes, with the inner membrane formed into folds that project into the interior of the organelle (**Figure 1–18**).

Microscopic examination by itself, however, gives little indication of what mitochondria do. Their function was discovered by breaking open cells and then spinning the soup of cell fragments in a centrifuge; this treatment separates the organelles according to their size and density. Purified mitochondria were then tested to see what chemical processes they could perform. This revealed that mitochondria are generators of chemical energy for the cell. They harness the energy from the oxidation of food molecules, such as sugars, to produce *adenosine triphosphate*, or *ATP*—the basic chemical fuel that powers most of the cell's activities. Because the mitochondrion consumes oxygen and releases CO_2 in the course of this activity, the entire process is called *cell respiration*—essentially, breathing at the level of a cell. Without mitochondria, animals, fungi, and plants would be unable to use oxygen to extract the energy they need from the food molecules that nourish them. The process of cell respiration is considered in detail in Chapter 14.

Mitochondria contain their own DNA and reproduce by dividing. Because they resemble bacteria in so many ways, they are thought to derive from bacteria that were engulfed by some ancestor of present-day eukaryotic

Figure 1–17 Mitochondria can vary in shape and size. This budding yeast cell, which contains a green fluorescent protein in its mitochondria, was viewed in a super-resolution confocal fluorescence microscope. In this three-dimensional image, the mitochondria are seen to form complex branched networks. (From A. Egner, S. Jakobs, and S.W. Hell, *Proc. Natl. Acad. Sci. U.S.A* 99:3370–3375, 2002. With permission from National Academy of Sciences.)

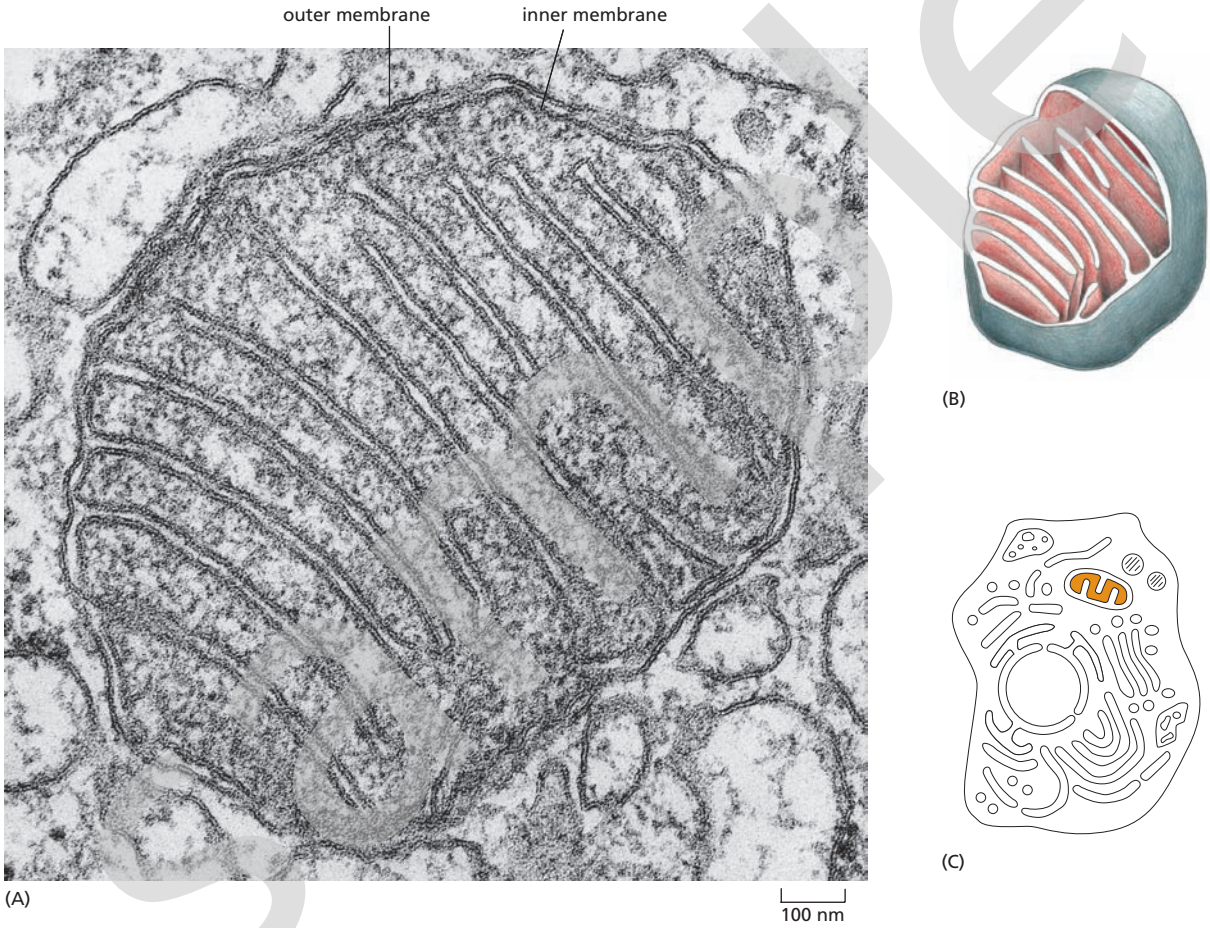


Figure 1–18 Mitochondria have a distinctive internal structure. (A) An electron micrograph of a cross section of a mitochondrion reveals the extensive infolding of the inner membrane. (B) This three-dimensional representation of the arrangement of the mitochondrial membranes shows the smooth outer membrane (*gray*) and the highly convoluted inner membrane (*red*). The inner membrane contains most of the proteins responsible for energy production in eukaryotic cells; it is highly folded to provide a large surface area for this activity. (C) In this schematic cell, the innermost compartment of the mitochondrion is colored *orange*. (A, courtesy of Daniel S. Friend, by permission of E.L. Bearer.)

cells (**Figure 1–19**). This evidently created a *symbiotic* relationship in which the host eukaryote and the engulfed bacterium helped each other to survive and reproduce.

Chloroplasts Capture Energy from Sunlight

Chloroplasts are large, green organelles that are found in the cells of plants and algae, but not in the cells of animals or fungi. These organelles have an even more complex structure than mitochondria: in addition to their two surrounding membranes, they possess internal stacks of membranes containing the green pigment *chlorophyll* (**Figure 1–20**).

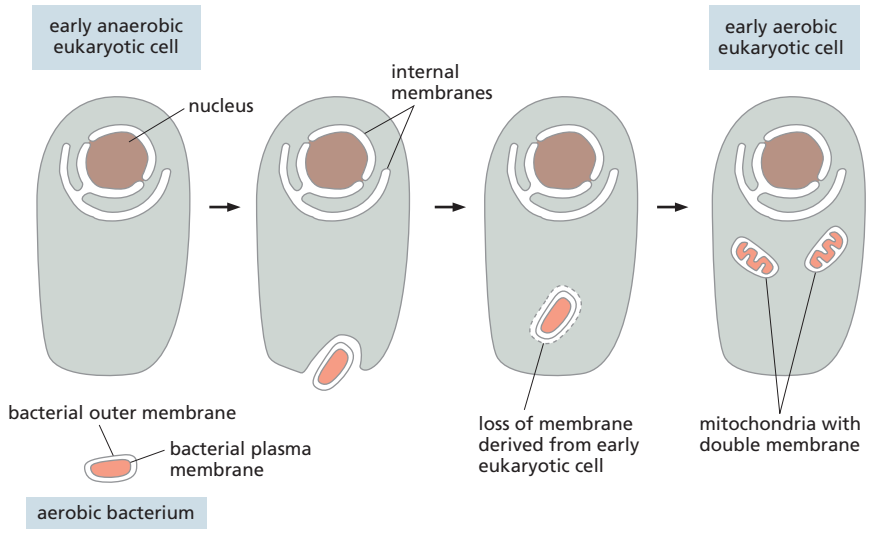


Figure 1–19 Mitochondria are thought to have evolved from engulfed bacteria. It is virtually certain that mitochondria evolved from aerobic bacteria that were engulfed by an archaea-derived, early anaerobic eukaryotic cell and survived inside it, living in symbiosis with their host. As shown in this model, the double membrane of present-day mitochondria is thought to have been derived from the plasma membrane and outer membrane of the engulfed bacterium; the membrane derived from the plasma membrane of the engulfing ancestral cell was ultimately lost.

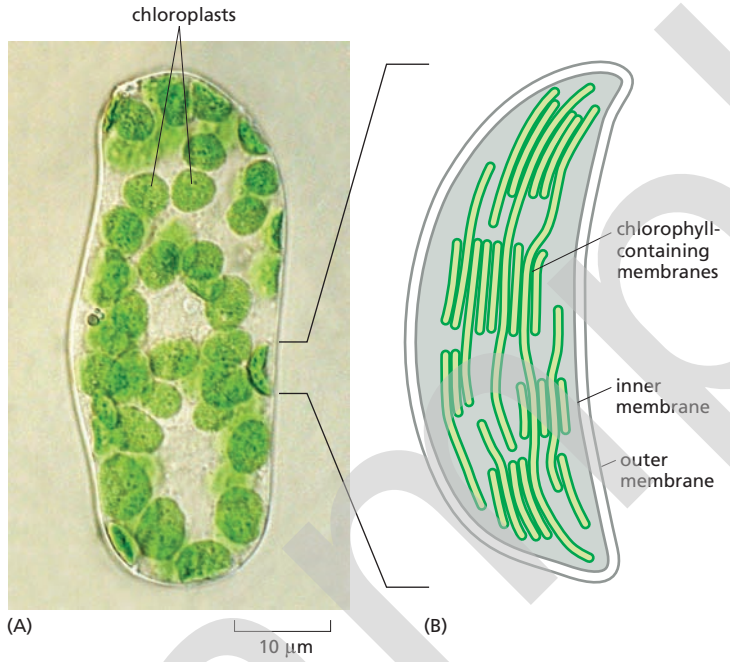


Figure 1–20 Chloroplasts in plant cells capture the energy of sunlight. (A) A single cell isolated from a leaf of a flowering plant, seen in the light microscope, showing many green chloroplasts. (B) A drawing of one of the chloroplasts, showing the inner and outer membranes, as well as the highly folded system of internal membranes containing the green chlorophyll molecules that absorb light energy. (A, courtesy of Preeti Dahiya.)

Chloroplasts carry out **photosynthesis**—trapping the energy of sunlight in their chlorophyll molecules and using this energy to drive the manufacture of energy-rich sugar molecules. In the process, they release oxygen as a molecular by-product. Plant cells can then extract this stored chemical energy when they need it, in the same way that animal cells do: by oxidizing these sugars and their breakdown products, mainly in the mitochondria. Chloroplasts thus enable plants to get their energy directly from sunlight. They also allow plants to produce the food molecules—and the oxygen—that mitochondria use to generate chemical energy in the form of ATP. How these organelles work together is discussed in Chapter 14.

Like mitochondria, chloroplasts contain their own DNA, reproduce by dividing in two, and are thought to have evolved from bacteria—in this case, from photosynthetic bacteria that were engulfed by an early aerobic eukaryotic cell (**Figure 1–21**).

Internal Membranes Create Intracellular Compartments with Different Functions

Nuclei, mitochondria, and chloroplasts are not the only membrane-enclosed organelles inside eukaryotic cells. The cytoplasm contains a

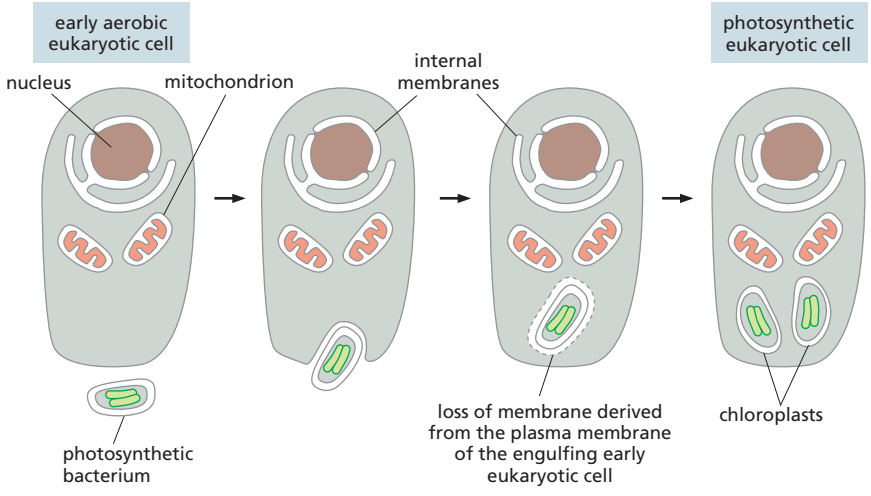


Figure 1–21 Chloroplasts almost certainly evolved from engulfed photosynthetic bacteria. The bacteria are thought to have been taken up by early eukaryotic cells that already contained mitochondria.

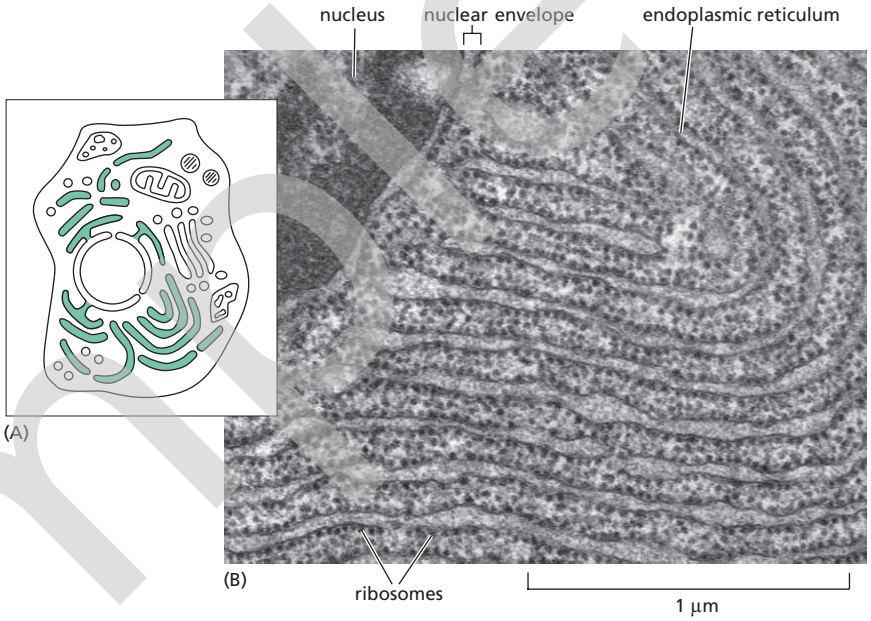


Figure 1–22 The endoplasmic reticulum produces many of the components of a eukaryotic cell. (A) Schematic diagram of an animal cell shows the endoplasmic reticulum (ER) in *green*. (B) Electron micrograph of a thin section of a mammalian pancreatic cell shows a small part of the ER, of which there are vast amounts in this cell type, which is specialized for protein secretion. Note that the ER is continuous with the membranes of the nuclear envelope. The black particles studding the region of the ER (and nuclear envelope) shown here are ribosomes, structures that translate RNAs into proteins. Because of its appearance, ribosome-coated ER is often called "rough ER" to distinguish it from the "smooth ER," which does not have ribosomes bound to it. (B, courtesy of Lelio Orci.)

profusion of other organelles that are surrounded by single membranes (see Figure 1–8A). Most of these structures are involved with the cell's ability to import raw materials and to export both useful substances and waste products that are produced by the cell (a topic we discuss in detail in Chapter 12).

The **endoplasmic reticulum** (**ER**) is an irregular maze of interconnected spaces enclosed by a membrane (**Figure 1–22**). It is the site where most cell-membrane components, as well as materials destined for export from the cell, are made. This organelle is enormously enlarged in cells that are specialized for the secretion of proteins. Stacks of flattened, membrane-enclosed sacs constitute the **Golgi apparatus** (**Figure 1–23**),

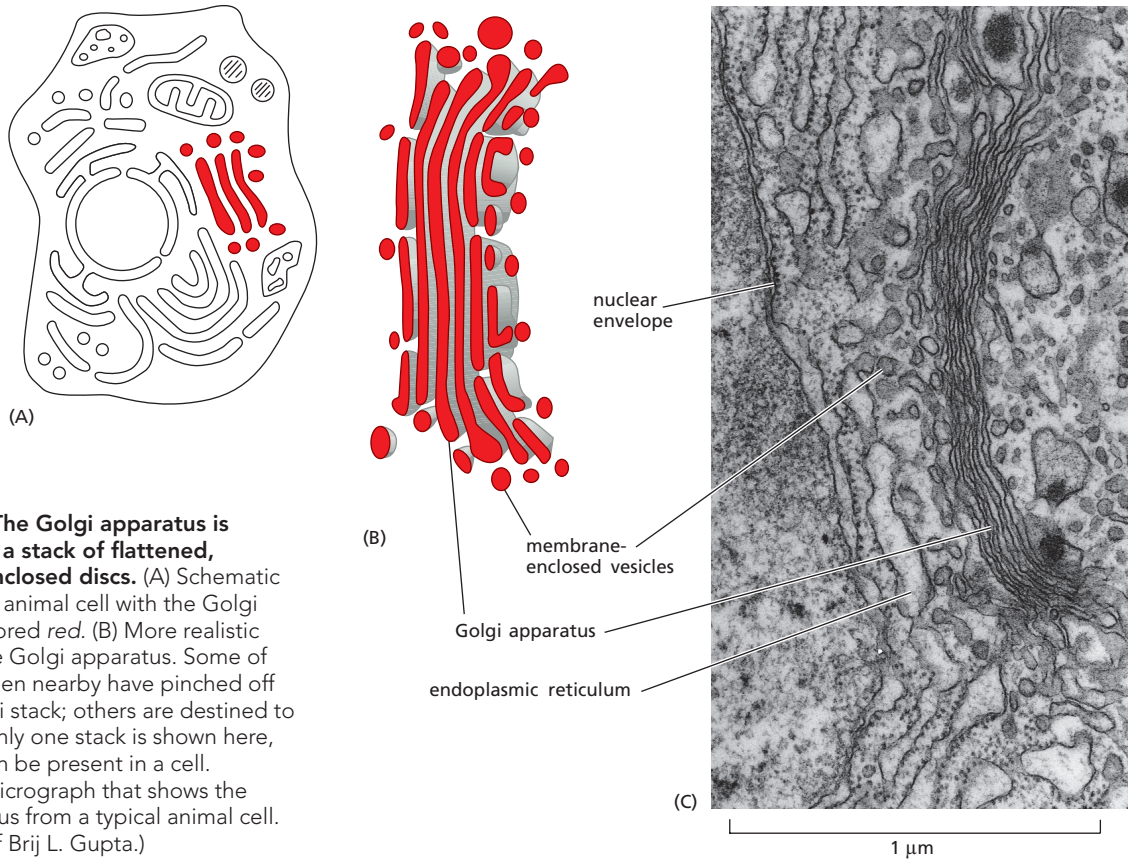


Figure 1–23 The Golgi apparatus is composed of a stack of flattened, membrane-enclosed discs. (A) Schematic diagram of an animal cell with the Golgi apparatus colored *red*. (B) More realistic drawing of the Golgi apparatus. Some of the vesicles seen nearby have pinched off from the Golgi stack; others are destined to fuse with it. Only one stack is shown here, but several can be present in a cell. (C) Electron micrograph that shows the Golgi apparatus from a typical animal cell. (C, courtesy of Brij L. Gupta.)

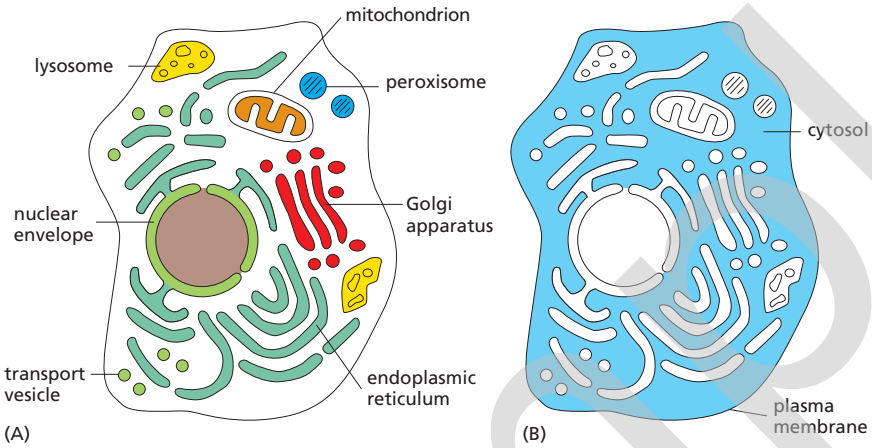


Figure 1–24 Membrane-enclosed organelles are distributed throughout the eukaryotic cell cytoplasm. (A) The various types of membrane-enclosed organelles, shown in different colors, are each specialized to perform a different function. (B) The cytoplasm that fills the space outside of these organelles is called the cytosol (colored *blue*).

which modifies and packages molecules made in the ER that are destined to be either secreted from the cell or transported to another cell compartment. *Lysosomes* are small, irregularly shaped organelles in which intracellular digestion occurs, releasing nutrients from ingested food particles into the cytosol and breaking down unwanted molecules for either recycling within the cell or excretion from the cell. Indeed, many of the large and small molecules within the cell are constantly being broken down and remade. *Peroxisomes* are small, membrane-enclosed vesicles that provide a sequestered environment for a variety of reactions in which hydrogen peroxide is used to inactivate toxic molecules. Membranes also form many types of small *transport vesicles* that ferry materials between one membrane-enclosed organelle and another. All of these membrane-enclosed organelles are highlighted in **Figure 1–24A**.

A continual exchange of materials takes place between the endoplasmic reticulum, the Golgi apparatus, the lysosomes, the plasma membrane, and the outside of the cell. The exchange is mediated by transport vesicles that pinch off from the membrane of one organelle and fuse with another, like tiny soap bubbles that bud from and combine with other bubbles. At the surface of the cell, for example, portions of the plasma membrane tuck inward and pinch off to form vesicles that carry material captured from the external medium into the cell—a process called *endocytosis* (**Figure 1–25**). Animal cells can engulf very large particles, or even entire foreign cells, by endocytosis. In the reverse process, called *exocytosis*, vesicles from inside the cell fuse with the plasma membrane and release their contents into the external medium (see Figure 1–25); most of the hormones and signal molecules that allow cells to communicate with one another are secreted from cells by exocytosis. How membrane-enclosed organelles move proteins and other molecules from place to place inside the eukaryotic cell is discussed in detail in Chapter 15.

The Cytosol Is a Concentrated Aqueous Gel of Large and Small Molecules

If we were to strip the plasma membrane from a eukaryotic cell and remove all of its membrane-enclosed organelles—including the nucleus, endoplasmic reticulum, Golgi apparatus, mitochondria, chloroplasts, and so on—we would be left with the **cytosol** (**Figure 1–24B**). In other words, the cytosol is the part of the cytoplasm that is not contained within intracellular membranes. In most cells, the cytosol is the largest single compartment. It contains a host of large and small molecules, crowded together so closely that it behaves more like a water-based gel than a

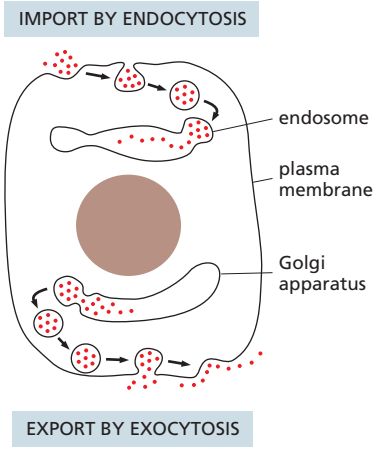


Figure 1–25 Eukaryotic cells engage in continual endocytosis and exocytosis across their plasma membrane. They import extracellular materials by endocytosis and secrete intracellular materials by exocytosis. Endocytosed material is first delivered to membrane-enclosed organelles called endosomes (discussed in Chapter 15).

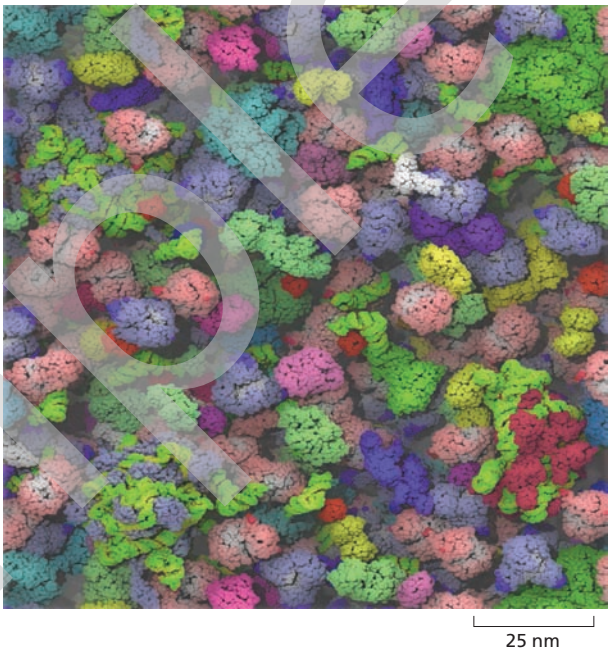


Figure 1–26 The cytosol is extremely crowded. This atomically detailed model of the cytosol of *E. coli* is based on the sizes and concentrations of 50 of the most abundant large molecules present in the bacterium. RNAs, proteins, and ribosomes are shown in different colors (Movie 1.2). (From S.R. McGuffee and A.H. Elcock, *PLoS Comput. Biol.* 6:e1000694, 2010.)

liquid solution (**Figure 1–26**). The cytosol is the site of many chemical reactions that are fundamental to the cell's existence. The early steps in the breakdown of nutrient molecules take place in the cytosol, for example, and it is here that most proteins are made by ribosomes.

QUESTION 1–5

Suggest a reason why it would be advantageous for eukaryotic cells to evolve elaborate internal membrane systems that allow them to import substances from the outside, as shown in Figure 1–25.

The Cytoskeleton Is Responsible for Directed Cell Movements

The cytosol is not just a structureless soup of chemicals and organelles. Using an electron microscope, one can see that in eukaryotic cells the cytosol is criss-crossed by long, fine filaments. Frequently, the filaments are seen to be anchored at one end to the plasma membrane or to radiate out from a central site adjacent to the nucleus. This system of protein filaments, called the **cytoskeleton**, is composed of three major filament types (**Figure 1–27**). The thinnest of these filaments are the *actin filaments*; they are abundant in all eukaryotic cells but occur in especially large numbers inside muscle cells, where they serve as a central part of the machinery responsible for muscle contraction. The thickest filaments in the cytosol are called *microtubules* (see Figure 1–7B), because they have the form of minute hollow tubes; in dividing cells, they become reorganized into a spectacular array that helps pull the duplicated chromosomes

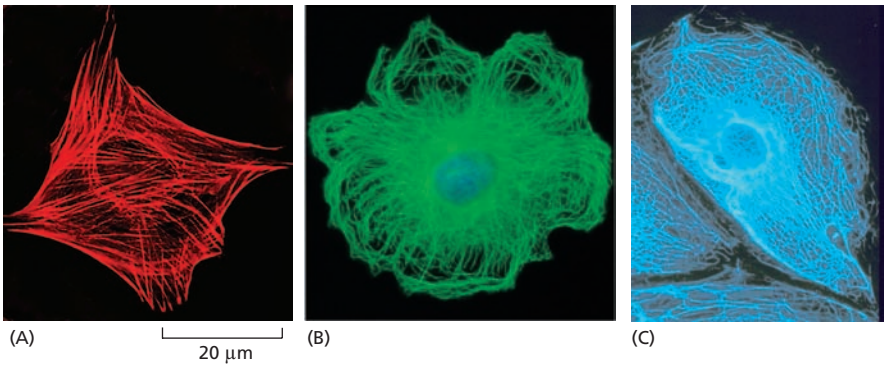


Figure 1–27 The cytoskeleton is a network of protein filaments that can be seen criss-crossing the cytoplasm of eukaryotic cells. The three major types of filaments can be detected using different fluorescent stains. Shown here are (A) actin filaments, (B) microtubules, and (C) intermediate filaments. Intermediate filaments are not found in the cytoplasm of cells with cell walls, such as plant cells. (A, Molecular Expressions at Florida State University; B, courtesy of Nancy Kedersha; C, courtesy of Clive Lloyd.)

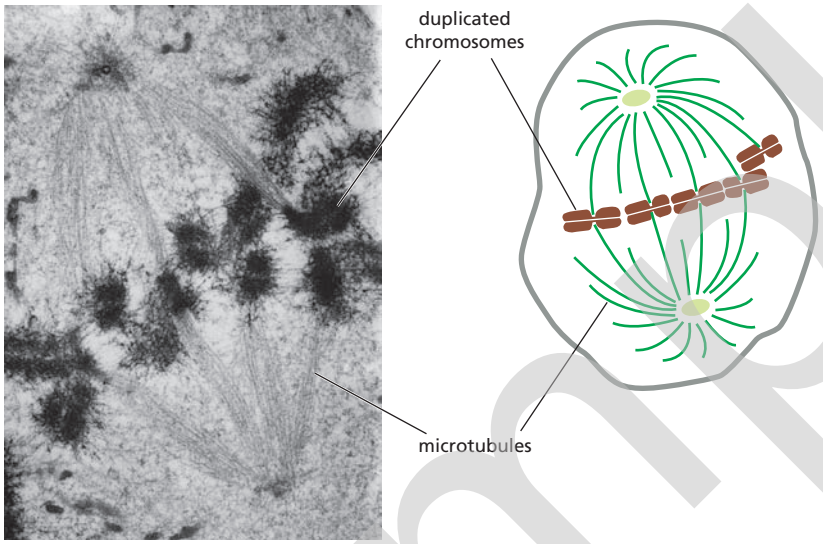


Figure 1–28 Microtubules help segregate the chromosomes in a dividing animal cell. A transmission electron micrograph and schematic drawing show duplicated chromosomes attached to the microtubules of a mitotic spindle (discussed in Chapter 18). When a cell divides, its nuclear envelope breaks down and its DNA condenses into visible chromosomes, each of which has duplicated to form a pair of conjoined chromosomes that will ultimately be pulled apart into separate daughter cells by the spindle microtubules. See also Panel 1–1, pp. 12–13. (Photomicrograph courtesy of Conly L. Rieder, Albany, New York.)

apart and distribute them equally to the two daughter cells (**Figure 1–28**). Intermediate in thickness between actin filaments and microtubules are the *intermediate filaments*, which serve to strengthen most animal cells. These three types of filaments, together with other proteins that attach to them, form a system of girders, ropes, and motors that gives the cell its mechanical strength, controls its shape, and drives and guides its movements (**Movie 1.3** and **Movie 1.4**).

Because the cytoskeleton governs the internal organization of the cell as well as its external features, it is as necessary to a plant cell—boxed in by a tough cell wall—as it is to an animal cell that freely bends, stretches, swims, or crawls. In a plant cell, for example, organelles such as mitochondria are driven in a constant stream around the cell interior along cytoskeletal tracks (**Movie 1.5**). And animal cells and plant cells alike depend on the cytoskeleton to separate their internal components into two daughter cells during cell division (see Figure 1–28).

The cytoskeleton's role in cell division may be its most ancient function. Even bacteria contain proteins that are distantly related to those that form the cytoskeletal elements involved in eukaryotic cell division; in bacteria, these proteins also form filaments that play a part in cell division. We examine the cytoskeleton in detail in Chapter 17, discuss its role in cell division in Chapter 18, and review how it responds to signals from outside the cell in Chapter 16.

The Cytosol Is Far from Static

The cell interior is in constant motion. The cytoskeleton is a dynamic jungle of protein ropes that are continually being strung together and taken apart; its filaments can assemble and then disappear in a matter of minutes. *Motor proteins* use the energy stored in molecules of ATP to trundle along these tracks and cables, carrying organelles and proteins throughout the cytoplasm, and racing across the width of the cell in seconds. In addition, the large and small molecules that fill every free space in the cell are knocked to and fro by random thermal motion, constantly colliding with one another and with other structures in the cell's crowded cytosol.

Of course, neither the bustling nature of the cell's interior nor the details of cell structure were appreciated when scientists first peered at cells in a microscope; our knowledge of cell structure accumulated slowly.

TABLE 1–1 HISTORICAL LANDMARKS IN DETERMINING CELL STRUCTURE

1665	Hooke uses a primitive microscope to describe small chambers in sections of cork that he calls "cells"
1674	Leeuwenhoek reports his discovery of protozoa. Nine years later, he sees bacteria for the first time
1833	Brown publishes his microscopic observations of orchids, clearly describing the cell nucleus
1839	Schleiden and Schwann propose the cell theory, stating that the nucleated cell is the universal building block of plant and animal tissues
1857	Kölliker describes mitochondria in muscle cells
1879	Flemming describes with great clarity chromosome behavior during mitosis in animal cells
1881	Cajal and other histologists develop staining methods that reveal the structure of nerve cells and the organization of neural tissue
1898	Golgi first sees and describes the Golgi apparatus by staining cells with silver nitrate
1902	Boveri links chromosomes and heredity by observing chromosome behavior during sexual reproduction
1952	Palade, Porter, and Sjöstrand develop methods of electron microscopy that enable many intracellular structures to be seen for the first time. In one of the first applications of these techniques, Huxley shows that muscle contains arrays of protein filaments—the first evidence of a cytoskeleton
1957	Robertson describes the bilayer structure of the cell membrane, seen for the first time in the electron microscope
1960	Kendrew describes the first detailed protein structure (sperm whale myoglobin) to a resolution of 0.2 nm using x-ray crystallography. Perutz proposes a lower-resolution structure for hemoglobin
1965	de Duve and his colleagues use a cell-fractionation technique to separate peroxisomes, mitochondria, and lysosomes from a preparation of rat liver
1968	Petran and collaborators make the first confocal microscope
1970	Frye and Edidin use fluorescent antibodies to show that plasma membrane molecules can diffuse in the plane of the membrane, indicating that cell membranes are fluid
1974	Lazarides and Weber use fluorescent antibodies to stain the cytoskeleton
1994	Chalfie and collaborators introduce green fluorescent protein (GFP) as a marker to follow the behavior of proteins in living cells
1990s–2000s	Betzig, Hell, and Moerner develop techniques for super-resolution fluorescence microscopy that allow observation of biological molecules too small to be resolved by conventional light or fluorescence microscopy

A few of the key discoveries are listed in **Table 1–1**. In addition, **Panel 1–2** (p. 25) summarizes the main differences between animal, plant, and bacterial cells.

Eukaryotic Cells May Have Originated as Predators

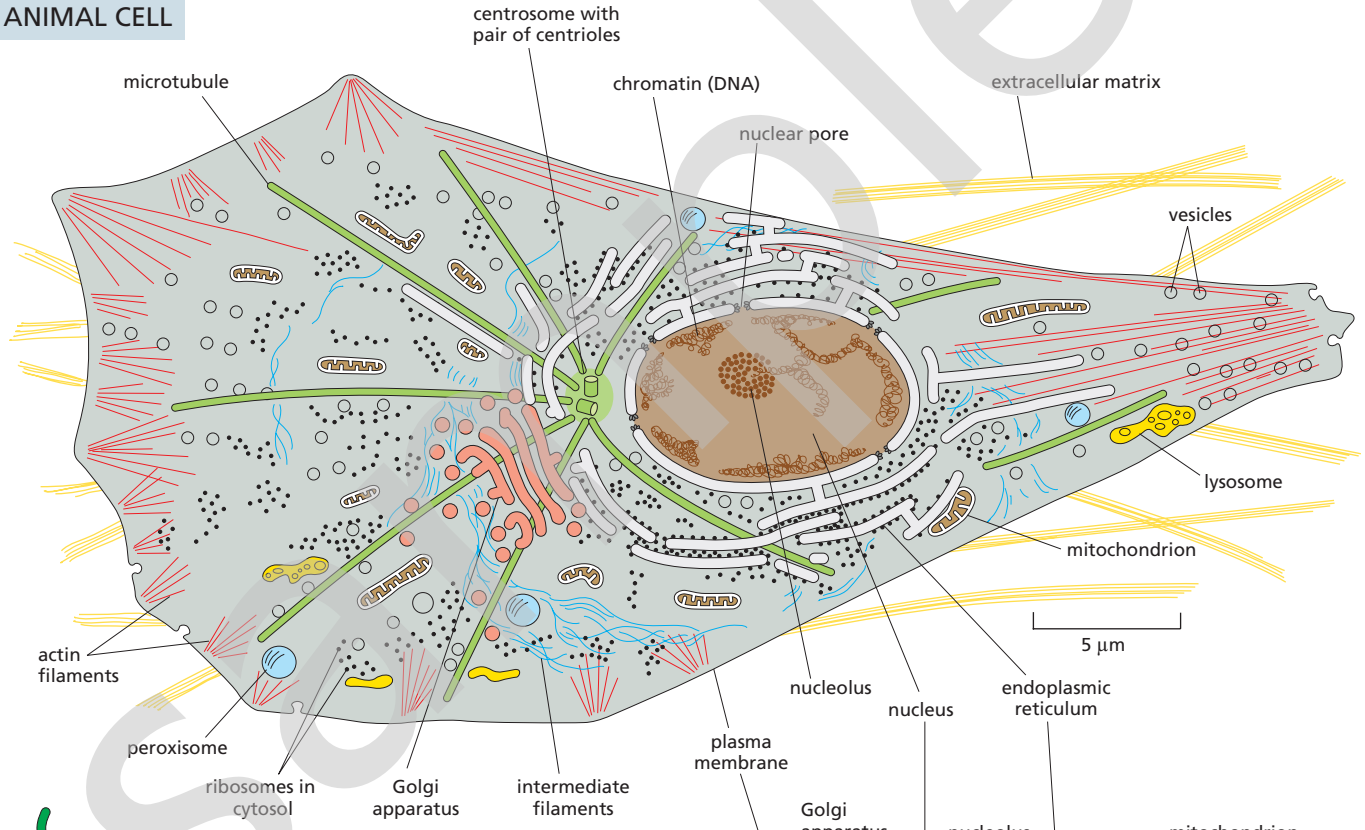
Eukaryotic cells are typically 10 times the length and 1000 times the volume of prokaryotic cells, although there is huge size variation within each category. They also possess a whole collection of features—a nucleus, a versatile cytoskeleton, mitochondria, and other organelles—that set them apart from bacteria and archaea.

When and how eukaryotes evolved these systems remains something of a mystery. Although eukaryotes, bacteria, and archaea must have diverged from one another very early in the history of life on Earth (discussed in Chapter 14), the eukaryotes did not acquire all of their distinctive features at the same time (**Figure 1–29**). According to one theory, the ancestral eukaryotic cell was a predator that fed by capturing other cells. Such a way of life requires a large size, a flexible membrane, and a cytoskeleton to help the cell move and eat. The nuclear compartment may have evolved to keep the DNA segregated from this physical and chemical

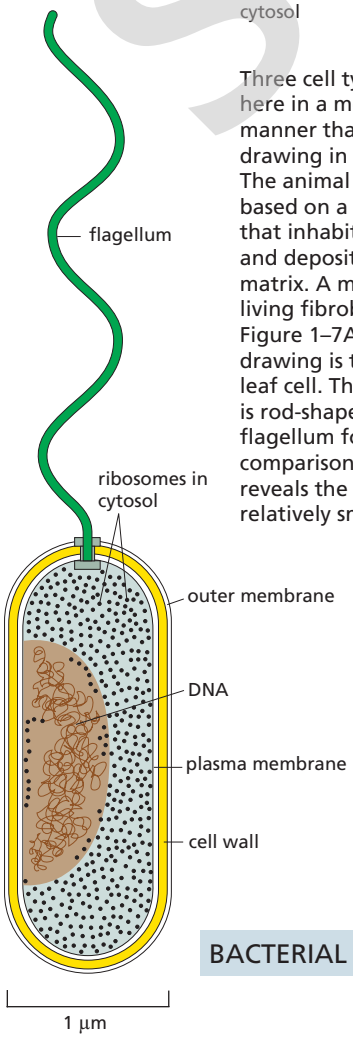
QUESTION 1–6

Discuss the relative advantages and disadvantages of light and electron microscopy. How could you best visualize a living skin cell, a yeast mitochondrion, a bacterium, and a microtubule?

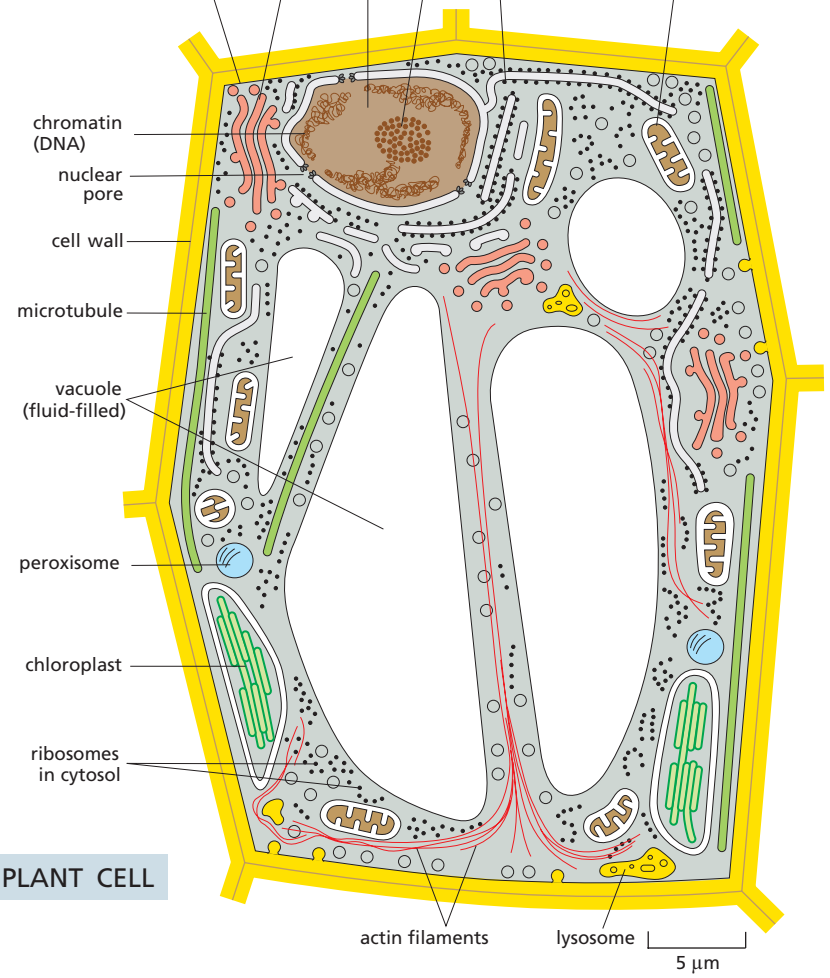
ANIMAL CELL



Three cell types are drawn here in a more realistic manner than in the schematic drawing in Figure 1–24. The animal cell drawing is based on a fibroblast, a cell that inhabits connective tissue and deposits extracellular matrix. A micrograph of a living fibroblast is shown in Figure 1–7A. The plant cell drawing is typical of a young leaf cell. The bacterium shown is rod-shaped and has a single flagellum for motility. A comparison of the scale bars reveals the bacterium's relatively small size.



BACTERIAL CELL



PLANT CELL

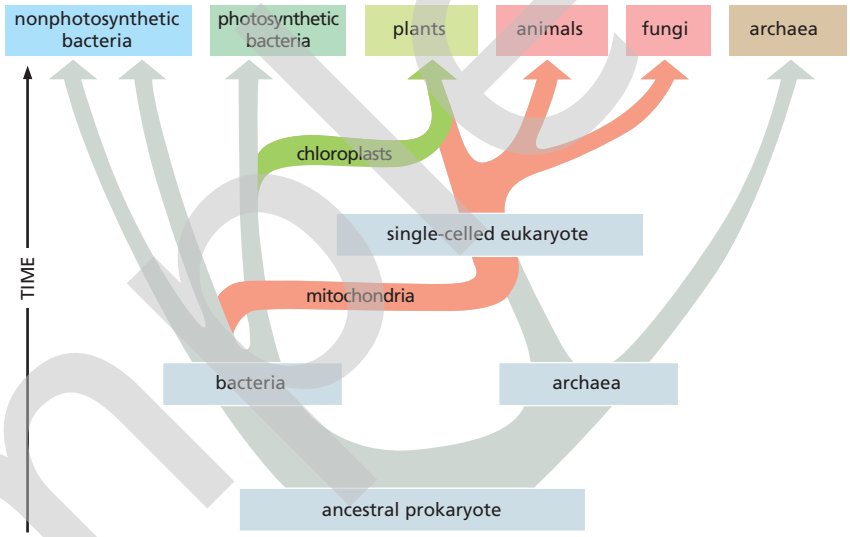


Figure 1–29 Where did eukaryotes come from? The eukaryotic, bacterial, and archaean lineages diverged from one another more than 3 billion years ago—very early in the evolution of life on Earth. Some time later, eukaryotes are thought to have acquired mitochondria; later still, a subset of eukaryotes acquired chloroplasts. Mitochondria are essentially the same in plants, animals, and fungi, and therefore were presumably acquired before these lines diverged about 1.5 billion years ago.

hurly-burly, so as to allow more delicate and complex control of the way the cell reads out its genetic information.

Such a primitive eukaryotic cell, with a nucleus and cytoskeleton, was most likely the sort of cell that engulfed the free-living, oxygen-consuming bacteria that were the likely ancestors of the mitochondria (see Figure 1–19). This partnership is thought to have been established 1.5 billion years ago, when the Earth's atmosphere first became rich in oxygen. A subset of these cells later acquired chloroplasts by engulfing photosynthetic bacteria (see Figure 1–21). The likely history of these endosymbiotic events is illustrated in Figure 1–29.

That single-celled eukaryotes can prey upon and swallow other cells is borne out by the behavior of many present-day **protozoans**: a class of free-living, motile, unicellular organisms. *Didinium*, for example, is a large, carnivorous protozoan with a diameter of about 150 μm—roughly 10 times that of the average human cell. It has a globular body encircled by two fringes of cilia, and its front end is flattened except for a single protrusion rather like a snout (**Figure 1–30A**). *Didinium* swims at high speed by means of its beating cilia. When it encounters a suitable prey, usually another type of protozoan, it releases numerous small, paralyzing darts from its snout region. *Didinium* then attaches to and devours

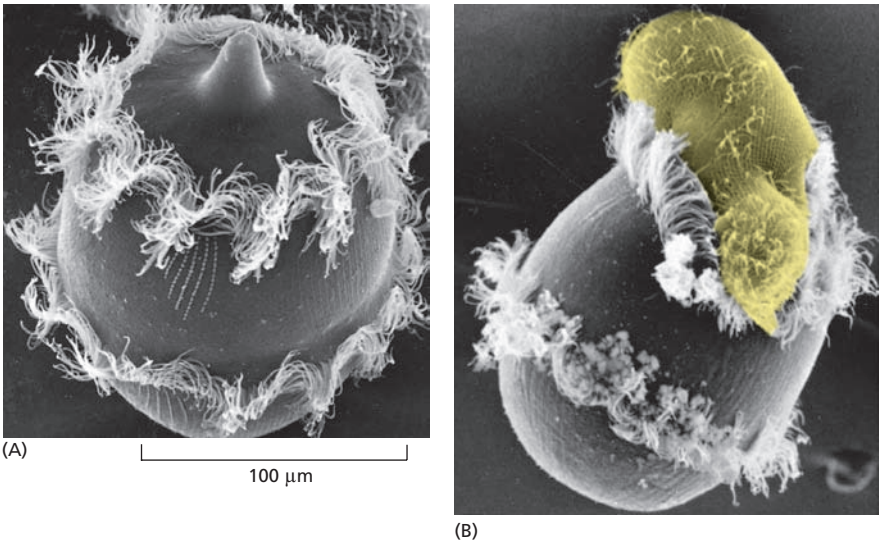


Figure 1–30 One protozoan eats another. (A) The scanning electron micrograph shows *Didinium* on its own, with its circumferential rings of beating cilia and its "snout" at the top. (B) *Didinium* is seen ingesting another ciliated protozoan, a *Paramecium*, artificially colored *yellow*. (Courtesy of D. Barlow.)

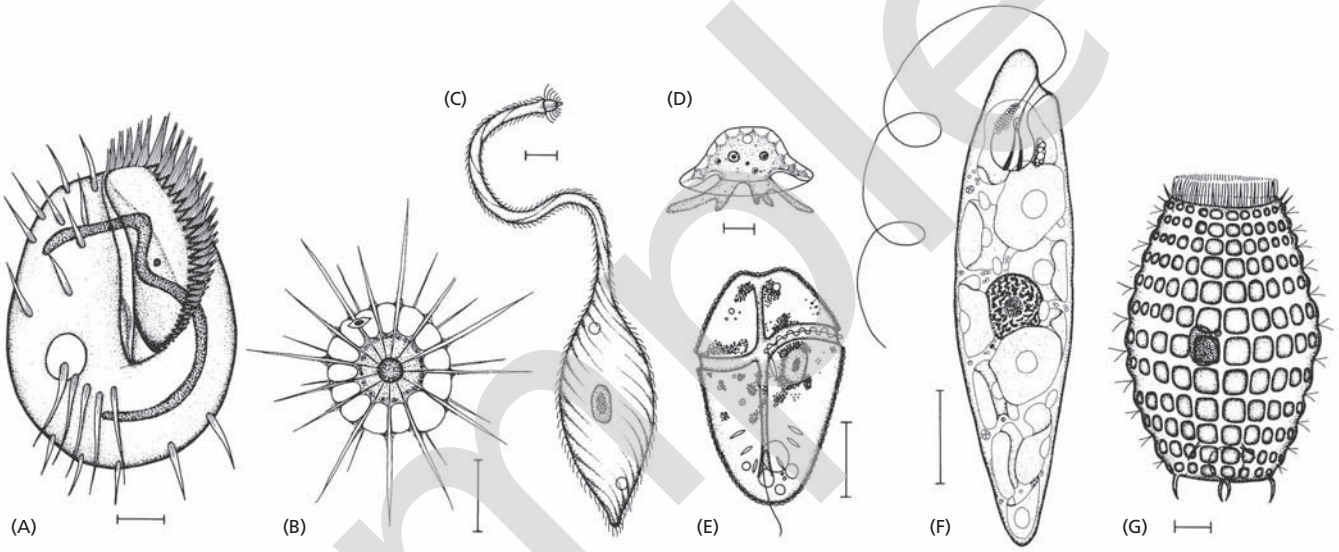


Figure 1–31 An assortment of protozoans illustrates the enormous variety within this class of single-celled eukaryotes. These drawings are done to different scales, but in each case the scale bar represents 10 μm. The organisms in (A), (C), and (G) are ciliates; (B) is a heliozoan; (D) is an amoeba; (E) is a dinoflagellate; and (F) is a euglenoid. To see the latter in action, watch Movie 1.6. Because these organisms can only be seen with the aid of a microscope, they are also referred to as microorganisms. (From M.A. Sleigh, The Biology of Protozoa. London: Edward Arnold, 1973. With permission from Edward Arnold.)

the other cell, inverting like a hollow ball to engulf its victim, which can be almost as large as itself (Figure 1–30B).

Not all protozoans are predators. They can be photosynthetic or carnivorous, motile or sedentary. Their anatomy is often elaborate and includes such structures as sensory bristles, photoreceptors, beating cilia, stalklike appendages, mouthparts, stinging darts, and musclelike contractile bundles. Although they are single cells, protozoans can be as intricate and versatile as many multicellular organisms (Figure 1–31). Much remains to be learned about fundamental cell biology from studies of these fascinating life-forms.

MODEL ORGANISMS

All cells are thought to be descended from a common ancestor, whose fundamental properties have been conserved through evolution. Thus, knowledge gained from the study of one organism contributes to our understanding of others, including ourselves. But certain organisms are easier than others to study in the laboratory. Some reproduce rapidly and are convenient for genetic manipulations; others are multicellular but transparent, so the development of all their internal tissues and organs can be viewed directly in the live animal. For reasons such as these, biologists have become dedicated to studying a few chosen species, pooling their knowledge to gain a deeper understanding than could be achieved if their efforts were spread over many different species. Although the roster of these representative organisms is continually expanding, a few stand out in terms of the breadth and depth of information that has been accumulated about them over the years—knowledge that contributes to our understanding of how all cells work. In this section, we examine some of these **model organisms** and review the benefits that each offers to the study of cell biology and, in many cases, to the promotion of human health.

Molecular Biologists Have Focused on *E. coli*

In molecular terms, we understand the workings of the bacterium *Escherichia coli—E. coli* for short—more thoroughly than those of any other living organism (see Figure 1–11). This small, rod-shaped cell normally lives in the gut of humans and other vertebrates, but it also grows happily and reproduces rapidly in a simple nutrient broth in a culture bottle.

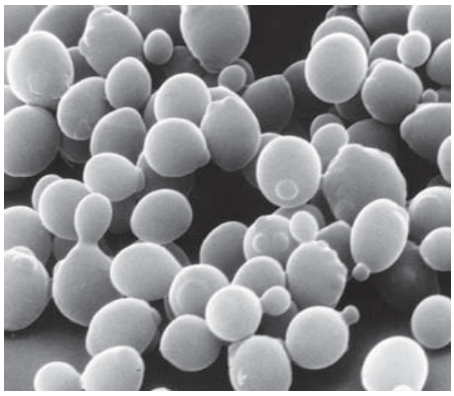


Figure 1–32 The yeast *Saccharomyces cerevisiae* is a model eukaryote. In this scanning electron micrograph, a number of the cells are captured in the process of dividing, which they do by budding. Another micrograph of the same species is shown in Figure 1–14. (Courtesy of Ira Herskowitz and Eric Schabtach.)

Most of our knowledge of the fundamental mechanisms of life—including how cells replicate their DNA and how they decode these genetic instructions to make proteins—has come from studies of *E. coli*. Subsequent research has confirmed that these basic processes occur in essentially the same way in our own cells as they do in *E. coli*.

Brewer's Yeast Is a Simple Eukaryote

We tend to be preoccupied with eukaryotes because we are eukaryotes ourselves. But humans are complicated and reproduce slowly. So to get a handle on the fundamental biology of eukaryotes, we study a simpler representative—one that is easier and cheaper to keep and reproduces more rapidly. A popular choice has been the budding yeast *Saccharomyces cerevisiae* (**Figure 1–32**)—the same microorganism that is used for brewing beer and baking bread.

S. cerevisiae is a small, single-celled fungus that is at least as closely related to animals as it is to plants. Like other fungi, it has a rigid cell wall, is relatively immobile, and possesses mitochondria but not chloroplasts. When nutrients are plentiful, *S. cerevisiae* reproduces almost as rapidly as a bacterium. Yet it carries out all the basic tasks that every eukaryotic cell must perform. Genetic and biochemical studies in yeast have been crucial to understanding many basic mechanisms in eukaryotic cells, including the cell-division cycle—the chain of events by which the nucleus and all the other components of a cell are duplicated and parceled out to create two daughter cells. The machinery that governs cell division has been so well conserved over the course of evolution that many of its components can function interchangeably in yeast and human cells (**How We Know**, pp. 30–31). Darwin himself would no doubt have been stunned by this dramatic example of evolutionary conservation.

Arabidopsis Has Been Chosen as a Model Plant

The large, multicellular organisms that we see around us—both plants and animals—seem fantastically varied, but they are much closer to one another, in their evolutionary origins and their basic cell biology, than they are to the great host of microscopic single-celled organisms. Whereas bacteria, archaea, and eukaryotes separated from each other more than 3 billion years ago, plants, animals, and fungi diverged only about 1.5 billion years ago, and the different species of flowering plants less than 200 million years ago (see Figure 1–29).

The close evolutionary relationship among all flowering plants means that we can gain insight into their cell and molecular biology by focusing on just a few convenient species for detailed analysis. Out of the several hundred thousand species of flowering plants on Earth today, molecular biologists have focused their efforts on a small weed, the common wall cress *Arabidopsis thaliana* (**Figure 1–33**), which can be grown indoors in large numbers: one plant can produce thousands of offspring within 8–10 weeks. Because genes found in *Arabidopsis* have counterparts in agricultural species, studying this simple weed provides insights into the development and physiology of the crop plants upon which our lives depend, as well as into the evolution of all the other plant species that dominate nearly every ecosystem on the planet.

Figure 1–33 *Arabidopsis thaliana*, the common wall cress, is a model plant. This small weed has become the favorite organism of plant molecular and developmental biologists. (Courtesy of Toni Hayden and the John Innes Centre.)

Figure 1–34 *Drosophila melanogaster* is a favorite among developmental biologists and geneticists. Molecular genetic studies on this small fly have provided a key to the understanding of how all animals develop. (Edward B. Lewis. Courtesy of the Archives, California Institute of Technology.)

Model Animals Include Flies, Worms, Fish, and Mice

Multicellular animals account for the majority of all named species of living organisms, and the majority of animal species are insects. It is fitting, therefore, that an insect, the small fruit fly *Drosophila melanogaster* (**Figure 1–34**), should occupy a central place in biological research. The foundations of classical genetics (which we discuss in Chapter 19) were built to a large extent on studies of this insect. More than 80 years ago, genetic analysis of the fruit fly provided definitive proof that genes—the units of heredity—are carried on chromosomes. In more recent times, *Drosophila*, more than any other organism, has shown us how the genetic instructions encoded in DNA molecules direct the development of a fertilized egg cell (or *zygote*) into an adult multicellular organism containing vast numbers of different cell types organized in a precise and predictable way. *Drosophila* mutants with body parts strangely misplaced or oddly patterned have provided the key to identifying and characterizing the genes that are needed to make a properly structured adult body, with gut, wings, legs, eyes, and all the other bits and pieces—all in their correct places. These genes—which are copied and passed on to every cell in the body—define how each cell will behave in its social interactions with its sisters and cousins, thus controlling the structures that the cells can create, a regulatory feat we return to in Chapter 8. More importantly, the genes responsible for the development of *Drosophila* have turned out to be amazingly similar to those of humans—far more similar than one would suspect from the outward appearances of the two species. Thus the fly serves as a valuable model for studying human development as well as the genetic basis of many human diseases.

Another widely studied animal is the nematode worm *Caenorhabditis elegans* (**Figure 1–35**), a harmless relative of the eelworms that attack the

QUESTION 1–7

Your next-door neighbor has donated $100 in support of cancer research and is horrified to learn that her money is being spent on studying brewer's yeast. How could you put her mind at ease?

Figure 1–35 *Caenorhabditis elegans* is a small nematode worm that normally lives in the soil. Most individuals are hermaphrodites, producing both sperm and eggs (the latter of which can be seen just beneath the skin along the underside of the animal). *C. elegans* was the first multicellular organism to have its complete genome sequenced. (Courtesy of Maria Gallegos.)

All living things are made of cells, and all cells—as we have discussed in this chapter—are fundamentally similar inside: they store their genetic instructions in DNA molecules, which direct the production of RNA molecules that direct the production of proteins. It is largely the proteins that carry out the cell's chemical reactions, give the cell its shape, and control its behavior. But how deep do these similarities between cells—and the organisms they comprise—really run? Are proteins from one organism interchangeable with proteins from another? Would an enzyme that breaks down glucose in a bacterium, for example, be able to digest the same sugar if it were placed inside a yeast cell or a cell from a lobster or a human? What about the molecular machines that copy and interpret genetic information? Are they functionally equivalent from one organism to another? Insights have come from many sources, but the most stunning and dramatic answer came from experiments performed on humble yeast cells. These studies, which shocked the biological community, focused on one of the most fundamental processes of life—cell division.

Division and discovery

All cells come from other cells, and the only way to make a new cell is through division of a preexisting one. To reproduce, a parent cell must execute an orderly sequence of reactions, through which it duplicates its contents and divides in two. This critical process of duplication and division—known as the *cell-division cycle*, or *cell cycle* for short—is complex and carefully controlled. Defects in any of the proteins involved can be devastating to the cell.

Fortunately for biologists, this acute reliance on crucial proteins makes them easy to identify and study. If a protein is essential for a given process, a mutation that results in an abnormal protein—or in no protein at all—can prevent the cell from carrying out the process. By isolating organisms that are defective in their cell-division cycle, scientists have worked backward to discover the proteins that control progress through the cycle.

The study of cell-cycle mutants has been particularly successful in yeasts. Yeasts are unicellular fungi and are popular organisms for such genetic studies. They are eukaryotes, like us, but they are small, simple, rapidly reproducing, and easy to manipulate genetically. Yeast mutants that are defective in their ability to complete cell division have led to the discovery of many genes that control the cell-division cycle—the so-called *Cdc* genes—and have provided a detailed understanding of how these genes, and the proteins they encode, actually work.

Paul Nurse and his colleagues used this approach to identify *Cdc* genes in the yeast *Schizosaccharomyces pombe*, which is named after the African beer from which it was first isolated. *S. pombe* is a rod-shaped cell, which grows by elongation at its ends and divides by fission into two, through the formation of a partition in the center of the rod (see Figure 1–1E). The researchers found that one of the *Cdc* genes they had identified, called *Cdc2*, was required to trigger several key events in the cell-division cycle. When that gene was inactivated by a mutation, the yeast cells would not divide. And when the cells were provided with a normal copy of the gene, their ability to reproduce was restored.

It's obvious that replacing a faulty *Cdc2* gene in *S. pombe* with a functioning *Cdc2* gene from the same yeast should repair the damage and enable the cell to divide normally. But what about using a similar cell-division gene from a different organism? That's the question the Nurse team tackled next.

Next of kin

Saccharomyces cerevisiae is another kind of yeast and is one of a handful of model organisms biologists have chosen to study to expand their understanding of how eukaryotic cells work. Also used to brew beer, *S. cerevisiae* divides by forming a small bud that grows steadily until it separates from the mother cell (see Figures 1–14 and 1–32). Although *S. cerevisiae* and *S. pombe* differ in their style of division, both rely on a complex network of interacting proteins to get the job done. But could the proteins from one type of yeast substitute for those of the other?

To find out, Nurse and his colleagues prepared DNA from healthy *S. cerevisiae*, and they introduced this DNA into *S. pombe* cells that contained a temperature-sensitive mutation in the *Cdc2* gene that kept the cells from dividing when the heat was turned up. And they found that some of the mutant *S. pombe* cells regained the ability to proliferate at the elevated temperature. If spread onto a culture plate containing a growth medium, the rescued cells could divide again and again to form visible colonies, each containing millions of individual yeast cells (**Figure 1–36**). Upon closer examination, the researchers discovered that these "rescued" yeast cells had received a fragment of DNA that contained the *S. cerevisiae* version of *Cdc2*—a gene that had been discovered in pioneering studies of the cell cycle by Lee Hartwell and colleagues.

The result was exciting, but perhaps not all that surprising. After all, how different can one yeast be from another? A more demanding test would be to use DNA

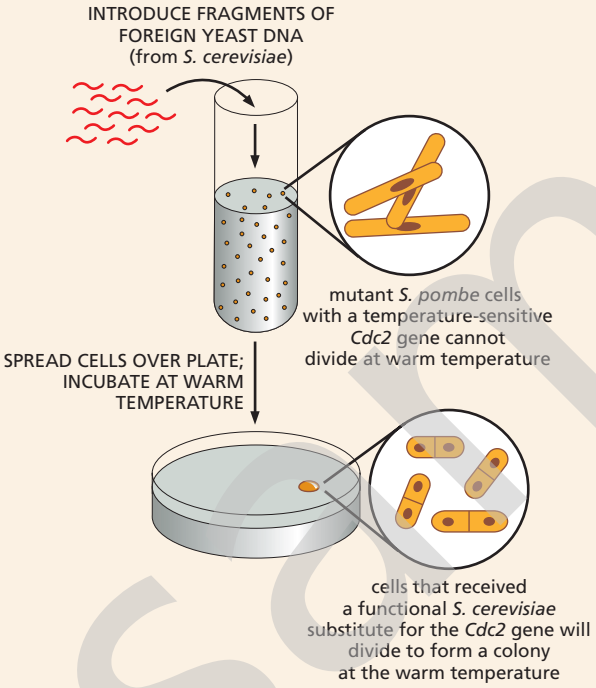


Figure 1–36 *S. pombe* mutants defective in a cell-cycle gene can be rescued by the equivalent gene from *S. cerevisiae*. DNA is collected from *S. cerevisiae* and broken into large fragments, which are introduced into a culture of mutant *S. pombe* cells dividing at room temperature. We discuss how DNA can be manipulated and transferred into different cell types in Chapter 10. These yeast cells are then spread onto a plate containing a suitable growth medium and are incubated at a warm temperature, at which the mutant Cdc2 protein is inactive. The rare cells that survive and proliferate on these plates have been rescued by incorporation of foreign DNA fragments containing the *Cdc2* gene, allowing them to divide normally at the higher temperature.

from a more distant relative. So Nurse's team repeated the experiment, this time using human DNA. And the results were the same. The human equivalent of the *S. pombe Cdc2* gene could rescue the mutant yeast cells, allowing them to divide normally.

Gene reading

This result was much more surprising—even to Nurse. The ancestors of yeast and humans diverged some 1.5 billion years ago. So it was hard to believe that these two organisms would orchestrate cell division in such a similar way. But the results clearly showed that the human and yeast proteins are functionally equivalent. Indeed, Nurse and colleagues demonstrated that the proteins are almost exactly the same size and consist of amino acids strung together in a very similar order; the human Cdc2 protein is identical to the *S. pombe* Cdc2 protein in 63% of its amino acids and is identical to the equivalent protein from *S. cerevisiae* in 58% of its amino acids (**Figure 1–37**). Together with Tim Hunt, who discovered a different cell-cycle protein called cyclin, Nurse and Hartwell shared a 2001 Nobel Prize for their studies of key regulators of the cell cycle.

The Nurse experiments showed that proteins from very different eukaryotes can be functionally interchangeable and suggested that the cell cycle is controlled in a similar fashion in every eukaryotic organism alive today. Apparently, the proteins that orchestrate the cycle in eukaryotes are so fundamentally important that they have been conserved almost unchanged over more than a billion years of eukaryotic evolution.

The same experiment also highlights another, even more basic point. The mutant yeast cells were rescued, not by direct injection of the human protein, but by introduction of a piece of human DNA. Thus the yeast cells could read and use this information correctly, indicating that, in eukaryotes, the molecular machinery for reading the information encoded in DNA is also similar from cell to cell and from organism to organism. A yeast cell has all the equipment it needs to interpret the instructions encoded in a human gene and to use that information to direct the production of a fully functional human protein.

The story of Cdc2 is just one of thousands of examples of how research in yeast cells has provided critical insights into human biology. Although it may sound paradoxical, the shortest, most efficient path to improving human health will often begin with detailed studies of the biology of simple organisms such as brewer's or baker's yeast.

```
human          ···FGLARAFGIPIRVYTHEVVTLWYRSPEVLLGSARYSTPVDIWSIGTIFAELATKLPLFHGDSEIDQLFRIPRALGTPNNEVWPEVESLQDYKNTFP···
S. pombe       ···FGLARSFGVPLRNYTHEIVTLWYRAPEVLLGSRHYSTGVDIWSVGCIFAENIRRSPLFPGDSEIDEIFKIPQVLGTPNEEVWPGVTLLQDYKSTFP···
S. cerevisiae  ···FGLARAFGVPLRAYTHEIVTLWYRAPEVLLGGKQYSTGVDTWSIGCIFAEHCNRLPIFSGDSEIDQIFKIPRVLGTPNEAIWPDIVYLPDFKPSFP···
```

Figure 1–37 The cell-division-cycle proteins from yeasts and human are very similar in their amino acid sequences. Identities between the amino acid sequences of a region of the human Cdc2 protein and a similar region of the equivalent proteins in *S. pombe* and *S. cerevisiae* are indicated by *green* shading. Each amino acid is represented by a single letter.

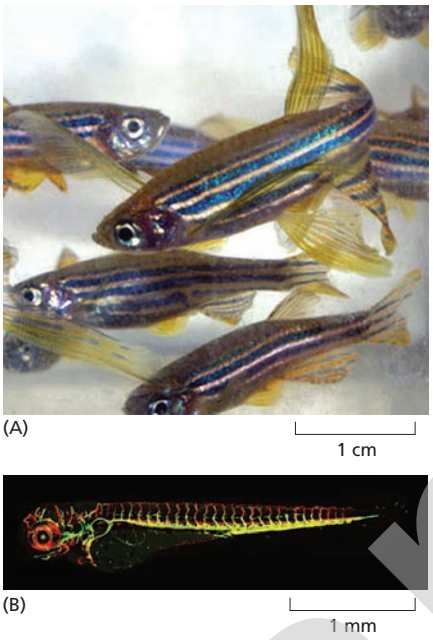


Figure 1–38 Zebrafish are popular models for studies of vertebrate development. (A) These small, hardy, tropical fish—a staple in many home aquaria—are easy and cheap to breed and maintain. (B) They are also ideal for developmental studies, as their transparent embryos develop outside the mother, making it easy to observe cells moving and changing their characters in the living organism as it develops. In this image of a two-day-old embryo, taken with a confocal microscope, a green fluorescent protein marks the developing lymphatic vessels and a red fluorescent protein marks developing blood vessels; regions where the two fluorescent markers coincide appear *yellow*. (A, courtesy of Steve Baskauf; B, from H.M. Jung et al., *Development* 144:2070–2081, 2017.)

roots of crops. Smaller and simpler than *Drosophila*, this creature develops with clockwork precision from a fertilized egg cell into an adult that has exactly 959 body cells (plus a variable number of egg and sperm cells)—an unusual degree of regularity for an animal. We now have a minutely detailed description of the sequence of events by which this occurs—as the cells divide, move, and become specialized according to strict and predictable rules. And a wealth of mutants are available for testing how the worm's genes direct this developmental ballet. Some 70% of human genes have some counterpart in the worm, and *C. elegans*, like *Drosophila*, has proved to be a valuable model for many of the developmental processes that occur in our own bodies. Studies of nematode development, for example, have led to a detailed molecular understanding of *apoptosis*, a form of programmed cell death by which animals dispose of surplus cells, a topic discussed in Chapter 18. This process is also of great importance in the development of cancer, as we discuss in Chapter 20.

Another animal that is providing molecular insights into developmental processes, particularly in vertebrates, is the *zebrafish* (**Figure 1–38A**). Because this creature is transparent for the first two weeks of its life, it provides an ideal system in which to observe how cells behave during development in a living animal (**Figure 1–38B**).

Mammals are among the most complex of animals, and the mouse has long been used as the model organism in which to study mammalian genetics, development, immunology, and cell biology. Thanks to modern molecular biological techniques, it is possible to breed mice with deliberately engineered mutations in any specific gene, or with artificially constructed genes introduced into them (as we discuss in Chapter 10). In this way, one can test what a given gene is required for and how it functions. Almost every human gene has a counterpart in the mouse, with a similar DNA sequence and function. Thus, this animal has proven an excellent model for studying genes that are important in both human health and disease.

Biologists Also Directly Study Humans and Their Cells

Humans are not mice—or fish or flies or worms or yeast—and so many scientists also study human beings themselves. Like bacteria or yeast, our individual cells can be harvested and grown in culture, where investigators can study their biology and more closely examine the genes that govern their functions. Given the appropriate surroundings, many human cell types—indeed, many cell types of animals or plants—will survive, proliferate, and even express specialized properties in a culture dish. Experiments using such cultured cells are sometimes said to be carried out *in vitro* (literally, "in glass") to contrast them with experiments on intact organisms, which are said to be carried out *in vivo* (literally, "in the living").

Although not true for all cell types, many cells—including those harvested from humans—continue to display the differentiated properties appropriate to their origin when they are grown in culture: fibroblasts, a major cell type in connective tissue, continue to secrete proteins that form the extracellular matrix; embryonic heart muscle cells contract spontaneously in the culture dish; nerve cells extend axons and make functional connections with other nerve cells; and epithelial cells join together to form continuous sheets, as they do inside the body (**Figure 1–39** and **Movie 1.7**). Because cultured cells are maintained in a controlled environment, they are accessible to study in ways that are often not possible *in vivo*. For example, cultured cells can be exposed to hormones or growth factors,

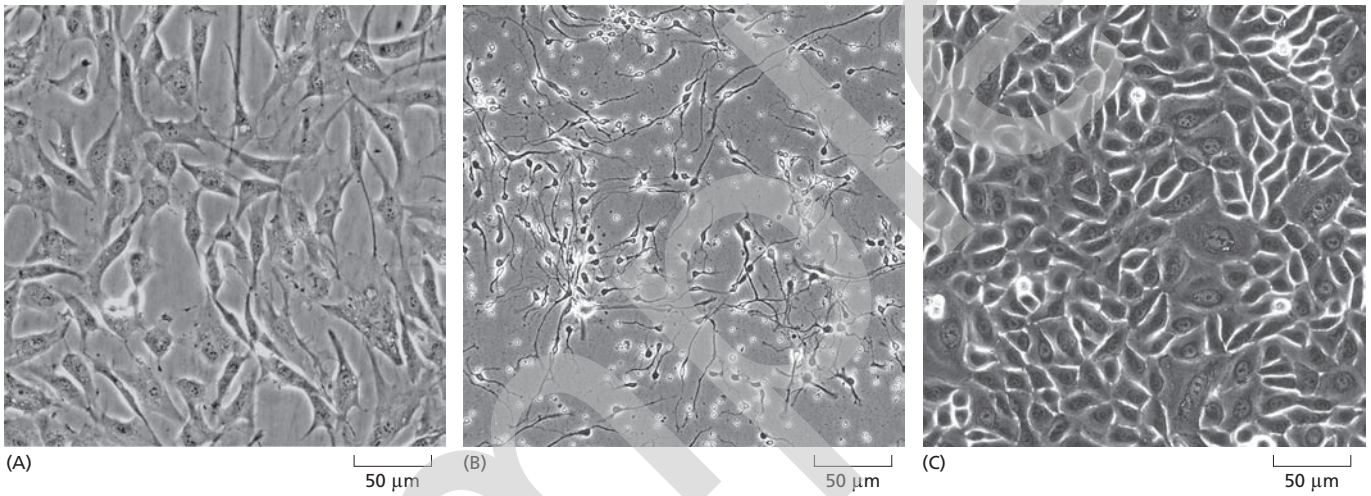


Figure 1–39 Cells in culture often display properties that reflect their origin. These phase-contrast micrographs show a variety of cell types in culture. (A) Fibroblasts from human skin. (B) Human neurons make connections with one another in culture. (C) Epithelial cells from human cervix form a cell sheet in culture. (Micrographs courtesy of ScienCell Research Laboratories, Inc.)

and the effects that these signal molecules have on the shape or behavior of the cells can be easily explored. Remarkably, certain human embryo cells can be coaxed into differentiating into multiple cell types, which can self-assemble into organlike structures that closely resemble a normal organ such as an eye or brain. Such *organoids* can be used to study developmental processes—and how they are derailed in certain human genetic diseases (discussed in Chapter 20).

In addition to studying our cells in culture, humans are also examined directly in clinics. Much of the research on human biology has been driven by medical interests, and the medical database on the human species is enormous. Although naturally occurring, disease-causing mutations in any given human gene are rare, the consequences are well documented. This is because humans are unique among animals in that they report and record their own genetic defects: in no other species are billions of individuals so intensively examined, described, and investigated.

Nevertheless, the extent of our ignorance is still daunting. The mammalian body is enormously complex, being formed from thousands of billions of cells, and one might despair of ever understanding how the DNA in a fertilized mouse egg cell directs the generation of a mouse rather than a fish, or how the DNA in a human egg cell directs the development of a human rather than a mouse. Yet the revelations of molecular biology have made the task seem eminently approachable. As much as anything, this new optimism has come from the realization that the genes of one type of animal have close counterparts in most other types of animals, apparently serving similar functions (**Figure 1–40**). We all have a common evolutionary origin, and under the surface it seems that we share the same molecular mechanisms. Flies, worms, fish, mice, and humans thus provide a key to understanding how animals in general are made and how their cells work.

Comparing Genome Sequences Reveals Life's Common Heritage

At a molecular level, evolutionary change has been remarkably slow. We can see in present-day organisms many features that have been preserved through more than 3 billion years of life on Earth—about one-fifth of the age of the universe. This evolutionary conservatism provides

Figure 1–40 Different species share similar genes. The human baby and the mouse shown here have remarkably similar white patches on their foreheads because they both have defects in the same gene (called *Kit*), which is required for the normal development, migration, and maintenance of some skin pigment cells. (Courtesy of R.A. Fleischman, *Proc. Natl. Acad. Sci. U.S.A.* 88:10885–10889, 1991.)

the foundation on which the study of molecular biology is built. To set the scene for the chapters that follow, therefore, we end this chapter by considering a little more closely the family relationships and basic similarities among all living things. This topic has been dramatically clarified by technological advances that have allowed us to determine the complete genome sequences of thousands of organisms, including our own species (as discussed in more detail in Chapter 9).

The first thing we note when we look at an organism's genome is its overall size and how many genes it packs into that length of DNA. Prokaryotes carry very little superfluous genetic baggage and, nucleotide-for-nucleotide, they squeeze a lot of information into their relatively small genomes. *E. coli*, for example, carries its genetic instructions in a single, circular, double-stranded molecule of DNA that contains 4.6 million nucleotide pairs and 4300 protein-coding genes. (We focus on the genes that code for proteins because they are the best characterized, and their numbers are the most certain. We review how genes are counted in Chapter 9.) The simplest known bacterium contains only about 500 protein-coding genes, but most prokaryotes have genomes that contain at least 1 million nucleotide pairs and 1000–8000 protein-coding genes. With these few thousand genes, prokaryotes are able to thrive in even the most hostile environments on Earth.

The compact genomes of typical bacteria are dwarfed by the genomes of typical eukaryotes. The human genome, for example, contains about 700 times more DNA than the *E. coli* genome, and the genome of an amoeba contains about 100 times more than ours (**Figure 1–41**). The rest of the

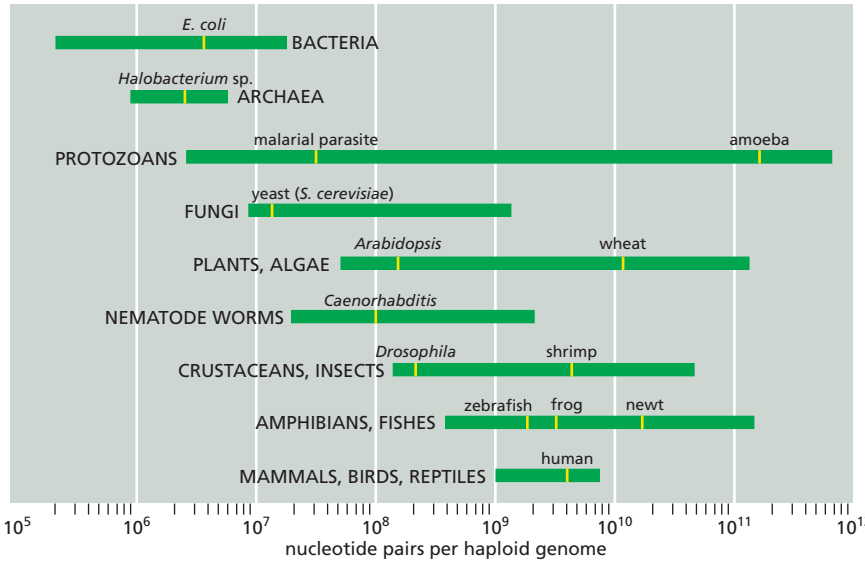


Figure 1–41 Organisms vary enormously in the size of their genomes. Genome size is measured in nucleotide pairs of DNA per haploid genome; that is, per single copy of the genome. (The body cells of sexually reproducing organisms such as ourselves are generally diploid: they contain two copies of the genome, one inherited from the mother, the other from the father.) Closely related organisms can vary widely in the quantity of DNA in their genomes (as indicated by the length of the *green* bars), even though they contain similar numbers of functionally distinct genes; this is because most of the DNA in large genomes does not code for protein, as discussed shortly. (Data from T.R. Gregory, 2008, Animal Genome Size Database: www.genomesize.com.)

TABLE 1–2 SOME MODEL ORGANISMS AND THEIR GENOMES

Organism	Genome Size* (Nucleotide Pairs)	Approximate Number of Protein-coding Genes
Homo sapiens (human)	3200×10^6	19,000
Mus musculus (mouse)	2800×10^6	22,000
Drosophila melanogaster (fruit fly)	180×10^6	14,000
Arabidopsis thaliana (plant)	103×10^6	28,000
Caenorhabditis elegans (roundworm)	100×10^6	22,000
Saccharomyces cerevisiae (yeast)	12.5×10^6	6600
Escherichia coli (bacterium)	4.6×10^6	4300

*Genome size includes an estimate for the amount of highly repeated, noncoding DNA sequence, which does not appear in genome databases.

model organisms we have described have genomes that fall somewhere between *E. coli* and human in terms of size. *S. cerevisiae* contains about 2.5 times as much DNA as *E. coli*; *D. melanogaster* has about 10 times more DNA than *S. cerevisiae*; and *M. musculus* has about 20 times more DNA than *D. melanogaster* (Table 1–2).

In terms of gene numbers, however, the differences are not so great. We have only about five times as many protein-coding genes as *E. coli*, for example. Moreover, many of our genes—and the proteins they encode—fall into closely related family groups, such as the family of hemoglobins, which has nine closely related members in humans. Thus the number of fundamentally different proteins in a human is not very many times more than in the bacterium, and the number of human genes that have identifiable counterparts in the bacterium is a significant fraction of the total.

This high degree of "family resemblance" is striking when we compare the genome sequences of different organisms. When genes from different organisms have very similar nucleotide sequences, it is highly probable that they descended from a common ancestral gene. Such genes (and their protein products) are said to be **homologous**. Now that we have the complete genome sequences of many different organisms from all three domains of life—archaea, bacteria, and eukaryotes—we can search systematically for homologies that span this enormous evolutionary divide. By taking stock of the common inheritance of all living things, scientists are attempting to trace life's origins back to the earliest ancestral cells. We return to this topic in Chapter 9.

Genomes Contain More Than Just Genes

Although our view of genome sequences tends to be "gene-centric," our genomes contain much more than just genes. The vast bulk of our DNA does not code for proteins or for functional RNA molecules. Instead, it includes a mixture of sequences that help regulate gene activity, plus sequences that seem to be dispensable. The large quantity of regulatory DNA contained in the genomes of eukaryotic multicellular organisms allows for enormous complexity and sophistication in the way different genes are brought into action at different times and places. Yet, in the end, the basic list of parts—the set of proteins that the cells can make, as specified by the DNA—is not much longer than the parts list of an automobile, and many of those parts are common not only to all animals, but also to the entire living world.

That DNA can program the growth, development, and reproduction of living cells and complex organisms is truly amazing. In the rest of this book, we will try to explain what is known about how cells work—by examining their component parts, how these parts work together, and how the genome of each cell directs the manufacture of the parts the cell needs to function and to reproduce.

ESSENTIAL CONCEPTS

- Cells are the fundamental units of life. All present-day cells are believed to have evolved from an ancestral cell that existed more than 3 billion years ago.
- All cells are enclosed by a plasma membrane, which separates the inside of the cell from its environment.
- All cells contain DNA as a store of genetic information and use it to guide the synthesis of RNA molecules and proteins. This molecular relationship underlies cells' ability to self-replicate.
- Cells in a multicellular organism, though they all contain the same DNA, can be very different because they turn on different sets of genes according to their developmental history and to signals they receive from their environment.
- Animal and plant cells are typically 5–20 μm in diameter and can be seen with a light microscope, which also reveals some of their internal components, including the larger organelles.
- The electron microscope reveals even the smallest organelles, but specimens require elaborate preparation and cannot be viewed while alive.
- Specific large molecules can be located in fixed or living cells by fluorescence microscopy.
- The simplest of present-day living cells are prokaryotes—bacteria and archaea: although they contain DNA, they lack a nucleus and most other organelles and probably resemble most closely the original ancestral cell.
- Different species of prokaryotes are diverse in their chemical capabilities and inhabit an amazingly wide range of habitats.
- Eukaryotic cells possess a nucleus and other organelles not found in prokaryotes. They probably evolved in a series of stages, including the acquisition of mitochondria by engulfment of aerobic bacteria and (for cells that carry out photosynthesis) the acquisition of chloroplasts by engulfment of photosynthetic bacteria.
- The nucleus contains the main genetic information of the eukaryotic organism, stored in very long DNA molecules.
- The cytoplasm of eukaryotic cells includes all of the cell's contents outside the nucleus and contains a variety of membrane-enclosed organelles with specialized functions: mitochondria carry out the final oxidation of food molecules and produce ATP; the endoplasmic reticulum and the Golgi apparatus synthesize complex molecules for export from the cell and for insertion in cell membranes; lysosomes digest large molecules; in plant cells and other photosynthetic eukaryotes, chloroplasts perform photosynthesis.
- Outside the membrane-enclosed organelles in the cytoplasm is the cytosol, a highly concentrated mixture of large and small molecules that carry out many essential biochemical processes.
- The cytoskeleton is composed of protein filaments that extend throughout the cytoplasm and are responsible for cell shape and movement and for the transport of organelles and large molecular complexes from one intracellular location to another.

- Free-living, single-celled eukaryotic microorganisms are complex cells that, in some cases, can swim, mate, hunt, and devour other microorganisms.
- Animals, plants, and some fungi are multicellular organisms that consist of diverse eukaryotic cell types, all derived from a single fertilized egg cell; the number of such cells cooperating to form a large, multicellular organism such as a human runs into thousands of billions.
- Biologists have chosen a small number of model organisms to study intensely, including the bacterium *E. coli*, brewer's yeast, a nematode worm, a fly, a small plant, a fish, mice, and humans themselves.
- The human genome has about 19,000 protein-coding genes, which is about five times as many as *E. coli* and about 5000 more than the fly.

KEY TERMS

archaeon
bacterium
cell
chloroplast
chromosome
cytoplasm
cytoskeleton
cytosol
DNA
electron microscope
endoplasmic reticulum
eukaryote
evolution
fluorescence microscope
genome
Golgi apparatus
homologous
micrometer
microscope
mitochondrion
model organism
nucleus
organelle
photosynthesis
plasma membrane
prokaryote
protein
protozoan
ribosome
RNA

QUESTIONS

QUESTION 1–8

By now you should be familiar with the following cell components. Briefly define what they are and what function they provide for cells.

A. cytosol

B. cytoplasm

C. mitochondria

D. nucleus

E. chloroplasts

F. lysosomes

G. chromosomes

H. Golgi apparatus

I. peroxisomes

J. plasma membrane

K. endoplasmic reticulum

L. cytoskeleton

M. ribosome

QUESTION 1–9

Which of the following statements are correct? Explain your answers.

A. The hereditary information of a cell is passed on by its proteins.

B. Bacterial DNA is found in the cytoplasm.

C. Plants are composed of prokaryotic cells.

D. With the exception of egg and sperm cells, all of the nucleated cells within a single multicellular organism have the same number of chromosomes.

E. The cytosol includes membrane-enclosed organelles such as lysosomes.

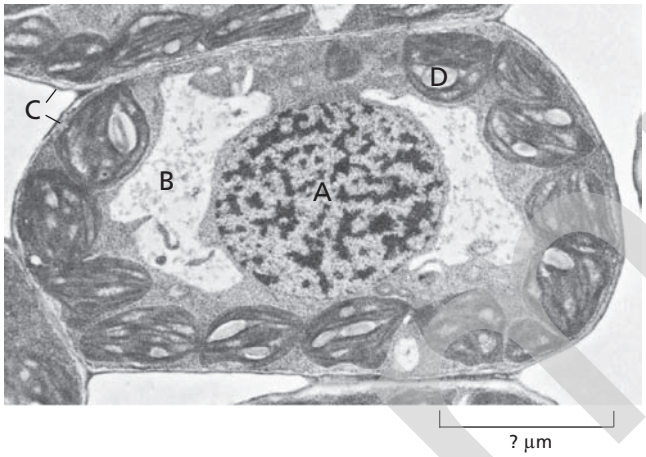
F. The nucleus and a mitochondrion are each surrounded by a double membrane.

G. Protozoans are complex organisms with a set of specialized cells that form tissues such as flagella, mouthparts, stinging darts, and leglike appendages.

H. Lysosomes and peroxisomes are the sites of degradation of unwanted materials.

QUESTION 1–10

Identify the different organelles indicated with letters in the electron micrograph of a plant cell shown below. Estimate the length of the scale bar in the figure.



QUESTION 1–11

There are three major classes of protein filaments that make up the cytoskeleton of a typical animal cell. What are they, and what are the differences in their functions? Which cytoskeletal filaments would be most plentiful in a muscle cell or in an epidermal cell making up the outer layer of the skin? Explain your answers.

QUESTION 1–12

Natural selection is such a powerful force in evolution because organisms or cells with even a small reproductive advantage will eventually outnumber their competitors. To illustrate how quickly this process can occur, consider a cell culture that contains 1 million bacterial cells that double every 20 minutes. A single cell in this culture acquires a mutation that allows it to divide faster, with a generation time of only 15 minutes. Assuming that there is an unlimited food supply and no cell death, how long would it take before the progeny of the mutated cell became predominant in the culture? (Before you go through the calculation, make a guess: do you think it would take about a day, a week, a month, or a year?) How many cells of either type are present in the culture at this time? (The number of cells N in the culture at time t is described by the equation $N = N_0 \times 2^{t/G}$, where N_0 is the number of cells at zero time and G is the generation time.)

QUESTION 1–13

When bacteria are cultured under adverse conditions—for example, in the presence of a poison such as an antibiotic—most cells grow and divide slowly. But it is not uncommon to find that the rate of proliferation is restored to normal after a few days. Suggest why this may be the case.

QUESTION 1–14

Apply the principle of exponential growth of a population of cells in a culture (as described in Question 1–12) to the cells in a multicellular organism, such as yourself. There are about 10^{13} cells in your body. Assume that one cell has acquired mutations that allow it to divide in an uncontrolled manner to become a cancer cell. Some cancer cells can proliferate with a generation time of about 24 hours. If none of the cancer cells died, how long would it take before 10^{13} cells in your body would be cancer cells? (Use the equation $N = N_0 \times 2^{t/G}$, with t the time and G the generation time. Hint: $10^{13} \approx 2^{43}$.)

QUESTION 1–15

"The structure and function of a living cell are dictated by the laws of chemistry, physics, and thermodynamics." Provide examples that support (or refute) this claim.

QUESTION 1–16

What, if any, are the advantages in being multicellular?

QUESTION 1–17

Draw to scale the outline of two spherical cells, one a bacterium with a diameter of 1 μm, the other an animal cell with a diameter of 15 μm. Calculate the volume, surface area, and surface-to-volume ratio for each cell. How would the latter ratio change if you included the internal membranes of the animal cell in the calculation of surface area (assume internal membranes have 15 times the area of the plasma membrane)? (The volume of a sphere is given by $4\pi r^3/3$ and its surface by $4\pi r^2$, where r is its radius.) Discuss the following hypothesis: "Internal membranes allowed bigger cells to evolve."

QUESTION 1–18

What are the arguments that all living cells evolved from a common ancestor cell? Imagine the very "early days" of evolution of life on Earth. Would you assume that the primordial ancestor cell was the first and only cell to form?

QUESTION 1–19

Looking at some pond water with a light microscope, you notice an unfamiliar rod-shaped cell about 200 μm long. Knowing that some exceptional bacteria can be as big as this or even bigger, you wonder whether your cell is a bacterium or a eukaryote. How will you decide? If it is not a eukaryote, how will you discover whether it is a bacterium or an archaeon?

CHAPTER **TWO** **2**

Chemical Components of Cells

CHEMICAL BONDS

SMALL MOLECULES IN CELLS

MACROMOLECULES IN CELLS

At first sight, it is difficult to comprehend that living creatures are merely chemical systems. Their incredible diversity of form, their seemingly purposeful behavior, and their ability to grow and reproduce all seem to set them apart from the world of solids, liquids, and gases that chemistry normally describes. Indeed, until the late nineteenth century, it was widely believed that all living things contained a vital force—an "animus"—that was responsible for their distinctive properties.

We now know that there is nothing in a living organism that disobeys chemical or physical laws. However, the chemistry of life is indeed a special kind. First, it is based overwhelmingly on carbon compounds, the study of which is known as *organic chemistry*. Second, it depends almost exclusively on chemical reactions that take place in a watery, or *aqueous*, environment and in the relatively narrow range of temperatures experienced on Earth. Third, it is enormously complex: even the simplest cell is vastly more complicated in its chemistry than any other chemical system known. Fourth, it is dominated and coordinated by collections of large **polymers**—molecules made of many chemical **subunits** linked end-to-end—whose unique properties enable cells and organisms to grow and reproduce and to do all the other things that are characteristic of life. Finally, the chemistry of life is tightly regulated: cells deploy a wide variety of mechanisms to make sure that each of their chemical reactions occurs at the proper rate, time, and place.

Because chemistry lies at the heart of all biology, in this chapter, we briefly survey the chemistry of the living cell. We will meet the molecules from which cells are made and examine their structures, shapes, and chemical properties. These molecules determine the size, structure, and functions

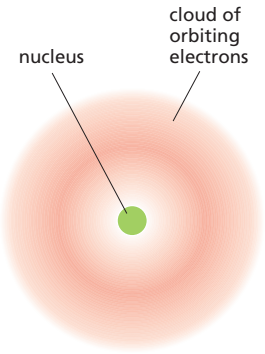


Figure 2–1 An atom consists of a nucleus surrounded by an electron cloud. The dense, positively charged nucleus contains nearly all of the atom's mass. The much lighter and negatively charged electrons occupy space around the nucleus, as governed by the laws of quantum mechanics. The electrons are depicted as a continuous cloud, because there is no way of predicting exactly where an electron is at any given instant. The density of shading of the cloud is an indication of the probability that electrons will be found there.

The diameter of the electron cloud ranges from about 0.1 nm (for hydrogen) to about 0.4 nm (for atoms of high atomic number). The nucleus is very much smaller: about 5×10^{-6} nm for carbon, for example. If this diagram were drawn to scale, the nucleus would not be visible.

of living cells. By understanding how they interact, we can begin to see how cells exploit the laws of chemistry and physics to survive, thrive, and reproduce.

CHEMICAL BONDS

Matter is made of combinations of *elements*—substances such as hydrogen or carbon that cannot be broken down or interconverted by chemical means. The smallest particle of an element that still retains its distinctive chemical properties is an *atom*. The characteristics of substances other than pure elements—including the materials from which living cells are made—depend on which atoms they contain and the way that these atoms are linked together in groups to form *molecules*. To understand living organisms, therefore, it is crucial to know how the chemical bonds that hold atoms together in molecules are formed.

Cells Are Made of Relatively Few Types of Atoms

Each **atom** has at its center a dense, positively charged nucleus, which is surrounded at some distance by a cloud of negatively charged **electrons**, held in orbit by electrostatic attraction to the nucleus (**Figure 2–1**). The nucleus consists of two kinds of subatomic particles: **protons**, which are positively charged, and *neutrons*, which are electrically neutral. The *atomic number* of an element is determined by the number of protons present in its atom's nucleus. An atom of hydrogen has a nucleus composed of a single proton; so hydrogen, with an atomic number of 1, is the lightest element. An atom of carbon has six protons in its nucleus and an atomic number of 6 (**Figure 2–2**).

The electric charge carried by each proton is exactly equal and opposite to the charge carried by a single electron. Because the whole atom is electrically neutral, the number of negatively charged electrons surrounding the nucleus is therefore equal to the number of positively charged protons that the nucleus contains; thus the number of electrons in an atom also equals the atomic number. All atoms of a given element have the same atomic number, and we will see shortly that it is this number that dictates each element's chemical behavior.

Neutrons have essentially the same mass as protons. They contribute to the structural stability of the nucleus: if there are too many or too few, the nucleus may disintegrate by radioactive decay. However, neutrons do not alter the chemical properties of the atom. Thus an element can exist in several physically distinguishable but chemically identical forms, called *isotopes*, each having a different number of neutrons but the same

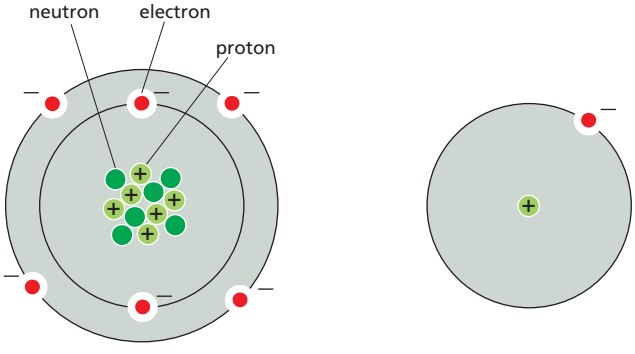


Figure 2–2 The number of protons in an atom determines its atomic number. Schematic representations of an atom of carbon and an atom of hydrogen are shown. The nucleus of every atom except hydrogen consists of both positively charged protons and electrically neutral neutrons; the atomic weight equals the number of protons plus neutrons. The number of electrons in an atom is equal to the number of protons, so that the atom has no net charge.

In contrast to Figure 2–1, the electrons are shown here as individual particles. The concentric *black* circles represent in a highly schematic form the "orbits" (that is, the different distributions) of the electrons. The neutrons, protons, and electrons are in reality minuscule in relation to the atom as a whole; their size is greatly exaggerated here.

number of protons. Multiple isotopes of almost all the elements occur naturally, including some that are unstable—and thus radioactive. For example, while most carbon on Earth exists as carbon 12, a stable isotope with six protons and six neutrons, also present are small amounts of an unstable isotope, carbon 14, which has six protons and eight neutrons. Carbon 14 undergoes radioactive decay at a slow but steady rate, a property that allows archaeologists to estimate the age of organic material.

The **atomic weight** of an atom, or the **molecular weight** of a molecule, is its mass relative to the mass of a hydrogen atom. This value is equal to the number of protons plus the number of neutrons that the atom or molecule contains; because electrons are so light, they contribute almost nothing to the total mass. Thus the major isotope of carbon has an atomic weight of 12 and is written as ^{12}C. The unstable carbon isotope just mentioned has an atomic weight of 14 and is written as ^{14}C. The mass of an atom or a molecule is generally specified in *daltons*, one dalton being an atomic mass unit essentially equal to the mass of a hydrogen atom.

Atoms are so small that it is hard to imagine their size. An individual carbon atom is roughly 0.2 nm in diameter, so it would take about 5 million of them, laid out in a straight line, to span a millimeter. One proton or neutron weighs approximately $1/(6 \times 10^{23})$ gram. As hydrogen has only one proton—thus an atomic weight of 1—1 gram of hydrogen contains 6×10^{23} atoms. For carbon—which has six protons and six neutrons, and an atomic weight of 12—12 grams contain 6×10^{23} atoms. This huge number, called **Avogadro's number**, allows us to relate everyday quantities of chemicals to numbers of individual atoms or molecules. If a substance has a molecular weight of X, X grams of the substance will contain 6×10^{23} molecules. This quantity is called one *mole* of the substance (**Figure 2–3**). The concept of mole is used widely in chemistry as a way to represent the number of molecules that are available to participate in chemical reactions.

There are about 90 naturally occurring elements, each differing from the others in the number of protons and electrons in its atoms. Living things, however, are made of only a small selection of these elements, four of which—carbon (C), hydrogen (H), nitrogen (N), and oxygen (O)—constitute 96% of any organism's weight. This composition differs markedly from that of the nonliving, inorganic environment on Earth (**Figure 2–4**) and is evidence that a distinctive type of chemistry operates in biological systems.

A mole is X grams of a substance, where X is the molecular weight of the substance. A mole will contain 6×10^{23} molecules of the substance.

1 mole of carbon weighs 12 g
1 mole of glucose weighs 180 g
1 mole of sodium chloride weighs 58 g

A one molar solution has a concentration of 1 mole of the substance in 1 liter of solution. A 1 M solution of glucose, for example, contains 180 g/L, and a one millimolar (1 mM) solution contains 180 mg/L.

The standard abbreviation for gram is g; the abbreviation for liter is L.

Figure 2–3 What's a mole? Some simple examples of moles and molar solutions.

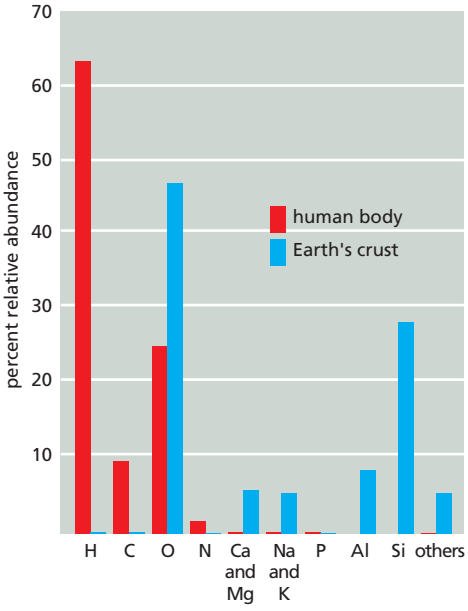


Figure 2–4 The distribution of elements in the Earth's crust differs radically from that in the human body. The abundance of each element is expressed here as a percentage of the total number of atoms present in a biological or geological sample (water included). Thus, for example, more than 60% of the atoms in the human body are hydrogen atoms, and nearly 30% of the atoms in the Earth's crust are silicon atoms (Si). The relative abundance of elements is similar in all living things.

The Outermost Electrons Determine How Atoms Interact

To understand how atoms come together to form the molecules that make up living organisms, we have to pay special attention to each atom's electrons. Protons and neutrons are welded tightly to one another in an atom's nucleus, and they change partners only under extreme conditions—during radioactive decay, for example, or in the interior of the sun or a nuclear reactor. In living tissues, only the electrons of an atom undergo rearrangements. They form the accessible part of the atom and specify the chemical rules by which atoms combine to form molecules.

Electrons are in continuous motion around the nucleus, but motions on this submicroscopic scale obey different laws from those we are familiar with in everyday life. These laws dictate that electrons in an atom can exist only in certain discrete regions of movement—very roughly speaking, in distinct orbits. Moreover, there is a strict limit to the number of electrons that can be accommodated in an orbit of a given type, a so-called *electron shell*. The electrons closest on average to the positively charged nucleus are attracted most strongly to it and occupy the inner,

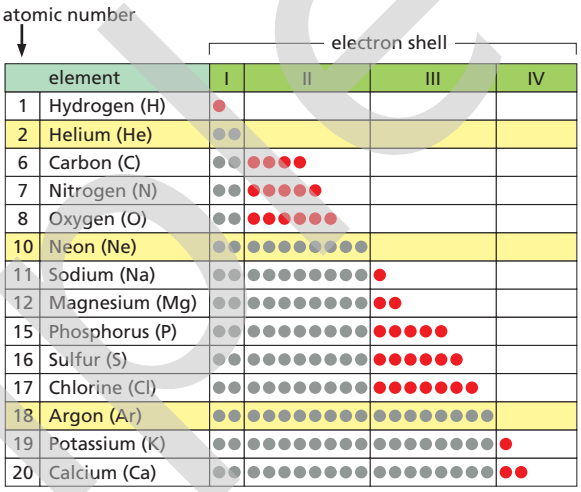


Figure 2–5 An element's chemical reactivity depends on the degree to which its outermost electron shell is filled. All of the elements commonly found in living organisms have outermost shells that are not completely filled. The electrons in these incomplete shells (here shown in *red*) can participate in chemical reactions with other atoms. Inert gases (*yellow*), in contrast, have completely filled outermost shells (*gray*) and are thus chemically unreactive.

QUESTION 2–1

A cup containing exactly 18 g, or 1 mole, of water was emptied into the Aegean Sea 3000 years ago. What are the chances that the same quantity of water, scooped today from the Pacific Ocean, would include at least one of these ancient water molecules? Assume perfect mixing and an approximate volume for the world's oceans of 1.5 billion cubic kilometers (1.5×10^9 km^3).

most tightly bound shell. This innermost shell can hold a maximum of two electrons. The second shell is farther away from the nucleus, and can hold up to eight electrons. The third shell can also hold up to eight electrons, which are even less tightly bound. The fourth and fifth shells can hold 18 electrons each. Atoms with more than four shells are very rare in biological molecules.

The arrangement of electrons in an atom is most stable when all the electrons are in the most tightly bound states that are possible for them—that is, when they occupy the innermost shells, closest to the nucleus. Therefore, with certain exceptions in the larger atoms, the electrons of an atom fill the shells in order—the first before the second, the second before the third, and so on. An atom whose outermost shell is entirely filled with electrons is especially stable and therefore chemically unreactive. Examples are helium with 2 electrons (atomic number 2), neon with 2 + 8 electrons (atomic number 10), and argon with 2 + 8 + 8 electrons (atomic number 18); these are all inert gases. Hydrogen, by contrast, has only one electron, which leaves its outermost shell half-filled, so it is highly reactive. The atoms found in living organisms all have outermost shells that are incompletely filled, and they are therefore able to react with one another to form molecules (**Figure 2–5**).

Because an incompletely filled electron shell is less stable than one that is completely filled, atoms with incomplete outer shells have a strong tendency to interact with other atoms so as to either gain or lose enough electrons to fill the outermost shell. This electron exchange can be achieved either by transferring electrons from one atom to another or by sharing electrons between two atoms. These two strategies generate the two types of **chemical bonds** that can bind atoms strongly to one another: an *ionic bond* is formed when electrons are donated by one atom to another, whereas a *covalent bond* is formed when two atoms share a pair of electrons (**Figure 2–6**).

An H atom, which needs only one more electron to fill its only shell, generally acquires this electron by sharing—forming one covalent bond with another atom. The other most common elements in living cells—C, N, and O, which have an incomplete second shell, and P and S, which have an incomplete third shell (see Figure 2–5)—also tend to share electrons; these elements thus fill their outer shells by forming several covalent bonds. The number of electrons an atom must acquire or lose (either by sharing or by transfer) to attain a filled outer shell determines the number of bonds that the atom can make.

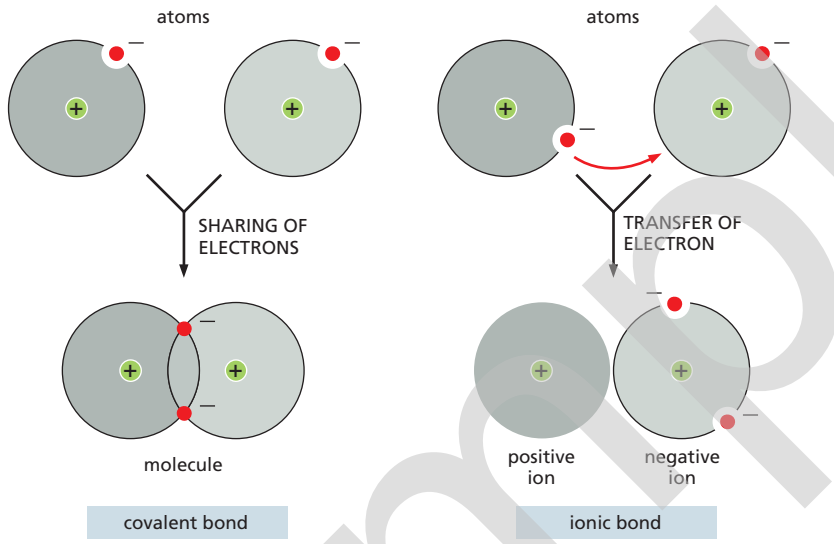
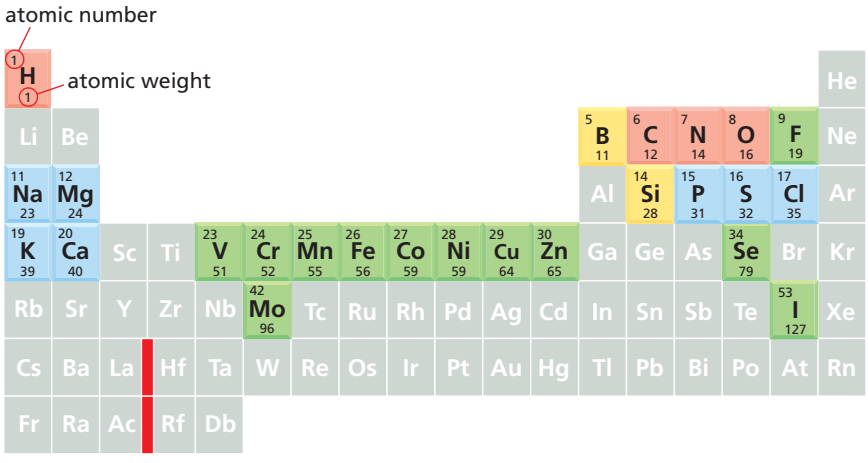


Figure 2–6 Atoms can attain a more stable arrangement of electrons in their outermost shell by interacting with one another. A covalent bond is formed when electrons are shared between atoms. An ionic bond is formed when electrons are transferred from one atom to the other. The two cases shown represent extremes; often, covalent bonds form with a partial transfer (unequal sharing of electrons), resulting in a polar covalent bond, as we discuss shortly.

Because the state of the outer electron shell determines the chemical properties of an element, when the elements are listed in order of their atomic number we see a periodic recurrence of elements that have similar properties. For example, an element with an incomplete second shell containing one electron will behave in a similar way as an element that has filled its second shell and has an incomplete third shell containing one electron. The metals, for example, have incomplete outer shells with just one or a few electrons, whereas, as we have just seen, the inert gases have full outer shells. This arrangement gives rise to the *periodic table* of the elements, outlined in **Figure 2–7**, in which the elements found in living organisms are highlighted in color.

Covalent Bonds Form by the Sharing of Electrons

All of the characteristics of a cell depend on the molecules it contains. A **molecule** is a cluster of atoms held together by **covalent bonds**, in which electrons are shared rather than transferred between atoms. The shared electrons complete the outer shells of the interacting atoms. In the simplest possible molecule—a molecule of hydrogen (H_2)—two H atoms, each with a single electron, share their electrons, thus filling their outermost shells. The shared electrons form a cloud of negative charge that is densest between the two positively charged nuclei. This electron density helps to hold the nuclei together by opposing the mutual repulsion between the positive charges of the nuclei, which would otherwise force them apart. The attractive and repulsive forces are precisely in balance



QUESTION 2–2

A carbon atom contains six protons and six neutrons.

A. What are its atomic number and atomic weight?

B. How many electrons does it have?

C. How many additional electrons must it add to fill its outermost shell? How does this affect carbon's chemical behavior?

D. Carbon with an atomic weight of 14 is radioactive. How does it differ in structure from nonradioactive carbon? How does this difference affect its chemical behavior?

Figure 2–7 When ordered by their atomic number into the periodic table, the elements fall into vertical columns in which the atoms have similar properties. This is because the atoms in the same vertical column must gain or lose the same number of electrons to attain a filled outer shell, and they therefore behave similarly when forming bonds with other atoms. Thus, for example, both magnesium (Mg) and calcium (Ca) tend to give away the two electrons in their outer shells to form ionic bonds with atoms such as chlorine (Cl), which need extra electrons to complete their outer shells.

The chemistry of life is dominated by lighter elements. The four elements highlighted in *red* constitute 99% of the total number of atoms present in the human body and about 96% of our total weight. An additional seven elements, highlighted in *blue*, together represent about 0.9% of our total number of atoms. Other elements, shown in *green*, are required in trace amounts by humans. It remains unclear whether those elements shown in *yellow* are essential in humans or not.

The atomic weights shown here are those of the most common isotope of each element. The vertical *red* line represents a break in the periodic table where a group of large atoms with similar chemical properties has been removed.

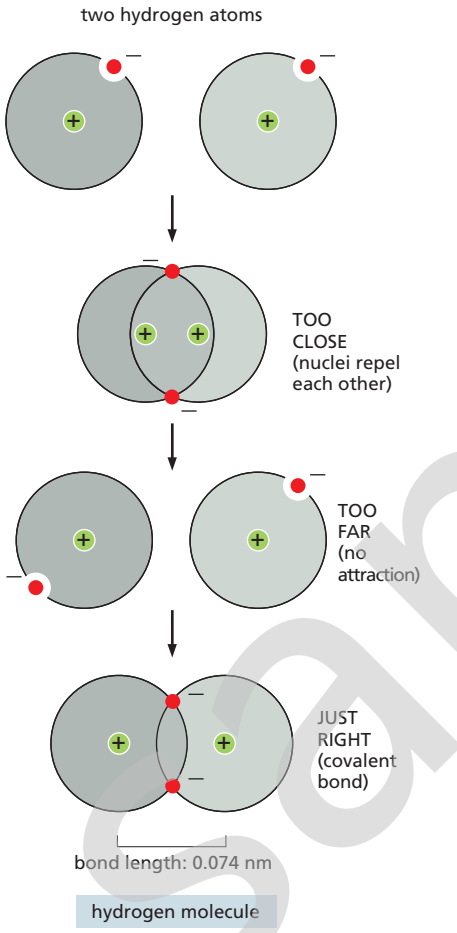


Figure 2–8 The hydrogen molecule is held together by a covalent bond. Each hydrogen atom in isolation has a single electron, which means that its first (and only) electron shell is incompletely filled. By coming together to form a hydrogen molecule (H_2, or hydrogen gas), the two atoms are able to share their electrons, so that each obtains a completely filled first shell, with the shared electrons adopting modified orbits around the two nuclei. The covalent bond between the two atoms has a defined length—0.074 nm, which is the distance between the two nuclei. If the atoms were closer together, the positively charged nuclei would repel each other; if they were farther apart, they would not be able to share electrons as effectively.

when these nuclei are separated by a characteristic distance, called the *bond length* (Figure 2–8).

Whereas an H atom can form only a single covalent bond, the other common atoms that form covalent bonds in cells—O, N, S, and P, as well as the all-important C—can form more than one. The outermost shells of these atoms, as we have seen, can accommodate up to eight electrons, and they form covalent bonds with as many other atoms as necessary to reach this number. Oxygen, with six electrons in its outer shell, is most stable when it acquires two extra electrons by sharing with other atoms, and it therefore forms up to two covalent bonds. Nitrogen, with five outer electrons, forms a maximum of three covalent bonds, while carbon, with four outer electrons, forms up to four covalent bonds—thus sharing four pairs of electrons (see Figure 2–5).

When one atom forms covalent bonds with several others, these multiple bonds have definite orientations in space relative to one another, reflecting the orientations of the orbits of the shared electrons. Covalent bonds between multiple atoms are therefore characterized by specific bond angles, as well as by specific bond lengths and bond energies (Figure 2–9). The four covalent bonds that can form around a carbon atom, for example, are arranged as if pointing to the four corners of a regular tetrahedron. The precise orientation of the covalent bonds around carbon dictates the three-dimensional geometry of all organic molecules.

Some Covalent Bonds Involve More Than One Electron Pair

Most covalent bonds involve the sharing of two electrons, one donated by each participating atom; these are called *single bonds*. Some covalent bonds, however, involve the sharing of more than one pair of electrons.

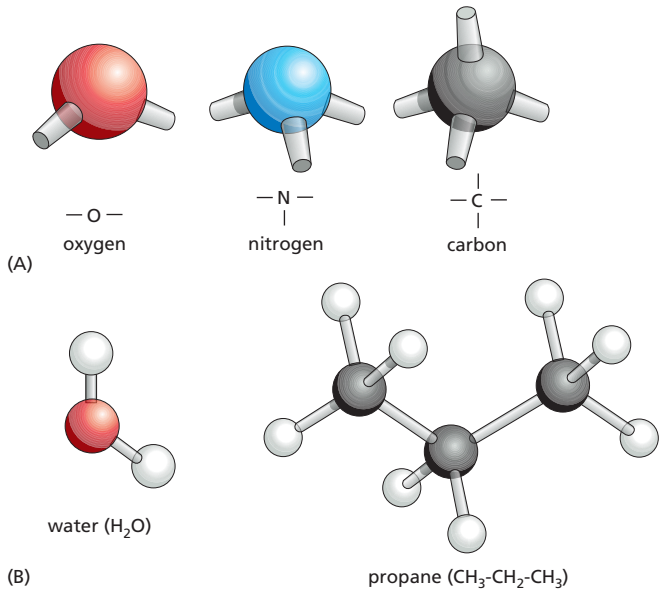


Figure 2–9 Covalent bonds are characterized by particular geometries. (A) The spatial arrangement of the covalent bonds that can be formed by oxygen, nitrogen, and carbon. (B) Molecules formed from these atoms therefore have precise three-dimensional structures defined by the bond angles and bond lengths for each covalent linkage. A water molecule, for example, forms a "V" shape with an angle close to 109°.

In these ball-and-stick models, the different colored balls represent different atoms, and the sticks represent the covalent bonds. The colors traditionally used to represent the different atoms—*black* (or *dark gray*) for carbon, *white* for hydrogen, *blue* for nitrogen, and *red* for oxygen—were established by the chemist August Wilhelm Hofmann in 1865, when he used a set of colored croquet balls to build molecular models for a public lecture on "the combining power of atoms."

Four electrons can be shared, for example, two coming from each participating atom; such a bond is called a *double bond*. Double bonds are shorter and stronger than single bonds and have a characteristic effect on the geometry of molecules containing them. A single covalent bond between two atoms generally allows the rotation of one part of a molecule relative to the other around the bond axis. A double bond prevents such rotation, producing a more rigid and less flexible arrangement of atoms (**Figure 2–10**). This restriction has a major influence on the three-dimensional shape of many macromolecules.

Some molecules contain atoms that share electrons in a way that produces bonds that are intermediate in character between single and double bonds. The highly stable benzene molecule, for example, is made up of a ring of six carbon atoms in which the bonding electrons are evenly distributed, although the arrangement is sometimes depicted as an alternating sequence of single and double bonds. **Panel 2–1** (pp. 66–67) reviews the covalent bonds commonly encountered in biological molecules.

Electrons in Covalent Bonds Are Often Shared Unequally

When the atoms joined by a single covalent bond belong to different elements, the two atoms usually attract the shared electrons to different degrees. Covalent bonds in which the electrons are shared unequally in this way are known as *polar covalent bonds*. A **polar** structure (in the electrical sense) is one in which the positive charge is concentrated toward one atom in the molecule (the positive pole) and the negative charge is concentrated toward another atom (the negative pole). The tendency of an atom to attract electrons is called its **electronegativity**, a property that was first described by the chemist Linus Pauling.

Knowing the electronegativity of atoms allows one to predict the nature of the bonds that will form between them. For example, when atoms with different electronegativities are covalently linked, their bonds will be polarized. Among the atoms typically found in biological molecules, oxygen and nitrogen (with electronegativities of 3.4 and 3.0, respectively) attract electrons relatively strongly, whereas an H atom (with an electronegativity of 2.1) attracts electrons relatively weakly. Thus the covalent bonds between O and H (O–H) and between N and H (N–H) are polar (**Figure 2–11**). An atom of C and an atom of H, by contrast, have similar electronegativities (carbon is 2.6, hydrogen 2.1) and attract electrons more equally. Thus the bond between carbon and hydrogen, C–H, is relatively nonpolar.

Covalent Bonds Are Strong Enough to Survive the Conditions Inside Cells

We have already seen that the covalent bond between two atoms has a characteristic length that depends on the atoms involved (see Figure 2–10). A further crucial property of any chemical bond is its strength. *Bond strength* is measured by the amount of energy that must be supplied to break the bond, usually expressed in units of either kilocalories per mole (kcal/mole) or kilojoules per mole (kJ/mole). A kilocalorie is the amount of energy needed to raise the temperature of 1 liter of water by 1°C. Thus, if 1 kilocalorie of energy must be supplied to break 6×10^{23} bonds of a specific type (that is, 1 mole of these bonds), then the strength of that bond is 1 kcal/mole. One kilocalorie is equal to about 4.2 kJ, which is the unit of energy universally employed by physical scientists and, increasingly, by cell biologists as well.

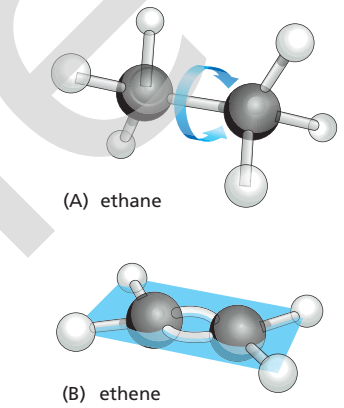


Figure 2–10 Carbon–carbon double bonds are shorter and more rigid than carbon–carbon single bonds. (A) The ethane molecule, with a single covalent bond between the two carbon atoms, shows the tetrahedral arrangement of the three single covalent bonds between each carbon atom and its three attached H atoms. The CH_3 groups, joined by a covalent C–C bond, can rotate relative to one another around the bond axis. (B) The double bond between the two carbon atoms in a molecule of ethene (ethylene) alters the bond geometry of the carbon atoms and brings all the atoms into the same plane; the double bond prevents the rotation of one CH_2 group relative to the other.

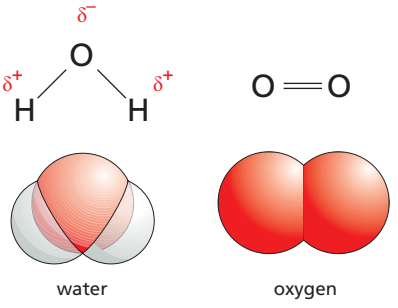


Figure 2–11 In polar covalent bonds, the electrons are shared unequally. Comparison of electron distributions in the polar covalent bonds in a molecule of water (H_2O) and the nonpolar covalent bonds in a molecule of oxygen (O_2). In H_2O, electrons are more strongly attracted to the oxygen nucleus than to the H nucleus, as indicated by the distributions of the partial negative (δ^-) and partial positive (δ^+) charges.

QUESTION 2–3

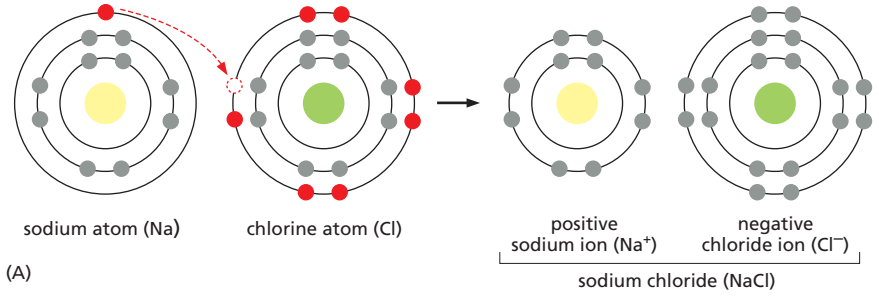
Discuss whether the following statement is correct: "An ionic bond can, in principle, be thought of as a very polar covalent bond. Polar covalent bonds, then, fall somewhere between ionic bonds at one end of the spectrum and nonpolar covalent bonds at the other end."

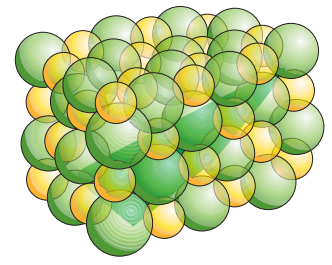
To get an idea of what bond strengths mean, it is helpful to compare them with the average energies of the impacts that molecules continually undergo owing to collisions with other molecules in their environment—their thermal, or heat, energy. Typical covalent bonds are stronger than these thermal energies by a factor of 100, so they are resistant to being pulled apart by thermal motions. In living organisms, covalent bonds are normally broken only during specific chemical reactions that are carefully controlled by highly specialized protein catalysts called *enzymes*.

Ionic Bonds Form by the Gain and Loss of Electrons

In some substances, the participating atoms are so different in electronegativity that their electrons are not shared at all—they are transferred completely to the more electronegative partner. The resulting bonds, called **ionic bonds**, are usually formed between atoms that can attain a completely filled outer shell most easily by donating electrons to—or accepting electrons from—another atom, rather than by sharing them. For example, returning to Figure 2–5, we see that a sodium (Na) atom can achieve a filled outer shell by giving up the single electron in its third shell. By contrast, a chlorine (Cl) atom can complete its outer shell by gaining just one electron. Consequently, if a Na atom encounters a Cl atom, an electron can jump from the Na to the Cl, leaving both atoms with filled outer shells. The offspring of this marriage between sodium, a soft and intensely reactive metal, and chlorine, a toxic green gas, is table salt (NaCl).

When an electron jumps from Na to Cl, both atoms become electrically charged **ions**. The Na atom that lost an electron now has one less electron than it has protons in its nucleus; it therefore has a net single positive charge (Na^+). The Cl atom that gained an electron now has one more electron than it has protons and has a net single negative charge (Cl^-). Because of their opposite charges, the Na^+ and Cl^- ions are attracted to each other and are thereby held together by an ionic bond (**Figure 2–12A**). Ions held together solely by ionic bonds are generally called *salts* rather than molecules. A NaCl crystal contains astronomical numbers of Na^+ and Cl^- ions packed together in a precise, three-dimensional array with their opposite charges exactly balanced: a crystal only 1 mm across contains about 2×10^{19} ions of each type (**Figure 2–12B and C**).





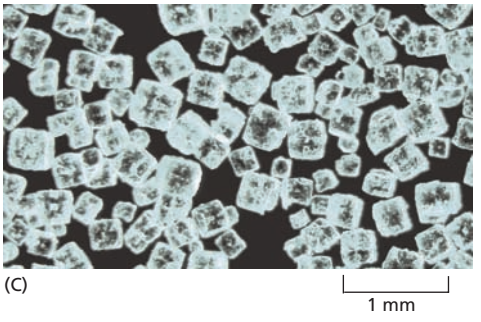


Figure 2–12 Sodium chloride is held together by ionic bonds. (A) An atom of sodium (Na) reacts with an atom of chlorine (Cl). Electrons of each atom are shown in their different shells; electrons in the chemically reactive (incompletely filled) outermost shells are shown in *red*. The reaction takes place with transfer of a single electron from sodium to chlorine, forming two electrically charged atoms, or ions, each with complete sets of electrons in their outermost shells. The two ions have opposite charge and are held together by electrostatic attraction. (B) The product of the reaction between sodium and chlorine, crystalline sodium chloride, contains sodium and chloride ions packed closely together in a regular array in which the charges are exactly balanced. (C) Color photograph of crystals of sodium chloride.

Because of the favorable interaction between ions and water molecules (which are polar), many salts (including NaCl) are highly soluble in water. They dissociate into individual ions (such as Na^+ and Cl^-), each surrounded by a group of water molecules. Positive ions are called *cations* and negative ions are called *anions*. Small inorganic ions such as Na^+, Cl^-, K^+, and Ca^{2+} play important parts in many biological processes, including the electrical activity of nerve cells, as we discuss in Chapter 12.

In aqueous solution, ionic bonds are 10–100 times weaker than the covalent bonds that hold atoms together in molecules. But, as we will see, such weak interactions nevertheless play an important role in the chemistry of living things.

Hydrogen Bonds Are Important Noncovalent Bonds for Many Biological Molecules

Water accounts for about 70% of a cell's weight, and most intracellular reactions occur in an aqueous environment. Thus the properties of water have put a permanent stamp on the chemistry of living things. In each molecule of water (H_2O), the two covalent H–O bonds are highly polar because the O is strongly attractive for electrons whereas the H is only weakly attractive. Consequently, in each water molecule, there is a preponderance of positive charge on the two H atoms and negative charge on the O. When a positively charged region of one water molecule (that is, one of its H atoms) comes close to a negatively charged region (that is, the O) of a second water molecule, the electrical attraction between them can establish a weak bond called a **hydrogen bond** (Figure 2–13A).

These bonds are much weaker than covalent bonds and are easily broken by random thermal motions. Thus each bond lasts only an exceedingly short time. But the combined effect of many weak bonds is far from trivial. Each water molecule can form hydrogen bonds through its two H atoms to two other water molecules, producing a network in which hydrogen bonds are being continually broken and formed (see Panel 2–3, pp. 70–71). It is because of these interlocking hydrogen bonds that water at room temperature is a liquid—with a high boiling point and high surface tension—and not a gas. Without hydrogen bonds, life as we know it could not exist.

Hydrogen bonds are not limited to water. In general, a hydrogen bond can form whenever a positively charged H atom held in one molecule by a polar covalent linkage comes close to a negatively charged atom—typically an oxygen or a nitrogen—belonging to another molecule (Figure 2–13B). Hydrogen bonds can also occur between different parts of a single large molecule, where they often help the molecule fold into a particular shape.

Like molecules (or salts) that carry positive or negative charges, substances that contain polar bonds and can form hydrogen bonds also mix well with water. Such substances are termed **hydrophilic**, meaning that they are "water-loving." A large proportion of the molecules in the aqueous environment of a cell fall into this category, including sugars, DNA, RNA, and a majority of proteins. **Hydrophobic** ("water-fearing") molecules, by contrast, are uncharged and form few or no hydrogen bonds, and they do not dissolve in water. These and other properties of water are reviewed in Panel 2–2 (pp. 68–69).

Four Types of Weak Interactions Help Bring Molecules Together in Cells

Much of biology depends on specific but transient interactions between one molecule and another. These associations are mediated by

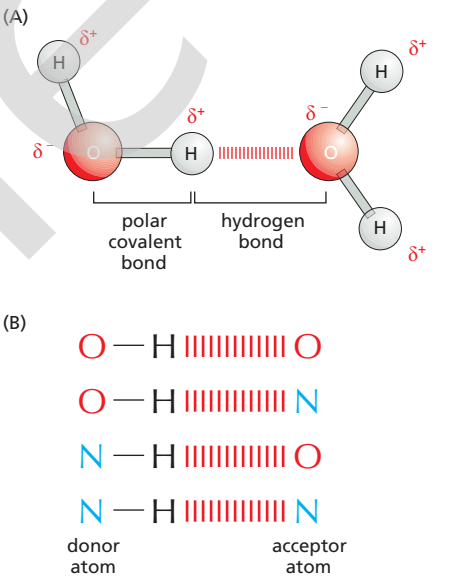


Figure 2–13 Noncovalent hydrogen bonds form between water molecules and between many other polar molecules. (A) A hydrogen bond forms between two water molecules. The slight positive charge associated with the hydrogen atom is electrically attracted to the slight negative charge of the oxygen atom. (B) In cells, hydrogen bonds commonly form between molecules that contain an oxygen or nitrogen. The atom bearing the hydrogen is considered the H-bond donor and the atom that interacts with the hydrogen is the H-bond acceptor.

QUESTION 2–4

True or false? "When NaCl is dissolved in water, the water molecules closest to the ions will tend to preferentially orient themselves so that their oxygen atoms face the sodium ions and face away from the chloride ions." Explain your answer.

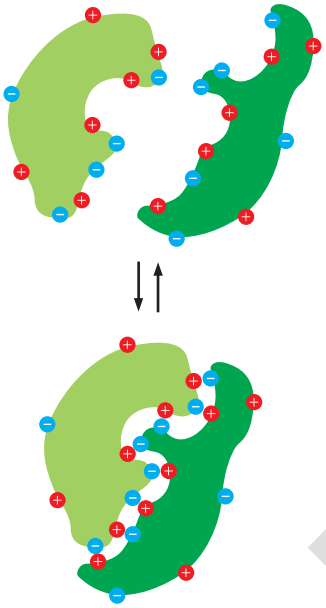


Figure 2–14 A large molecule, such as a protein, can bind to another protein through noncovalent interactions on the surface of each molecule. In the aqueous environment of a cell, many individual weak interactions could cause the two proteins to recognize each other specifically and form a tight complex. Shown here is a set of electrostatic attractions between complementary positive and negative charges.

noncovalent bonds, such as the hydrogen bonds just discussed. Although these noncovalent bonds are individually quite weak, their energies can sum to create an effective force between two molecules.

The ionic bonds that hold together the Na^+ and Cl^- ions in a salt crystal (see Figure 2–12) represent a second form of noncovalent bond called an **electrostatic attraction**. Electrostatic attractions are strongest when the atoms involved are fully charged, as are Na^+ and Cl^- ions. But a weaker electrostatic attraction can occur between molecules that contain polar covalent bonds (see Figure 2–11). Like hydrogen bonds, electrostatic attractions are extremely important in biology. For example, any large molecule with many polar groups will have a pattern of partial positive and negative charges on its surface. When such a molecule encounters a second molecule with a complementary set of charges, the two will be drawn to each other by electrostatic attraction. Even though water greatly reduces the strength of these attractions in most biological settings, the large number of weak noncovalent bonds that form on the surfaces of large molecules can nevertheless promote strong and specific binding (**Figure 2–14**).

A third type of noncovalent bond, called a **van der Waals attraction**, comes into play when any two atoms approach each other closely. These nonspecific interactions spring from fluctuations in the distribution of electrons in every atom, which can generate a transient attraction when the atoms are in very close proximity. These weak attractions occur in all types of molecules, even those that are nonpolar and cannot form ionic or hydrogen bonds. The relative lengths and strengths of these three types of noncovalent bonds are compared to the length and strength of covalent bonds in **Table 2–1**.

The fourth effect that often brings molecules together is not, strictly speaking, a bond at all. In an aqueous environment, a **hydrophobic force** is generated by a pushing of nonpolar surfaces out of the hydrogen-bonded water network, where they would otherwise physically interfere with the highly favorable interactions between water molecules. Hydrophobic forces play an important part in promoting molecular interactions—in particular, in building cell membranes, which are constructed largely from *lipid molecules* with long hydrocarbon tails. In these molecules, the H atoms are covalently linked to C atoms by nonpolar bonds (see Panel 2–1, pp. 66–67). Because the H atoms have almost no net positive charge, they cannot form effective hydrogen bonds to other molecules, including water. As a result, lipids can form the thin membrane barriers that keep the aqueous interior of the cell separate from the surrounding aqueous environment.

All four types of weak chemical interactions important in biology are reviewed in **Panel 2–3** (pp. 70–71).

TABLE 2–1 LENGTH AND STRENGTH OF SOME CHEMICAL BONDS

Bond Type	Length* (nm)	Strength (kJ/mole)	
		In Vacuum	In Water
Covalent	0.10	377 [90]**	377 [90]
Noncovalent: ionic bond	0.25	335 [80]	12.6 [3]
Noncovalent: hydrogen bond	0.17	16.7 [4]	4.2 [1]
Noncovalent: van der Waals attraction (per atom)	0.35	0.4 [0.1]	0.4 [0.1]

*The bond lengths and strengths listed are approximate, because the exact values will depend on the atoms involved.
**Values in brackets are kcal/mole. 1 kJ = 0.239 kcal and 1 kcal = 4.184 kJ.

Some Polar Molecules Form Acids and Bases in Water

One of the simplest kinds of chemical reaction, and one that has profound significance for cells, takes place when a molecule with a highly polar covalent bond between a hydrogen and another atom dissolves in water. The hydrogen atom in such a bond has given up its electron almost entirely to the companion atom, so it exists as an almost naked positively charged hydrogen nucleus—in other words, a *proton* (H^+). When the polar molecule becomes surrounded by water molecules, the proton will be attracted to the partial negative charge on the oxygen atom of an adjacent water molecule (see Figure 2–11); this proton can thus dissociate from its original partner and associate instead with the oxygen atom of the water molecule, generating a **hydronium ion** (H_3O^+) (**Figure 2–15A**). The reverse reaction—in which a hydronium ion releases a proton—also takes place very readily, so in an aqueous solution, billions of protons are constantly flitting to and fro between one molecule and another.

Substances that release protons when they dissolve in water, thus forming H_3O^+, are termed **acids**. The higher the concentration of H_3O^+, the more acidic the solution. Even in pure water, H_3O^+ is present at a concentration of 10^{-7} M, as a result of the movement of protons from one water molecule to another (**Figure 2–15B**). By tradition, the H_3O^+ concentration is usually referred to as the H^+ concentration, even though most protons in an aqueous solution are present as H_3O^+. To avoid the use of unwieldy numbers, the concentration of H^+ is expressed using a logarithmic scale called the **pH scale**. Pure water has a pH of 7.0 and is thus neutral—that is, neither acidic (pH <7) nor basic (pH >7).

Acids are characterized as being strong or weak, depending on how readily they give up their protons to water. Strong acids, such as hydrochloric acid (HCl), lose their protons easily. Acetic acid, on the other hand, is a weak acid because it holds on to its proton fairly tightly when dissolved in water. Many of the acids important in the cell—such as molecules containing a carboxyl (COOH) group—are weak acids (see Panel 2–2, pp. 68–69). Their tendency to give up a proton with some reluctance is exploited in a variety of cellular reactions.

Because protons can be passed readily to many types of molecules in cells, thus altering the molecules' characters, the H^+ concentration inside a cell—its pH—must be closely controlled. Acids will give up their protons more readily if the H^+ concentration is low (and the pH is high) and will hold onto their protons (or accept them back) when the H^+ concentration is high (and the pH is low).

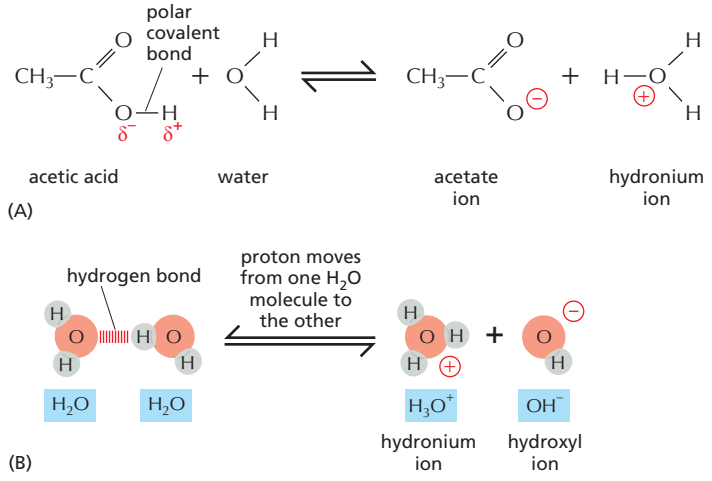


Figure 2–15 Protons move continuously from one molecule to another in aqueous solutions. (A) The reaction that takes place when a molecule of acetic acid dissolves in water. At pH 7, nearly all of the acetic acid molecules are present as acetate ions. (B) Water molecules are continually exchanging protons with each other to form hydronium and hydroxyl ions. These ions in turn rapidly recombine to form water molecules.

	[H^+] moles/liter	pH	[OH^-] moles/liter	some solutions and their pH values
ACIDIC	1	0	10^{-14}	battery acid (0.5)
	10^{-1}	1	10^{-13}	stomach acid (1.5)
	10^{-2}	2	10^{-12}	lemon juice (2.3), cola (2.5)
	10^{-3}	3	10^{-11}	orange juice (3.5)
	10^{-4}	4	10^{-10}	beer (4.5)
	10^{-5}	5	10^{-9}	black coffee (5.0), acid rain (5.6)
	10^{-6}	6	10^{-8}	urine (6.0), milk (6.5)
NEUTRAL	10^{-7}	7	10^{-7}	pure water (7.0)
BASIC	10^{-8}	8	10^{-6}	sea water (8.0)
	10^{-9}	9	10^{-5}	hand soap (9.5)
	10^{-10}	10	10^{-4}	milk of magnesia (10.5)
	10^{-11}	11	10^{-3}	household ammonia (11.9)
	10^{-12}	12	10^{-2}	non-phosphate detergent (12.0)
	10^{-13}	13	10^{-1}	bleach (12.5)
	10^{-14}	14	1	caustic soda (13.5)

Figure 2–16 In aqueous solutions, the concentration of hydroxyl (OH^-) ions increases as the concentration of H_3O^+ (or H^+) ions decreases. The product of the two values, [OH^-] x [H^+], is always 10^{-14} (moles/liter)^2. At neutral pH, [OH^-] = [H^+], and both ions are present at 10^{-7} M. Also shown are examples of common solutions along with their approximate pH values.

Molecules that accept protons when dissolved in water are called **bases**. Just as the defining property of an acid is that it raises the concentration of H_3O^+ ions by donating a proton to a water molecule, so the defining property of a base is that it raises the concentration of hydroxyl (OH^-) ions by removing a proton from a water molecule. Sodium hydroxide (NaOH) is basic (the term *alkaline* is also used). NaOH is considered a strong base because it readily dissociates in aqueous solution to form Na^+ ions and OH^- ions. Weak bases—which have a weak tendency to accept a proton from water—however, are more important in cells. Many biologically important weak bases contain an amino (NH_2) group, which can generate OH^- by taking a proton from water: $-NH_2 + H_2O \rightarrow -NH_3^+ + OH^-$ (see Panel 2–2, pp. 68–69).

Because an OH^- ion combines with a proton to form a water molecule, an increase in the OH^- concentration forces a decrease in the H^+ concentration, and vice versa (**Figure 2–16**). A pure solution of water contains an equal concentration (10^{-7} M) of both ions, rendering it neutral (pH 7). The interior of a cell is kept close to neutral by the presence of **buffers**: mixtures of weak acids and bases that will adjust proton concentrations around pH 7 by releasing protons (acids) or taking them up (bases) whenever the pH changes. This give-and-take keeps the pH of the cell relatively constant under a variety of conditions.

QUESTION 2–5

A. Are there H_3O^+ ions present in pure water at neutral pH (i.e., at pH = 7.0)? If so, how are they formed?
B. If they exist, what is the ratio of H_3O^+ ions to H_2O molecules at neutral pH? (Hint: the molecular weight of water is 18, and 1 liter of water weighs 1 kg.)

SMALL MOLECULES IN CELLS

Having looked at the ways atoms combine to form small molecules and how these molecules behave in an aqueous environment, we now examine the main classes of small molecules found in cells and their biological roles. Amazingly, we will see that a few basic categories of molecules, formed from just a handful of different elements, give rise to all the extraordinary richness of form and behavior displayed by living things.

A Cell Is Formed from Carbon Compounds

If we disregard water, nearly all the molecules in a cell are based on carbon. Carbon is outstanding among all the elements in its ability to form large molecules. Because a carbon atom is small and has four electrons and four vacancies in its outer shell, it readily forms four covalent bonds

with other atoms (see Figure 2–9). Most importantly, one carbon atom can link to other carbon atoms through highly stable covalent C–C bonds, producing rings and chains that can form the backbone of complex molecules with no obvious upper limit to their size. These carbon-containing compounds are called **organic molecules**. By contrast, all other molecules, including water, are said to be **inorganic**.

In addition to containing carbon, the organic molecules produced by cells frequently contain specific combinations of atoms, such as the methyl ($–CH_3$), hydroxyl (–OH), carboxyl (–COOH), carbonyl (–C=O), phosphoryl ($–PO_3^{2–}$), and amino ($–NH_2$) groups. Each of these **chemical groups** has distinct chemical and physical properties that influence the behavior of the molecule in which the group occurs, including whether the molecule tends to gain or lose protons when dissolved in water and with which other molecules it will interact. Knowing these groups and their chemical properties greatly simplifies understanding the chemistry of life. The most common chemical groups and some of their properties are summarized in Panel 2–1 (pp. 66–67).

Cells Contain Four Major Families of Small Organic Molecules

The small organic molecules of the cell are carbon compounds with molecular weights in the range 100–1000 that contain up to 30 or so carbon atoms. They are usually found free in solution in the cytosol and have many different roles. Some are used as *monomer* subunits to construct the cell's polymeric *macromolecules*—its proteins, nucleic acids, and large polysaccharides. Others serve as energy sources, being broken down and transformed into other small molecules in a maze of intracellular metabolic pathways. Many have more than one role in the cell—acting, for example, as both a potential subunit for a macromolecule and as an energy source. The small organic molecules are much less abundant than the organic macromolecules, accounting for only about one-tenth of the total mass of organic matter in a cell. But small organic molecules adopt a huge variety of chemical forms. Nearly 4000 different kinds of small organic molecules have been detected in the well-studied bacterium *Escherichia coli*.

All organic molecules are synthesized from—and are broken down into—the same set of simple compounds. Both their synthesis and their breakdown occur through sequences of simple chemical changes that are limited in variety and follow step-by-step rules. As a consequence, the compounds in a cell are chemically related, and most can be classified into a small number of distinct families. Broadly speaking, cells contain four major families of small organic molecules: the *sugars*, the *fatty acids*, the *amino acids*, and the *nucleotides* (**Figure 2–17**). Although many compounds present in cells do not fit into these categories, these four families of small organic molecules—together with the macromolecules made by linking them into long chains—account for a large fraction of a cell's mass (**Table 2–2**).

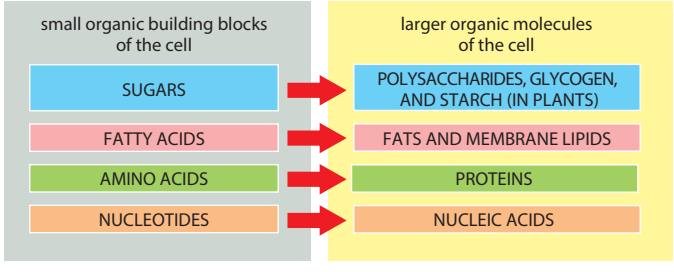


Figure 2–17 Sugars, fatty acids, amino acids, and nucleotides are the four main families of small organic molecules in cells. They form the monomeric building blocks, or subunits, for larger organic molecules, including most of the macromolecules and other molecular assemblies of the cell. Some, like the sugars and the fatty acids, are also energy sources.

TABLE 2–2 THE CHEMICAL COMPOSITION OF A BACTERIAL CELL

Substance	Percent of Total Cell Weight	Approximate Number of Types in Each Class
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	3000
Phospholipids	2	4*
Macromolecules (nucleic acids, proteins, and polysaccharides)	24	3000

*There are four classes of phospholipids, each of which exists in many varieties (discussed in Chapter 4).

Sugars Are both Energy Sources and Subunits of Polysaccharides

The simplest **sugars**—the monosaccharides—are compounds with the general formula $(CH_2O)_n$, where n is usually 3, 4, 5, or 6. Glucose, for example, has the formula $C_6H_{12}O_6$ (**Figure 2–18**). Because of this simple formula, sugars, and the larger molecules made from them, are called *carbohydrates*. The formula, however, does not adequately define the molecule: the same set of carbons, hydrogens, and oxygens can be joined together by covalent bonds in a variety of ways, creating structures with different shapes. Thus glucose can be converted into a different sugar—mannose or galactose—simply by switching the orientations of specific –OH groups relative to the rest of the molecule (**Panel 2–4**, pp. 72–73). In addition, each of these sugars can exist in either of two forms, called the D-form and the L-form, which are mirror images of each other. Sets of molecules with the same chemical formula but different structures are called *isomers*, and mirror-image pairs of such molecules are called

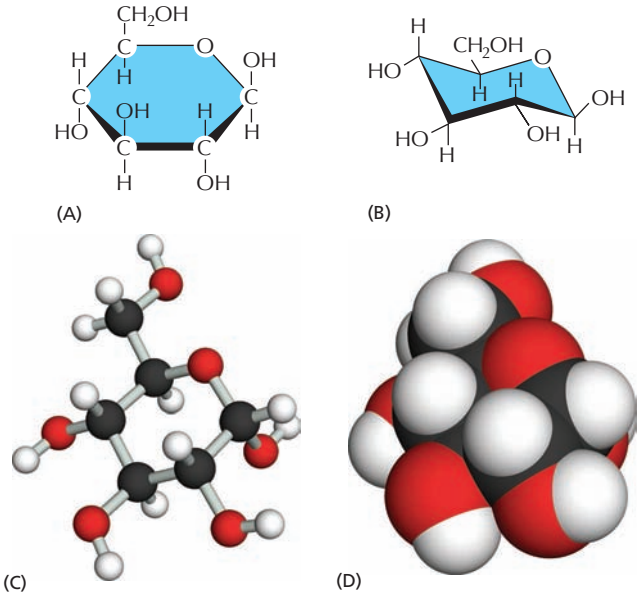


Figure 2–18 The structure of glucose, a monosaccharide, can be represented in several ways. (A) A structural formula in which the atoms are shown as chemical symbols, linked together by solid lines representing the covalent bonds. The thickened lines are used to indicate the plane of the sugar ring and to show that the –H and –OH groups are not in the same plane as the ring. (B) Another kind of structural formula that shows the three-dimensional structure of glucose in a so-called "chair configuration." (C) A ball-and-stick model in which the three-dimensional arrangement of the atoms in space is indicated. (D) A space-filling model, which, as well as depicting the three-dimensional arrangement of the atoms, also shows the relative sizes and surface contours of the molecule (**Movie 2.1**). The atoms in (C) and (D) are colored as in Figure 2–9: C, *black*; H, *white*; O, *red*. This is the conventional color-coding for these atoms and will be used throughout this book.

optical isomers. Isomers are widespread among organic molecules in general, and they play a major part in generating the enormous variety of sugars. A more complete outline of sugar structures and chemistry is presented in Panel 2–4.

Monosaccharides can be linked by covalent bonds—called glycosidic bonds—to form larger carbohydrates. Two monosaccharides linked together make a disaccharide, such as sucrose, which is composed of a glucose and a fructose unit. Larger sugar polymers range from the *oligosaccharides* (trisaccharides, tetrasaccharides, and so on) up to giant *polysaccharides*, which can contain thousands of monosaccharide subunits (*monomers*). In most cases, the prefix *oligo-* is used to refer to molecules made of a small number of monomers, typically 2 to 10 in the case of oligosaccharides. Polymers, in contrast, can contain hundreds or thousands of subunits.

The way sugars are linked together illustrates some common features of biochemical bond formation. A bond is formed between an –OH group on one sugar and an –OH group on another by a **condensation reaction**, in which a molecule of water is expelled as the bond is formed (**Figure 2–19**). The subunits in other biological polymers, including nucleic acids and proteins, are also linked by condensation reactions in which water is expelled. The bonds created by all of these condensation reactions can be broken by the reverse process of **hydrolysis**, in which a molecule of water is consumed. Generally speaking, condensation reactions, which synthesize larger molecules from smaller subunits, are energetically unfavorable; hydrolysis reactions, which break down larger molecules into smaller subunits, are energetically favorable (**Figure 2–20**).

Because each monosaccharide has several free hydroxyl groups that can form a link to another monosaccharide (or to some other compound), sugar polymers can be branched, and the number of possible polysaccharide structures is extremely large. For this reason, it is much more difficult to determine the arrangement of sugars in a complex polysaccharide than it is to determine the nucleotide sequence of a DNA molecule or the amino acid sequence of a protein, in which each unit is joined to the next in exactly the same way.

The monosaccharide *glucose* has a central role as an energy source for cells, as we explain in Chapter 13. It is broken down to smaller molecules in a series of reactions, releasing energy that the cell can harness to do useful work. Cells use simple polysaccharides composed only of glucose units—principally *glycogen* in animals and *starch* in plants—as long-term stores of glucose, held in reserve for energy production.

Sugars do not function exclusively in the production and storage of energy. They are also used, for example, to make mechanical supports. The most abundant organic molecule on Earth—the *cellulose* that forms plant cell walls—is a polysaccharide of glucose. Another extraordinarily abundant organic substance, the *chitin* of insect exoskeletons and fungal cell walls, is also a polysaccharide—in this case, a linear polymer of a sugar derivative called *N*-acetylglucosamine (see Panel 2–4, pp. 72–73). Other polysaccharides, which tend to be slippery when wet, are the main components of slime, mucus, and gristle.

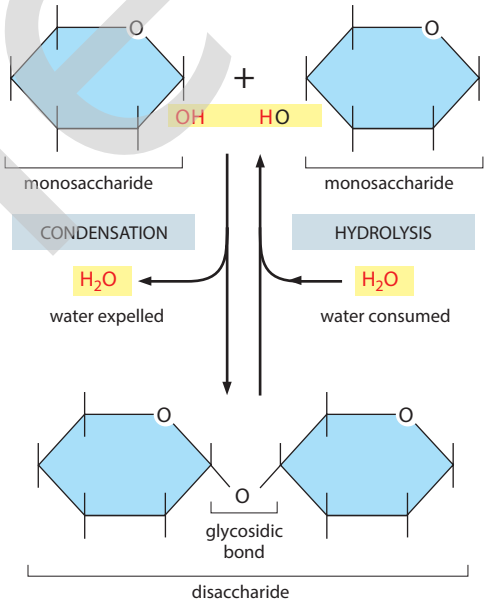


Figure 2–19 Two monosaccharides can be linked by a covalent glycosidic bond to form a disaccharide. This reaction belongs to a general category of reactions termed *condensation reactions*, in which two molecules join together as a result of the loss of a water molecule. The reverse reaction (in which water is added) is termed *hydrolysis*.

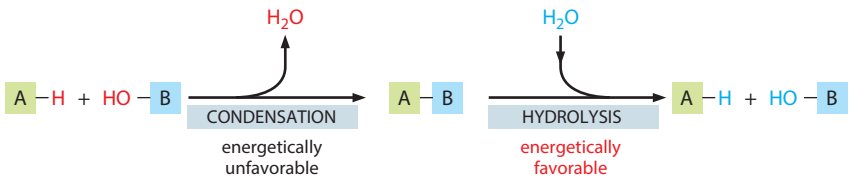


Figure 2–20 Condensation and hydrolysis are reverse reactions. The large polymeric macromolecules of the cell are formed from subunits (or monomers) by condensation reactions, and they are broken down by hydrolysis. Condensation reactions are energetically unfavorable; thus macromolecule formation requires an input of energy, as we discuss in Chapter 3.

Smaller oligosaccharides can be covalently linked to proteins to form *glycoproteins*, or to lipids to form glycolipids (**Panel 2–5**, pp. 74–75), which are both found in cell membranes. The sugar side chains attached to glycoproteins and glycolipids in the plasma membrane are thought to help protect the cell surface and often help cells adhere to one another. Differences in the types of cell-surface sugars form the molecular basis for the human blood groups, information that dictates which blood types can be used during transfusions.

Fatty Acid Chains Are Components of Cell Membranes

A **fatty acid** molecule, such as *palmitic acid*, has two chemically distinct regions. One is a long hydrocarbon chain, which is hydrophobic and not very reactive chemically. The other is a carboxyl (–COOH) group, which behaves as an acid (carboxylic acid): in an aqueous solution, it is ionized ($–COO^-$), extremely hydrophilic, and chemically reactive (**Figure 2–21**). Molecules—such as fatty acids—that possess both hydrophobic and hydrophilic regions are termed *amphipathic*. Almost all the fatty acid molecules in a cell are covalently linked to other molecules by their carboxylic acid group (see Panel 2–5, pp. 74–75).

The hydrocarbon tail of palmitic acid is *saturated*: it has no double bonds between its carbon atoms and contains the maximum possible number of hydrogens. Some other fatty acids, such as oleic acid, have *unsaturated* tails, with one or more double bonds along their length. The double bonds create kinks in the hydrocarbon tails, interfering with their ability to pack together. Fatty acid tails are found in cell membranes, where the tightness of their packing affects the fluidity of the membrane. The many different fatty acids found in cells differ only in the length of their hydrocarbon chains and in the number and position of the carbon–carbon double bonds (see Panel 2–5).

Fatty acids serve as a concentrated food reserve in cells: they can be broken down to produce about six times as much usable energy, gram for gram, as glucose. Fatty acids are stored in the cytoplasm of many cells in the form of fat droplets composed of *triacylglycerol* molecules—compounds made of three fatty acid chains covalently joined to a glycerol molecule (**Figure 2–22** and see Panel 2–5). Triacylglycerols are the animal fats found in meat, butter, and cream, and the plant oils such as corn oil and olive oil. When a cell needs energy, the fatty acid chains

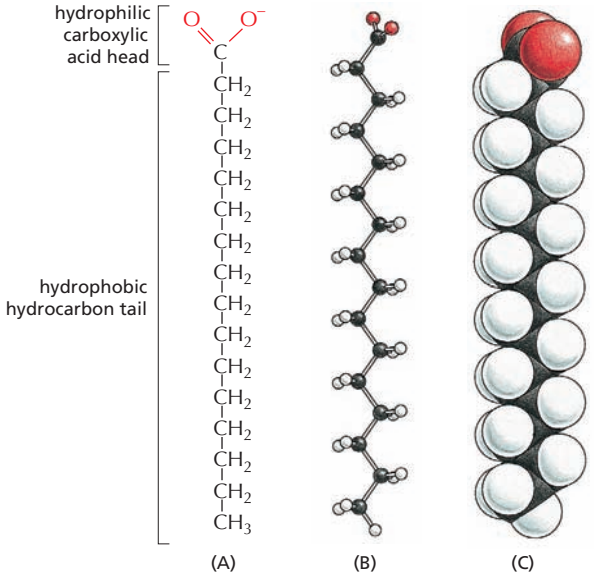


Figure 2–21 Fatty acids have both hydrophobic and hydrophilic components. The hydrophobic hydrocarbon chain is attached to a hydrophilic carboxylic acid group. Different fatty acids have different hydrocarbon tails. Palmitic acid is shown here. (A) Structural formula, showing the carboxylic acid head group in its ionized form, as it exists in water at pH 7. (B) Ball-and-stick model. (C) Space-filling model (**Movie 2.2**).

can be released from triacylglycerols and broken down into two-carbon units. These two-carbon units are identical to those derived from the breakdown of glucose, and they enter the same energy-yielding reaction pathways, as described in Chapter 13.

Fatty acids and their derivatives, including triacylglycerols, are examples of **lipids**. Lipids are loosely defined as molecules that are insoluble in water but soluble in fat and organic solvents such as benzene. They typically contain long hydrocarbon chains, as in the fatty acids, or multiple linked aromatic rings, as in the *steroids* (see Panel 2–5).

The most unique function of fatty acids is in the establishment of the **lipid bilayer**, the structure that forms the basis for all cell membranes. These thin sheets, which enclose all cells and surround their internal organelles, are composed largely of *phospholipids* (**Figure 2–23**).

Like triacylglycerols, most phospholipids are constructed mainly from fatty acids and glycerol. In these phospholipids, however, the glycerol is joined to two fatty acid chains, rather than to three as in triacylglycerols. The remaining –OH group on the glycerol is linked to a hydrophilic phosphate group, which in turn is attached to a small hydrophilic compound such as choline (see Panel 2–5, pp. 74–75). With their two hydrophobic fatty acid tails and a hydrophilic, phosphate-containing head, phospholipids are strongly amphipathic. This characteristic amphipathic composition and shape gives them very different physical and chemical properties from triacylglycerols, which are predominantly hydrophobic. In addition to phospholipids, cell membranes contain differing amounts of other lipids, including *glycolipids*, which are structurally similar to phospholipids but contain one or more sugars instead of a phosphate group.

Thanks to their amphipathic nature, pure phospholipids readily form membranes in water. These lipids can spread over the surface of water to form a monolayer, with their hydrophobic tails facing the air and their hydrophilic heads in contact with the water. Alternatively, two of these phospholipid layers can readily combine tail-to-tail in water to form the phospholipid sandwich that is the lipid bilayer (see Chapter 11).

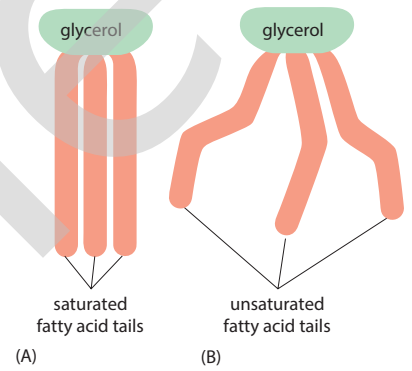


Figure 2–22 The properties of fats depend on the length and saturation of the fatty acid chains they carry. Fatty acids are stored in the cytosol of many cells in the form of droplets of *triacylglycerol* molecules made of three fatty acid chains joined to a glycerol molecule. (A) Saturated fats are found in meat and dairy products. (B) Plant oils, such as corn oil, contain unsaturated fatty acids, which may be monounsaturated (containing one double bond) or polyunsaturated (containing multiple double bonds). The presence of these double bonds causes plant oils to be liquid at room temperature. Although fats are essential in the diet, saturated fats raise the concentration of cholesterol in the blood, which tends to clog the arteries, increasing the risk of heart attacks and strokes.

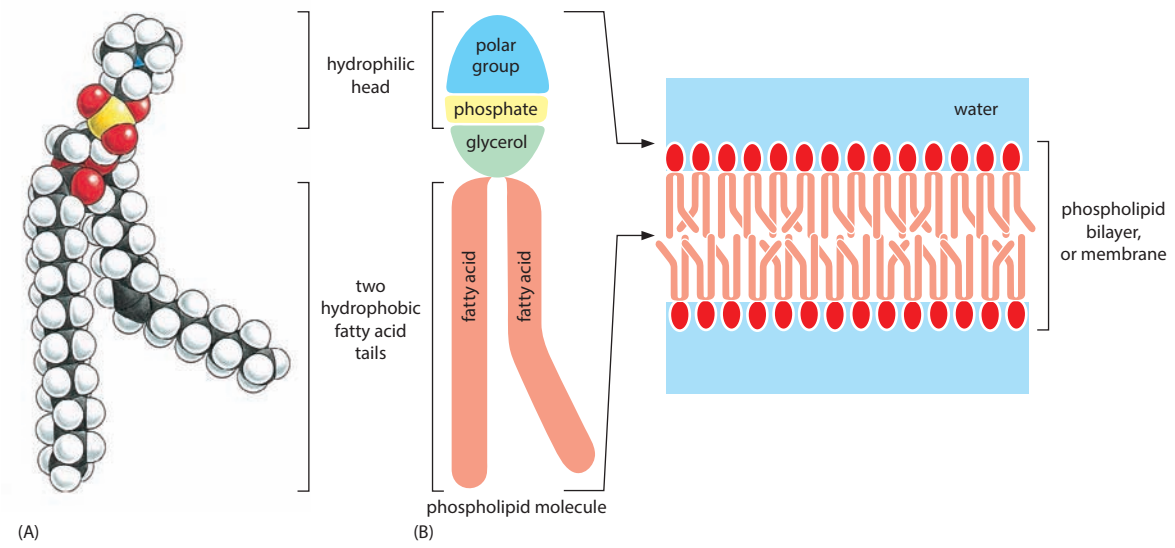


Figure 2–23 Phospholipids can aggregate to form cell membranes. Phospholipids contain two hydrophobic fatty acid tails and a hydrophilic head. (A) Phosphatidylcholine is the most common phospholipid in cell membranes. (B) Diagram showing how, in an aqueous environment, the hydrophobic tails of phospholipids pack together to form a lipid bilayer. In the lipid bilayer, the hydrophilic heads of the phospholipid molecules are on the outside, facing the aqueous environment, and the hydrophobic tails are on the inside, where water is excluded.