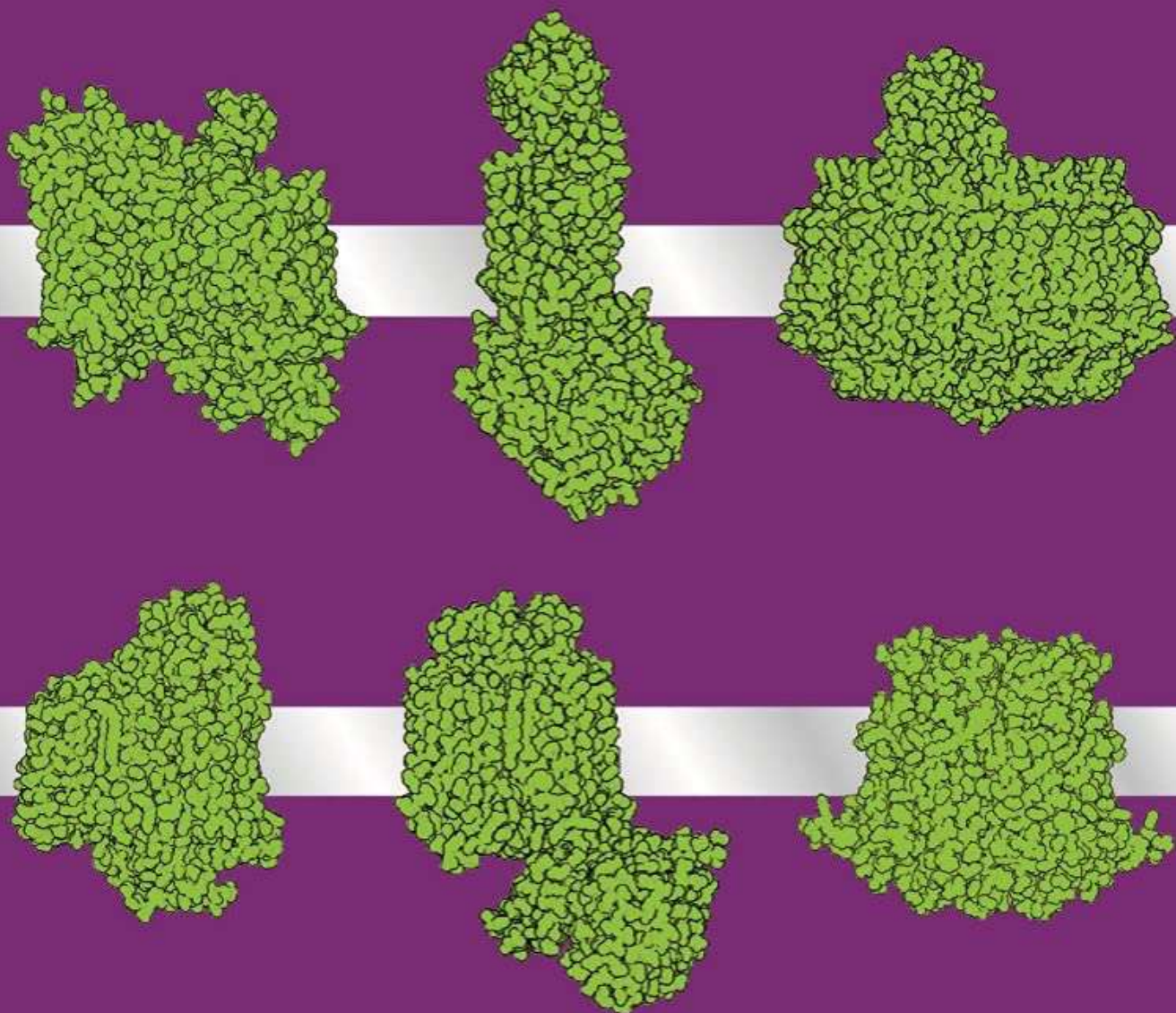


MOLECULAR BIOLOGY OF THE CELL

SEVENTH EDITION



ALBERTS HEALD JOHNSON MORGAN RAFF ROBERTS WALTER

Molecular Biology of **THE CELL**

Seventh Edition

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With problems by

John Wilson

Tim Hunt



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Preface

Why a cell biology textbook? What is its value in a world of online resources so vast that any information you might want about cells is, in principle, freely available a few taps away?

The answer is that a textbook provides what open-ended Internet searches cannot—a curation of knowledge and an expert, accurate guide to the beauty and complexities of cells. Our book provides a narrative that leads the reader logically and progressively through the key concepts, components, and experiments in such a way that readers can build for themselves a memorable, conceptual framework for cell biology—a framework that will allow them to understand and critically evaluate the exciting rush of new discoveries. That is what we have tried to do in *Molecular Biology of the Cell* for each of its seven editions.

This edition was completed during the COVID-19 pandemic. Many of the questions that this global crisis generated are cell biological questions—including how the virus gets into our cells, how it replicates, how our immune system responds, how vaccines are developed, and how scientists produce the molecular details of virus structure. Required for the rapid development of safe and effective COVID-19 vaccines, answers to all of these questions can be found in this textbook. To make room for them, as well as for many other major recent advances in our knowledge, much previous content had to be removed.

Understanding the inner workings of cells requires more than words. Our book contains more than 1500 illustrations that create a parallel narrative, closely interwoven with the text. Each figure has been designed to highlight a key concept. The unique clarity, simplicity, and consistency of the figures across chapters, achieved by use of a common set of icon designs and colors (for example, DNA *red* and proteins *green*), enables students to scan them as chapter overviews. In this edition, important protein structures are depicted and their Protein Data Bank (PDB) codes provided; these codes link to tools on the RCSB PDB website (www.rcsb.org), where students can more fully explore the proteins that lie at the core of cell biology. In addition, more than 180 narrated movies have been produced for the book, each linked to the text to provide additional insights.

John Wilson and Tim Hunt have again contributed their distinctive and imaginative problems to help students gain a more active understanding of the text. The end-of-chapter problems emphasize experiments and quantitative approaches in order to encourage critical thinking. Their Digital Problems Book in Smartwork greatly expands on these self-assessment problems and includes data analysis and video review questions that are based on the movie links in the textbook.

Many millions of scientific papers are relevant to cell biology, and many important new ones are published daily. The challenge for textbook writers is to sort through this overwhelming wealth of information to produce a clear and accurate conceptual platform for understanding how cells work. We have aimed high, seeking primarily to support the education of cell biology students, including the next generation of bioscientists, but also to support active scientists pursuing new fundamental research and the search for practical advances to improve the human condition.

So, why read a textbook? We live in a world that presents humanity with many challenging problems related to cell biology, including declining biodiversity, climate change, food insecurity, environmental degradation, resource depletion, and animal and plant diseases. We hope that this new edition of our textbook will help the reader to better understand these problems and—for many—to contribute to solving them.

Note to the Reader

What's New in the Seventh Edition?

Every chapter in the Seventh Edition has been significantly updated with information on new discoveries in the field of cell biology. Examples of this new content include:

- Updated information on the continuing impact of human genome research, including what has been learned from sequencing hundreds of thousands of human genomes (Chapter 4), and updated coverage of tumor genomes (Chapter 20).
- New research on pathogens, diseases, and methods of combating them, including discussion of COVID-19 (Chapters 1, 5, and 23) and mRNA vaccines (Chapter 24).
- Updated research on cellular organization, including new information on biomolecular condensates (Chapters 3, 6, 7, 12, and 14) and on chromosome organization by DNA loop extrusion (Chapters 4, 7, and 17).
- Expanded coverage of new microscope technologies, including superresolution light microscopy and atomic resolution electron microscopy (Chapter 9), and new research breakthroughs from cryo-electron microscopy, such as stretch-activated Piezo channels (Chapter 11).
- New coverage of evolution, including a new discussion on the diversity of life (Chapter 1), plus updates on both human (Chapter 4) and HIV (Chapter 23) evolution.

In addition, a quarter of the book's illustrations are either completely new or significantly updated for accuracy, clarity, and visual appeal.

Finally, we are thrilled to offer online assessment, for the first time, with the Digital Problems Book in Smartwork—reimagining the classic companion text, *The Problems Book*, for twenty-first century instructors and students.

Structure of the Book

Although the chapters of this book can be read independently of one another, they are arranged in a logical sequence of five parts. The first three chapters of Part I cover elementary principles and basic biochemistry. They can serve either as an introduction for those who have not studied biochemistry or as a refresher course for those who have. Part II deals with the storage, expression, and transmission of genetic information. Part III presents the principles of the main experimental methods for investigating and analyzing cells; here, a section titled “Mathematical Analysis of Cell Function” in Chapter 8 provides an extra dimension in our understanding of cell regulation and function. Part IV describes the internal organization of the cell. Part V follows the behavior of cells in multicellular systems, starting with how cells become attached to each other and concluding with chapters on pathogens and infection and on the innate and adaptive immune systems.

End-of-Chapter Problems

A selection of problems, written by John Wilson and Tim Hunt, appears in the text at the end of each chapter. Solutions to these problems are available on the Norton Teaching Tools site.

References

A concise list of selected references is included at the end of each chapter. These are arranged in alphabetical order by author surname under the main chapter section headings. These references often include the original papers in which the most critical discoveries were first reported. The ebook also includes the DOI identifier for the references, making it easy for students to access the articles.

Glossary Terms

Throughout the book, boldface type has been used to highlight key terms at the point in a chapter where the main discussion occurs. Italic type is used to set off important terms with a lesser degree of emphasis. At the end of the book is an expanded glossary, covering all the major terms common to cell biology; it should be the first resort for a reader who encounters an unfamiliar technical word.

Website for Students

Resources for students are available at **digital.wwnorton.com/mboc7**. The complete glossary as well as a set of flashcards are available on this student website.

Nomenclature for Genes and Proteins

Each species has its own conventions for naming genes; the only common feature is that they are always set in italics. In some species (such as humans), gene names are spelled out all in capital letters; in other species (such as zebrafish), all in lowercase; in yet others (most mouse genes), with the first letter in uppercase and the rest in lowercase; or (as in *Drosophila*) with different combinations of uppercase and lowercase, according to whether the first mutant allele to be discovered produced a dominant or recessive phenotype. Conventions for naming protein products are equally varied.

This typographical chaos drives everyone crazy. Moreover, there are many occasions, especially in a book such as this, where we need to refer to a gene generically—without specifying the mouse version, the human version, the chick version, or the hippopotamus version—because the gene variants across species are all equivalent for the purposes of our discussion. What convention then should we use?

We have decided in this book to follow a uniform rule. We write all gene names with the first letter in uppercase and the rest in lowercase, and all in italics, thus: *Bazooka*, *Cdc2*, *Dishevelled*, *Egl1*. The corresponding protein, where it is named after the gene, will be written in the same way, but in roman rather than italic letters: Bazooka, Cdc2, Dishevelled, Egl1. When it is necessary to specify the organism, this can be done with a prefix to the gene name.

For completeness, we list a few further details of naming rules that we shall follow. In some instances, an added letter in the gene name is traditionally used to distinguish between genes that are related by function or evolution; for those genes, we put that letter in uppercase if it is usual to do so (*LacZ*, *RecA*, *HoxA4*). Proteins are more of a problem. Many of them have names in their own right, assigned to them before the gene was named. Such protein names take many forms, although most of them traditionally begin with a lowercase letter (actin, hemoglobin, catalase); others are acronyms (such as GFP, for green fluorescent protein, or BMP4, for bone morphogenetic protein 4). To force all such protein names into a uniform style would do too much violence to established usages, and we shall simply write them in the traditional way. For the corresponding gene names in all these cases, we shall nevertheless follow our standard rule: *Actin*, *Hemoglobin*, *Catalase*, *Bmp4*, *Gfp*.

For those who wish to know them, the table shows some of the official conventions for individual species—conventions that we shall mostly violate in this book, in the manner shown.

Organism	Species-specific convention		Unified convention used in this book	
	Gene	Protein	Gene	Protein
Mouse	<i>Hoxa4</i>	Hoxa4	<i>HoxA4</i>	HoxA4
	<i>Bmp4</i>	BMP4	<i>Bmp4</i>	BMP4
	<i>integrin α-1, Itgα1</i>	integrin α 1	<i>Integrin α1, Itgα1</i>	integrin α 1
Human	<i>HOXA4</i>	HOXA4	<i>HoxA4</i>	HoxA4
Zebrafish	<i>cyclops, cyc</i>	Cyclops, Cyc	<i>Cyclops, Cyc</i>	Cyclops, Cyc
<i>Caenorhabditis</i>	<i>unc-6</i>	UNC-6	<i>Unc6</i>	Unc6
<i>Drosophila</i>	<i>sevenless, sev</i> (named after recessive phenotype)	Sevenless, SEV	<i>Sevenless, Sev</i>	Sevenless, Sev
	<i>Deformed, Dfd</i> (named after dominant mutant phenotype)	Deformed, DFD	<i>Deformed, Dfd</i>	Deformed, Dfd
Yeast				
<i>Saccharomyces cerevisiae</i> (budding yeast)	<i>CDC28</i>	Cdc28, Cdc28p	<i>Cdc28</i>	Cdc28
<i>Schizosaccharomyces pombe</i> (fission yeast)	<i>Cdc2</i>	Cdc2, Cdc2p	<i>Cdc2</i>	Cdc2
<i>Arabidopsis</i>	<i>GAI</i>	GAI	<i>Gai</i>	GAI
<i>Escherichia coli</i>	<i>uvrA</i>	UvrA	<i>UvrA</i>	UvrA

Resources for Instructors

digital.wwnorton.com/mboc7

Designed to enrich the classroom experience, Instructor Resources are available at digital.wwnorton.com/mboc7. Adopting instructors can obtain access to the site from their sales representative, who can be identified by visiting www.wwnorton.com/educator and clicking the “Find My Rep” button.

The Digital Problems Book in Smartwork

For the first time, the popular print supplement *Molecular Biology of the Cell: The Problems Book* is now available in Smartwork. Easier for instructors to assign and more helpful to students because of each question’s pedagogical scaffolding, the Digital Problems Book in Smartwork features the questions authored by Tim Hunt and John Wilson adapted for digital delivery. An enormous library of almost 3500 questions that include critical thinking questions, data analysis questions, and animation and video questions, allows instructors to deliver the exact type of assessment that their students need. The Digital Problems Book in Smartwork comes at no additional cost with all new copies of *Molecular Biology of the Cell*.

Question Detail

ODD ENZYME KINETICS FOR O⁶-METHYLGUANINE REPAIR IN DNA [BLOOM'S 4] [ART]

1st attempt

See Hint

The alkylation repair system in bacteria removes the methyl group from O⁶-methylguanine, converting it to guanine and preventing mutation. The enzyme mechanism is somewhat peculiar. The kinetics of removal were studied by incubating 1.25, 2.50, or 5.00 ng of the pure enzyme with DNA containing ³H-O⁶-methylguanine. At various times, samples were taken, and the DNA was analyzed to determine how much of the mutagenic base remained (see the figure). When the experiment was repeated at 5°C instead of 37°C, the initial rates of removal were slower, but the same end points were achieved.

What, if anything, is peculiar about the kinetics of removal of the methyl group from the O⁶-methylguanine?

Time (minutes)	1.25 ng (% remaining)	2.50 ng (% remaining)	5.00 ng (% remaining)
0	100	100	100
1	~85	~60	~10
2	~80	~55	~5
4	~78	~52	~2
6	~75	~50	~1

Choose one:

- ☐ A. One would expect the extent of reaction to increase with increasing enzyme concentration, as seen here.
- ☐ B. It is strange that removal of the methyl groups stops at a plateau that depends on enzyme concentration.
- ☐ C. The extent of removal does not change with temperature, which is unusual for enzyme-catalyzed reactions.
- ☐ D. The rate of removal of methyl groups increases with increasing enzyme concentration, as expected.

SUBMIT ANSWER

Norton Teaching Tools

The Norton Teaching Tools site for *Molecular Biology of the Cell* provides creative and engaging resources to refresh a syllabus or to design a new one. Dynamic, experienced instructors have created primary literature suggestions, active learning activities, lecture PowerPoint files, descriptions of all of the animations and videos, and much more. All of the teaching tools are aligned with chapter topics and organized by activity type, making it easily sortable. The site also features tips for assigning Norton's digital learning tools and addressing the most common course challenges.

Animations and Videos

Under the authorial direction of Michele M. McDonough and Thomas A. Volpe, both of Northwestern University, the animations and video library has been thoroughly updated and expanded. The more than 180 animations and videos are integrated into the ebook and also available to students and instructors at digital .wwnorton.com/mboc7. Instructors can view descriptions of each on the Norton Teaching Tools site.

Norton Ebook

The purchase of any new print copy of the Seventh Edition of *Molecular Biology of the Cell* includes access to the Norton Ebook version of the text at no additional cost. The Norton Ebook can be purchased as an affordable stand-alone option that provides an active reading experience, enabling students to take notes, bookmark, search, highlight, and read offline. All of the videos and animations appear directly in the ebook, and instructors can add notes that students can see as they are reading the text.

Art of *Molecular Biology of the Cell*, Seventh Edition

The images from the book are available in two convenient formats: PowerPoint and JPEG, and in both labeled and unlabeled versions.

Figure-integrated Lecture Outlines

The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations and can be customized. For example, the content of these presentations can be combined with videos, questions from the book, or activities in the Norton Teaching Tools site, in order to create unique lectures that facilitate interactive learning.

Test Bank

Updated for the Seventh Edition, the test bank includes a variety of question formats: multiple choice, short answer, fill-in-the-blank, true-false, and matching. The test bank was created with the philosophy that a good exam should require students to reflect upon and integrate information as a part of a sound understanding. Questions are classified by section and difficulty, making it easy to construct tests and quizzes. The test bank question library includes about 70 questions per chapter, ensuring instructors can find the right questions for their exams. It will be delivered through Norton Testmaker, which brings the high-quality questions in the test bank online. Create assessments for your course without downloading files or installing specialized software, customize test bank questions, and easily export your tests to Microsoft Word or Common Cartridge files for your learning management system (LMS).

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Brief Contents

PART I	INTRODUCTION TO THE CELL	
Chapter 1	Cells, Genomes, and the Diversity of Life	1
Chapter 2	Cell Chemistry and Bioenergetics	49
Chapter 3	Proteins	115
PART II	BASIC GENETIC MECHANISMS	
Chapter 4	DNA, Chromosomes, and Genomes	183
Chapter 5	DNA Replication, Repair, and Recombination	253
Chapter 6	How Cells Read the Genome: From DNA to Protein	321
Chapter 7	Control of Gene Expression	397
PART III	WAYS OF WORKING WITH CELLS	
Chapter 8	Analyzing Cells, Molecules, and Systems	475
Chapter 9	Visualizing Cells and Their Molecules	563
PART IV	INTERNAL ORGANIZATION OF THE CELL	
Chapter 10	Membrane Structure	603
Chapter 11	Small-Molecule Transport and Electrical Properties of Membranes	637
Chapter 12	Intracellular Organization and Protein Sorting	683
Chapter 13	Intracellular Membrane Traffic	749
Chapter 14	Energy Conversion and Metabolic Compartmentation: Mitochondria and Chloroplasts	811
Chapter 15	Cell Signaling	873
Chapter 16	The Cytoskeleton	949
Chapter 17	The Cell Cycle	1027
Chapter 18	Cell Death	1089
PART V	CELLS IN THEIR SOCIAL CONTEXT	
Chapter 19	Cell Junctions and the Extracellular Matrix	1105
Chapter 20	Cancer	1163
Chapter 21	Development of Multicellular Organisms	1217
Chapter 22	Stem Cells in Tissue Homeostasis and Regeneration	1279
Chapter 23	Pathogens and Infection	1313
Chapter 24	The Innate and Adaptive Immune Systems	1353

Special Features

TABLE 1–2	Some Model Organisms and Their Genomes	29
TABLE 2–1	Covalent and Noncovalent Chemical Bonds	51
TABLE 2–2	Relationship Between the Standard Free-Energy Change, ΔG° , and the Equilibrium Constant	69
PANEL 2–1	Chemical Bonds and Groups Commonly Encountered in Biological Molecules	94
PANEL 2–2	Water and Its Influence on the Behavior of Biological Molecules	96
PANEL 2–3	The Principal Types of Weak Noncovalent Bonds That Hold Macromolecules Together	98
PANEL 2–4	An Outline of Some of the Types of Sugars Commonly Found in Cells	100
PANEL 2–5	Fatty Acids and Other Lipids	102
PANEL 2–6	A Survey of the Nucleotides	104
PANEL 2–7	Free Energy and Biological Reactions	106
PANEL 2–8	Details of the 10 Steps of Glycolysis	108
PANEL 2–9	The Complete Citric Acid Cycle	110
PANEL 3–1	The 20 Amino Acids Found in Proteins	118
TABLE 3–3	Macromolecular Machines Compared to Biomolecular Condensates and Membrane-enclosed Compartments	175
TABLE 3–4	Some Molecules Covalently Attached to Proteins That Regulate Protein Function	175
TABLE 4–1	Some Vital Statistics for the Human Genome	194
TABLE 5–4	Three Major Classes of Transposable Elements	308
TABLE 6–1	Principal Types of RNAs Produced in Cells	327
PANEL 7–1	Common Structural Motifs in Transcription Regulators	404
PANEL 8–1	Review of Classical Genetics	520
PANEL 9–1	Protein Structure Determination Using CryoEM	594
TABLE 11–1	A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell	638
PANEL 11–1	The Derivation of the Nernst Equation	656
TABLE 12–1	Relative Volumes Occupied by the Major Intracellular Compartments in a Liver Cell (Hepatocyte)	684
TABLE 14–1	Quantity of Organelles and Organelle DNA in Some Cells and Tissues	815
TABLE 14–2	Mitochondrial Functions	819
PANEL 14–1	Redox Potentials	825
TABLE 14–3	Product Yields from the Oxidation of Sugars and Fats	836
TABLE 15–3	Four Major Families of Heterotrimeric G Proteins	907
TABLE 15–4	Some Extracellular Signal Proteins That Act Via RTKs	911
TABLE 15–5	The Ras Superfamily of Monomeric GTPases	915
TABLE 15–6	Some Extracellular Signal Proteins That Act Through Cytokine Receptors and the JAK–STAT Signaling Pathway	925
PANEL 16–2	The Polymerization of Actin and Tubulin	960
TABLE 16–1	Chemical Inhibitors of Actin and Microtubules	964
PANEL 16–3	Actin Filaments	965
PANEL 16–4	Microtubules	994
TABLE 16–2	Major Types of Intermediate Filament Proteins in Vertebrate Cells	1007
TABLE 17–1	The Major Cyclins and Cdks of Vertebrates and Budding Yeast	1034
TABLE 17–2	Summary of the Major Cell-Cycle Regulatory Proteins	1041
PANEL 17–1	The Principal Stages of M Phase (Mitosis and Cytokinesis) in an Animal Cell	1048
TABLE 19–1	Anchoring Junctions	1107
TABLE 19–2	Some Types of Collagen and Their Properties	1134
TABLE 19–3	Some Types of Integrins	1149
TABLE 20–2	Viruses Associated with Human Cancers	1202
TABLE 22–1	Blood Cells	1286
TABLE 23–1	Viruses That Cause Human Disease	1323
TABLE 24–2	Properties of the Major Classes of Antibodies in Humans	1375
TABLE 24–3	Properties of Human Class I and Class II MHC Proteins	1388
TABLE 24–4	Some Vaccines Approved for Human Use	1398

Contents

Chapter 1 Cells, Genomes, and the Diversity of Life	1		
THE UNIVERSAL FEATURES OF LIFE ON EARTH	2		
All Cells Store Their Hereditary Information in the Form of Double-Strand DNA Molecules	2	The Expression Levels of All the Genes of an Organism Can Be Determined	37
All Cells Replicate Their Hereditary Information by Templated Polymerization	3	<i>Arabidopsis</i> Has Been Chosen as a Model Plant	38
All Cells Transcribe Portions of Their DNA into RNA Molecules	5	The World of Animal Cells Is Mainly Represented by a Worm, a Fly, a Fish, a Mouse, and a Human	38
All Cells Use Proteins as Catalysts	6	Studies in the Fruit Fly <i>Drosophila</i> Provide a Key to Vertebrate Development	39
All Cells Translate RNA into Protein in the Same Way	6	The Frog and the Zebrafish Provide Highly Accessible Vertebrate Models	40
Each Protein Is Encoded by a Specific Gene	7	The Mouse Is the Predominant Mammalian Model Organism	41
Life Requires a Continual Input of Free Energy	7	The COVID-19 Pandemic Has Focused Scientists on the SARS-CoV-2 Coronavirus	42
All Cells Function as Biochemical Factories	8	Humans Are Unique in Reporting on Their Own Peculiarities To Understand Cells and Organisms Will Require Mathematics, Computers, and Quantitative Information	44
All Cells Are Enclosed in a Plasma Membrane Across Which Nutrients and Waste Materials Must Pass	8	Summary	45
Cells Operate at a Microscopic Scale Dominated by Random Thermal Motion	9	Problems	46
A Living Cell Can Exist with 500 Genes	10	References	47
Summary	10		
GENOME DIVERSIFICATION AND THE TREE OF LIFE	10	Chapter 2 Cell Chemistry and Bioenergetics	49
The Tree of Life Has Three Major Domains: Eukaryotes, Bacteria, and Archaea	11	THE CHEMICAL COMPONENTS OF A CELL	49
Eukaryotes Make Up the Domain of Life That Is Most Familiar to Us	13	Water Is Held Together by Hydrogen Bonds	50
On the Basis of Genome Analysis, Bacteria Are the Most Diverse Group of Organisms on the Planet	13	Four Types of Noncovalent Attractions Help Bring Molecules Together in Cells	51
Archaea: The Most Mysterious Domain of Life	15	Some Polar Molecules Form Acids and Bases in Water	52
Organisms Occupy Most of Our Planet	15	A Cell Is Formed from Carbon Compounds	53
Cells Can Be Powered by a Wide Variety of Free-Energy Sources	15	Cells Contain Four Major Families of Small Organic Molecules	53
Some Cells Fix Nitrogen and Carbon Dioxide for Other Cells	17	The Chemistry of Cells Is Dominated by Macromolecules with Remarkable Properties	54
Genomes Diversify Over Evolutionary Time, Producing New Types of Organisms	18	Noncovalent Bonds Specify Both the Precise Shape of a Macromolecule and Its Binding to Other Molecules	55
New Genes Are Generated from Preexisting Genes	19	Summary	56
Gene Duplications Give Rise to Families of Related Genes Within a Single Genome	20	CATALYSIS AND THE USE OF ENERGY BY CELLS	57
The Function of a Gene Can Often Be Deduced from Its Nucleotide Sequence	20	Cell Metabolism Is Organized by Enzymes	57
More Than 200 Gene Families Are Common to All Three Domains of Life	21	Biological Order Is Made Possible by the Release of Heat Energy from Cells	58
Summary	21	Cells Obtain Energy by the Oxidation of Organic Molecules	61
EUKARYOTES AND THE ORIGIN OF THE EUKARYOTIC CELL	22	Oxidation and Reduction Involve Electron Transfers	62
Eukaryotic Cells Contain a Variety of Organelles	22	Enzymes Lower the Activation-Energy Barriers That Block Chemical Reactions	63
Mitochondria Evolved from a Symbiotic Bacterium Captured by an Ancient Archaeon	23	Enzymes Can Drive Substrate Molecules Along Specific Reaction Pathways	64
Chloroplasts Evolved from a Symbiotic Photosynthetic Bacterium Engulfed by an Ancient Eukaryotic Cell	25	How Enzymes Find Their Substrates: The Enormous Rapidity of Molecular Motions	65
Eukaryotes Have Hybrid Genomes	26	The Free-Energy Change for a Reaction, ΔG , Determines Whether It Can Occur Spontaneously	66
Eukaryotic Genomes Are Big	27	The Concentration of Reactants Influences the Free-Energy Change and a Reaction's Direction	67
Eukaryotic Genomes Are Rich in Regulatory DNA	28	The Standard Free-Energy Change, ΔG° , Makes It Possible to Compare the Energetics of Different Reactions	67
Eukaryotic Genomes Define the Program of Multicellular Development	29	The Equilibrium Constant and ΔG° Are Readily Derived from Each Other	68
Many Eukaryotes Live as Solitary Cells	30	The Free-Energy Changes of Coupled Reactions Are Additive	69
Summary	31	Activated Carrier Molecules Are Essential for Biosynthesis	69
MODEL ORGANISMS	31	The Formation of an Activated Carrier Is Coupled to an Energetically Favorable Reaction	70
Mutations Reveal the Functions of Genes	32	ATP Is the Most Widely Used Activated Carrier Molecule	71
Molecular Biology Began with a Spotlight on One Bacterium and Its Viruses	33	Energy Stored in ATP Is Often Harnessed to Join Two Molecules Together	72
The Focus on <i>E. coli</i> as a Model Organism Has Accelerated Many Subsequent Discoveries	35		
A Yeast Serves as a Minimal Model Eukaryote	36		

NADH and NADPH Are Important Electron Carriers	73
There Are Many Other Activated Carrier Molecules in Cells	75
The Synthesis of Biological Polymers Is Driven by ATP Hydrolysis	76
Summary	78
HOW CELLS OBTAIN ENERGY FROM FOOD	80
Glycolysis Is a Central ATP-producing Pathway	80
Glycolysis Illustrates How Enzymes Couple Oxidation to Energy Storage	83
Fermentations Produce ATP in the Absence of Oxygen	84
Organisms Store Food Molecules in Special Reservoirs	85
Between Meals, Most Animal Cells Derive Their Energy from Fatty Acids Obtained from Fat	86
Sugars and Fats Are Both Degraded to Acetyl CoA in Mitochondria	87
The Citric Acid Cycle Generates NADH by Oxidizing Acetyl Groups to CO ₂	88
Electron Transport Drives the Synthesis of the Majority of the ATP in Most Cells	90
Many Biosynthetic Pathways Begin with Glycolysis or the Citric Acid Cycle	90
Animals Must Obtain All the Nitrogen and Sulfur They Need from Food	91
Metabolism Is Highly Organized and Regulated	92
Summary	93
Problems	112
References	114
 Chapter 3 Proteins	 115
THE ATOMIC STRUCTURE OF PROTEINS	115
The Structure of a Protein Is Specified by Its Amino Acid Sequence	115
Proteins Fold into a Conformation of Lowest Energy	121
The α Helix and the β Sheet Are Common Folding Motifs	121
Four Levels of Organization Are Considered to Contribute to Protein Structure	123
Protein Domains Are the Modular Units from Which Larger Proteins Are Built	124
Proteins Also Contain Unstructured Regions	126
All Protein Structures Are Dynamic, Interconverting Rapidly Between an Ensemble of Closely Related Conformations Because of Thermal Energy	126
Function Has Selected for a Tiny Fraction of the Many Possible Polypeptide Chains	126
Proteins Can Be Classified into Many Families	127
Some Protein Domains Are Found in Many Different Proteins	129
The Human Genome Encodes a Complex Set of Proteins, Revealing That Much Remains Unknown	130
Protein Molecules Often Contain More Than One Polypeptide Chain	130
Some Globular Proteins Form Long Helical Filaments	131
Protein Molecules Can Have Elongated, Fibrous Shapes	132
Covalent Cross-Linkages Stabilize Extracellular Proteins	133
Protein Molecules Often Serve as Subunits for the Assembly of Large Structures	134
Many Structures in Cells Are Capable of Self-Assembly	136
Assembly Factors Often Aid the Formation of Complex Biological Structures	136
When Assembly Processes Go Wrong: The Case of Amyloid Fibrils	137
Amyloid Structures Can Also Perform Useful Functions in Cells	139
Summary	140
PROTEIN FUNCTION	140
All Proteins Bind to Other Molecules	140
The Surface Conformation of a Protein Determines Its Chemistry	142
Sequence Comparisons Between Protein Family Members Highlight Crucial Ligand-binding Sites	142
Proteins Bind to Other Proteins Through Several Types of Interfaces	143
Antibody Binding Sites Are Especially Versatile	144
The Equilibrium Constant Measures Binding Strength	145
Enzymes Are Powerful and Highly Specific Catalysts	146
Substrate Binding Is the First Step in Enzyme Catalysis	146

Enzymes Speed Reactions by Selectively Stabilizing Transition States	148
Enzymes Can Use Simultaneous Acid and Base Catalysis	148
Lysozyme Illustrates How an Enzyme Works	149
Tightly Bound Small Molecules Add Extra Functions to Proteins	152
The Cell Regulates the Catalytic Activities of Its Enzymes	155
Allosteric Enzymes Have Two or More Binding Sites That Interact	155
Two Ligands Whose Binding Sites Are Coupled Must Reciprocally Affect Each Other's Binding	157
Symmetrical Protein Assemblies Produce Cooperative Allosteric Transitions	158
Many Changes in Proteins Are Driven by Protein Phosphorylation	159
A Eukaryotic Cell Contains a Large Collection of Protein Kinases and Protein Phosphatases	159
The Regulation of the Src Protein Kinase Reveals How a Protein Can Function as a Microprocessor	161
Regulatory GTP-binding Proteins Are Switched On and Off by the Gain and Loss of a Phosphate Group	162
Proteins Can Be Regulated by the Covalent Addition of Other Proteins	162
An Elaborate Ubiquitin-conjugating System Is Used to Mark Proteins	163
Protein Complexes with Interchangeable Parts Make Efficient Use of Genetic Information	164
A GTP-binding Protein Shows How Large Protein Movements Can Be Generated from Small Ones	166
Motor Proteins Produce Directional Movement in Cells	167
Proteins Often Form Large Complexes That Function as Protein Machines	167
The Disordered Regions in Proteins Are Critical for a Set of Different Functions	168
Scaffolds Bring Sets of Interacting Macromolecules Together and Concentrate Them in Selected Regions of a Cell	170
Macromolecules Can Self-assemble to Form Biomolecular Condensates	171
Classical Studies of Phase Separation Have Relevance for Biomolecular Condensates	173
A Comparison of Three Important Types of Large Biological Assemblies	174
Many Proteins Are Controlled by Covalent Modifications That Direct Them to Specific Sites Inside the Cell	175
A Complex Network of Protein Interactions Underlies Cell Function	176
Protein Structures Can Be Predicted and New Proteins Designed	178
Summary	179
Problems	179
References	181
 Chapter 4 DNA, Chromosomes, and Genomes	 183
THE STRUCTURE AND FUNCTION OF DNA	185
A DNA Molecule Consists of Two Complementary Chains of Nucleotides	185
The Structure of DNA Provides a Mechanism for Heredity	187
In Eukaryotes, DNA Is Enclosed in a Cell Nucleus	189
Summary	189
CHROMOSOMAL DNA AND ITS PACKAGING	189
IN THE CHROMATIN FIBER	189
Eukaryotic DNA Is Packaged into a Set of Chromosomes	190
Chromosomes Contain Long Strings of Genes	191
The Nucleotide Sequence of the Human Genome Shows How Our Genes Are Arranged	193
Each DNA Molecule That Forms a Linear Chromosome Must Contain a Centromere, Two Telomeres, and Replication Origins	195
DNA Molecules Are Highly Condensed in Chromosomes	197
Nucleosomes Are a Basic Unit of Eukaryotic Chromosome Structure	197
The Structure of the Nucleosome Core Particle Reveals How DNA Is Packaged	198
Nucleosomes Have a Dynamic Structure and Are Frequently Subjected to Changes Catalyzed by ATP-dependent Chromatin-remodeling Complexes	200

Attractions Between Nucleosomes Compact the Chromatin Fiber	202	We Can Trace Human History by Analyzing Genomes	244
Summary	203	The Sequencing of Hundreds of Thousands of Human Genomes Reveals Much Variation	245
THE EFFECT OF CHROMATIN STRUCTURE ON DNA FUNCTION	203	Most of the Variants Observed in the Human Population Are Common Alleles, with at Most a Weak Effect on Phenotype	246
Different Regions of the Human Genome Are Packaged Very Differently in Chromatin	204	Forensic Analyses Exploit Special DNA Sequences with Unusually High Mutation Rates	247
Heterochromatin Is Highly Condensed and Restricts Gene Expression	204	An Understanding of Human Variation Is Critical for Improving Medicine	248
The Heterochromatic State Can Spread Along a Chromosome and Be Inherited from One Cell Generation to the Next	205	Summary	248
The Core Histones Are Covalently Modified at Many Different Sites	206	Problems	249
Chromatin Acquires Additional Variety Through the Site-specific Insertion of a Small Set of Histone Variants	208	References	251
Covalent Modifications and Histone Variants Can Act in Concert to Control Chromosome Functions	208	Chapter 5 DNA Replication, Repair, and Recombination	253
A Complex of Reader and Writer Proteins Can Spread Specific Chromatin Modifications Along a Chromosome	210	THE MAINTENANCE OF DNA SEQUENCES	253
Barrier DNA-Protein Complexes Block the Spread of Reader-Writer Complexes and Thereby Separate Neighboring Chromatin Domains	212	Mutation Rates Are Extremely Low	253
Centromeres Have a Special, Inherited Chromatin Structure	213	Low Mutation Rates Are Necessary for Life as We Know It	254
Some Forms of Chromatin Can Be Directly Inherited	215	Summary	255
The Abnormal Perturbations of Heterochromatin That Arise During Tumor Progression Contribute to Many Cancers	215	DNA REPLICATION MECHANISMS	255
Summary	217	Base-pairing Underlies DNA Replication and DNA Repair	255
THE GLOBAL STRUCTURE OF CHROMOSOMES	217	The DNA Replication Fork Is Asymmetrical	256
Chromosomes Are Folded into Large Loops of Chromatin	217	The High Fidelity of DNA Replication Requires Several Proofreading Mechanisms	258
Polytene Chromosomes Are Uniquely Useful for Visualizing Chromatin Structures	218	DNA Replication in the 5'-to-3' Direction Allows Efficient Error Correction	260
Chromosome Loops Decondense When the Genes Within Them Are Expressed	220	A Special Nucleotide-polymerizing Enzyme Synthesizes Short RNA Primer Molecules	260
Mammalian Interphase Chromosomes Occupy Discrete Territories in the Nucleus, with Their Heterochromatin and Euchromatin Distributed Differently	220	Special Proteins Help to Open Up the DNA Double Helix in Front of the Replication Fork	261
A Biochemical Technique Called Hi-C Reveals Details of Chromosome Organization	221	A Sliding Ring Holds a Moving DNA Polymerase onto the DNA	262
Chromosomal DNA Is Organized into Loops by Large Protein Rings	223	The Proteins at a Replication Fork Cooperate to Form a Replication Machine	263
Euchromatin and Heterochromatin Separate Spatially in the Nucleus	225	DNA Replication Is Fundamentally Similar in Eukaryotes and Bacteria	265
Mitotic Chromosomes Are Highly Condensed	227	A Strand-directed Mismatch Repair System Removes Replication Errors That Remain in the Wake of the Replication Machine	267
Summary	228	The Accidental Incorporation of Ribonucleotides During DNA Replication Is Corrected	269
HOW GENOMES EVOLVE	229	DNA Topoisomerases Prevent DNA Tangling During Replication	269
Genome Comparisons Reveal Functional DNA Sequences by Their Conservation Throughout Evolution	230	Summary	272
Genome Alterations Are Caused by Failures of the Normal Mechanisms for Copying and Maintaining DNA, as Well as by Transposable DNA Elements	231	THE INITIATION AND COMPLETION OF DNA REPLICATION IN CHROMOSOMES	272
The Genome Sequences of Two Species Differ in Proportion to the Length of Time Since They Have Separately Evolved	232	DNA Synthesis Begins at Replication Origins	272
Phylogenetic Trees Constructed from a Comparison of DNA Sequences Trace the Relationships of All Organisms	233	Bacterial Chromosomes Typically Have a Single Origin of DNA Replication	273
A Comparison of Human and Mouse Chromosomes Shows How the Structures of Genomes Diverge	234	Eukaryotic Chromosomes Contain Multiple Origins of Replication	273
The Size of a Vertebrate Genome Reflects the Relative Rates of DNA Addition and DNA Loss in a Lineage	236	In Eukaryotes, DNA Replication Takes Place During Only One Part of the Cell Cycle	276
Multispecies Sequence Comparisons Identify Many Conserved DNA Sequences of Unknown Function	237	Eukaryotic Origins of Replication Are "Licensed" for Replication by the Assembly of an Origin Recognition Complex	276
Changes in Previously Conserved Sequences Can Help Decipher Critical Steps in Evolution	238	Features of the Human Genome That Specify Origins of Replication Remain to Be Fully Understood	277
Mutations in the DNA Sequences That Control Gene Expression Have Driven Many of the Evolutionary Changes in Vertebrates	239	Properties of the ORC Ensure That Each Region of the DNA Is Replicated Once and Only Once in Each S Phase	277
Gene Duplication Also Provides an Important Source of Genetic Novelty During Evolution	240	New Nucleosomes Are Assembled Behind the Replication Fork	279
Duplicated Genes Diverge	240	Termination of DNA Replication Occurs Through the Ordered Disassembly of the Replication Fork	280
The Evolution of the Globin Gene Family Shows How DNA Duplications Contribute to the Evolution of Organisms	241	Telomerase Replicates the Ends of Chromosomes	281
Genes Encoding New Proteins Can Be Created by the Recombination of Exons	242	Telomeres Are Packaged into Specialized Structures That Protect the Ends of Chromosomes	282
Neutral Mutations Often Spread to Become Fixed in a Population, with a Probability That Depends on Population Size	243	Telomere Length Is Regulated by Cells and Organisms	282
		Summary	284
		DNA REPAIR	284
		Without DNA Repair, Spontaneous DNA Damage Would Rapidly Change DNA Sequences	286
		The DNA Double Helix Is Readily Repaired	288
		DNA Damage Can Be Removed by More Than One Pathway	288

Coupling Nucleotide Excision Repair to Transcription Ensures That the Cell's Most Important DNA Is Efficiently Repaired	290	In Eukaryotes, Transcription Initiation Also Requires Activator, Mediator, and Chromatin-modifying Proteins	334
The Chemistry of the DNA Bases Facilitates Damage Detection	290	Transcription Elongation in Eukaryotes Requires Accessory Proteins	335
Special Translesion DNA Polymerases Are Used in Emergencies	292	Transcription Creates Superhelical Tension	335
Double-Strand Breaks Are Efficiently Repaired	292	Transcription Elongation in Eukaryotes Is Tightly Coupled to RNA Processing	337
DNA Damage Delays Progression of the Cell Cycle	295	RNA Capping Is the First Modification of Eukaryotic Pre-mRNAs	338
Summary	295	RNA Splicing Removes Intron Sequences from Newly Transcribed Pre-mRNAs	339
HOMOLOGOUS RECOMBINATION	296	Nucleotide Sequences Signal Where Splicing Occurs	341
Homologous Recombination Has Common Features in All Cells	296	RNA Splicing Is Performed by the Spliceosome	341
DNA Base-pairing Guides Homologous Recombination	296	The Spliceosome Uses ATP Hydrolysis to Produce a Complex Series of RNA-RNA Rearrangements	343
Homologous Recombination Can Flawlessly Repair Double-Strand Breaks in DNA	297	Other Properties of Pre-mRNA and Its Synthesis Help to Explain the Choice of Proper Splice Sites	345
Specialized Processing of Double-Strand Breaks Commits Repair to Homologous Recombination	298	RNA Splicing Has Remarkable Plasticity	346
Strand Exchange Is Directed by the RecA/Rad51 Protein	298	Spliceosome-catalyzed RNA Splicing Evolved from RNA Self-splicing Mechanisms	347
Homologous Recombination Can Rescue Broken and Stalled DNA Replication Forks	299	RNA-processing Enzymes Generate the 3' End of Eukaryotic mRNAs	348
DNA Repair by Homologous Recombination Entails Risks to the Cell	300	Mature Eukaryotic mRNAs Are Selectively Exported from the Nucleus	349
Homologous Recombination Is Crucial for Meiosis	301	Noncoding RNAs Are Also Synthesized and Processed in the Nucleus	351
Meiotic Recombination Begins with a Programmed Double-Strand Break	302	The Nucleolus Is a Ribosome-producing Factory	353
Holliday Junctions Are Recognized by Enzymes That Drive Branch Migration	302	The Nucleus Contains a Variety of Subnuclear Biomolecular Condensates	355
Homologous Recombination Produces Crossovers Between Maternal and Paternal Chromosomes During Meiosis	304	Summary	357
Homologous Recombination Often Results in Gene Conversion	305	FROM RNA TO PROTEIN	358
Summary	306	An mRNA Sequence Is Decoded in Sets of Three Nucleotides	358
TRANSDUCTION AND CONSERVATIVE SITE-SPECIFIC RECOMBINATION	306	tRNA Molecules Match Amino Acids to Codons in mRNA	359
Through Transposition, Mobile Genetic Elements Can Insert into Any DNA Sequence	307	tRNAs Are Covalently Modified Before They Exit from the Nucleus	361
DNA-only Transposons Can Move by a Cut-and-Paste Mechanism	307	Specific Enzymes Couple Each Amino Acid to Its Appropriate tRNA Molecule	361
Some DNA-only Transposons Move by Replicating Themselves	309	Editing by tRNA Synthetases Ensures Accuracy	363
Some Viruses Use a Transposition Mechanism to Move Themselves into Host-Cell Chromosomes	309	Amino Acids Are Added to the C-terminal End of a Growing Polypeptide Chain	364
Some RNA Viruses Replicate and Express Their Genomes Without Using DNA as an Intermediate	311	The RNA Message Is Decoded in Ribosomes	365
Retroviral-like Retrotransposons Resemble Retroviruses, but Cannot Move from Cell to Cell	313	Elongation Factors Drive Translation Forward and Improve Its Accuracy	368
A Large Fraction of the Human Genome Is Composed of Nonretroviral Retrotransposons	313	Induced Fit and Kinetic Proofreading Help Biological Processes Overcome the Inherent Limitations of Complementary Base-Pairing	369
Different Transposable Elements Predominate in Different Organisms	314	Accuracy in Translation Requires a Large Expenditure of Free Energy	370
Genome Sequences Reveal the Approximate Times at Which Transposable Elements Have Moved	314	The Ribosome Is a Ribozyme	371
Conservative Site-specific Recombination Can Reversibly Rearrange DNA	315	Nucleotide Sequences in mRNA Signal Where to Start Protein Synthesis	373
Conservative Site-specific Recombination Can Be Used to Turn Genes On or Off	316	Stop Codons Mark the End of Translation	374
Bacterial Conservative Site-specific Recombinases Have Become Powerful Tools for Cell and Developmental Biologists	317	Proteins Are Made on Polyribosomes	375
Summary	317	There Are Minor Variations in the Standard Genetic Code	375
Problems	318	Inhibitors of Prokaryotic Protein Synthesis Are Useful as Antibiotics	376
References	320	Quality-Control Mechanisms Act to Prevent Translation of Damaged mRNAs	378
		Stalled Ribosomes Can Be Rescued	379
Chapter 6 How Cells Read the Genome: From DNA to Protein	321	The Ribosome Coordinates the Folding, Enzymatic Modification, and Assembly of Newly Synthesized Proteins	380
FROM DNA TO RNA	323	Molecular Chaperones Help Guide the Folding of Most Proteins	380
RNA Molecules Are Single-Stranded	324	Proper Folding of Newly Synthesized Proteins Is Also Aided by Translation Speed and Subunit Assembly	383
Transcription Produces RNA Complementary to One Strand of DNA	325	Proteins That Ultimately Fail to Fold Correctly Are Marked for Destruction by Polyubiquitin	384
RNA Polymerases Carry Out DNA Transcription	325	The Proteasome Is a Compartmentalized Protease with Sequestered Active Sites	384
Cells Produce Different Categories of RNA Molecules	327	Many Proteins Are Controlled by Regulated Destruction	386
Signals Encoded in DNA Tell RNA Polymerase Where to Start and Stop	328	There Are Many Steps from DNA to Protein	387
Bacterial Transcription Start and Stop Signals Are Heterogeneous in Nucleotide Sequence	329	Summary	388
Transcription Initiation in Eukaryotes Requires Many Proteins	331	THE RNA WORLD AND THE ORIGINS OF LIFE	389
To Initiate Transcription, RNA Polymerase II Requires a Set of General Transcription Factors	332	Single-Strand RNA Molecules Can Fold into Highly Elaborate Structures	390
		Ribozymes Can Be Produced in the Laboratory	390

RNA Can Both Store Information and Catalyze Chemical Reactions	391	Transcription Circuits Allow the Cell to Carry Out Logic Operations	433
How Did Protein Synthesis Evolve?	392	Summary	434
All Present-Day Cells Use DNA as Their Hereditary Material	393	MECHANISMS THAT REINFORCE CELL MEMORY IN PLANTS AND ANIMALS	435
Summary	393	Patterns of DNA Methylation Can Be Inherited When Vertebrate Cells Divide	435
Problems	394	CG-Rich Islands Are Associated with Many Genes in Mammals	436
References	395	Genomic Imprinting Is Based on DNA Methylation	438
		A Chromosome-wide Alteration in Chromatin Structure Can Be Inherited	440
Chapter 7 Control of Gene Expression	397	The Mammalian X-Inactivation in Females Is Triggered by the Synthesis of a Long Noncoding RNA	442
AN OVERVIEW OF GENE CONTROL	397	Stable Patterns of Gene Expression Can Be Transmitted to Daughter Cells	443
The Different Cell Types of a Multicellular Organism Contain the Same DNA	397	Summary	445
Different Cell Types Synthesize Different Sets of RNAs and Proteins	398	POST-TRANSCRIPTIONAL CONTROLS	445
The Spectrum of mRNAs Present in a Cell Can Be Used to Accurately Identify the Cell Type	400	Transcription Attenuation Causes the Premature Termination of Some RNA Molecules	445
External Signals Can Cause a Cell to Change the Expression of Its Genes	400	Riboswitches Probably Represent Ancient Forms of Gene Control	446
Gene Expression Can Be Regulated at Many of the Steps in the Pathway from DNA to RNA to Protein	401	Alternative RNA Splicing Can Produce Different Forms of a Protein from the Same Gene	446
Summary	402	The Definition of a Gene Has Been Modified Since the Discovery of Alternative RNA Splicing	448
CONTROL OF TRANSCRIPTION BY SEQUENCE-SPECIFIC DNA-BINDING PROTEINS	402	Back Splicing Can Produce Circular RNA Molecules	449
The Sequence of Nucleotides in the DNA Double Helix Can Be Read by Proteins	402	A Change in the Site of RNA Transcript Cleavage and Poly-A Addition Can Change the C-terminus of a Protein	449
Transcription Regulators Contain Structural Motifs That Can Read DNA Sequences	403	Nucleotides in mRNA Can Be Covalently Modified	450
Dimerization of Transcription Regulators Increases Their Affinity and Specificity for DNA	406	RNA Editing Can Change the Meaning of the RNA Message	451
Many Transcription Regulators Bind Cooperatively to DNA	407	The Human AIDS Virus Illustrates How RNA Transport from the Nucleus Can Be Regulated	452
Nucleosome Structure Promotes Cooperative Binding of Transcription Regulators	408	mRNAs Can Be Localized to Specific Regions of the Cytosol	453
DNA-Binding by Transcription Regulators Is Dynamic	409	Untranslated Regions of mRNAs Control Their Translation	456
Summary	410	The Phosphorylation of an Initiation Factor Regulates Protein Synthesis Globally	457
TRANSCRIPTION REGULATORS SWITCH GENES ON AND OFF	410	Initiation at AUG Codons Upstream of the Translation Start Can Regulate Eukaryotic Translation Initiation	458
The Tryptophan Repressor Switches Genes Off	410	Internal Ribosome Entry Sites Also Provide Opportunities for Translational Control	458
Repressors Turn Genes Off and Activators Turn Them On	411	Changes in mRNA Stability Can Control Gene Expression	459
Both an Activator and a Repressor Control the Lac Operon	412	Regulation of mRNA Stability Involves P-bodies and Stress Granules	461
DNA Looping Can Occur During Bacterial Gene Regulation	412	Summary	462
Complex Switches Control Gene Transcription in Eukaryotes	414	REGULATION OF GENE EXPRESSION BY NONCODING RNAs	462
A Eukaryotic Gene Control Region Includes Many <i>cis</i> -Regulatory Sequences	414	Small Noncoding RNA Transcripts Regulate Many Animal and Plant Genes Through RNA Interference	462
Eukaryotic Transcription Regulators Work in Groups	415	miRNAs Regulate mRNA Translation and Stability	463
Activator Proteins Promote the Assembly of RNA Polymerase at the Start Point of Transcription	416	RNA Interference Also Serves as a Cell Defense Mechanism	464
Eukaryotic Transcription Activators Direct the Modification of Local Chromatin Structure	417	RNA Interference Can Direct Heterochromatin Formation	465
Some Transcription Activators Work by Releasing Paused RNA Polymerase	418	piRNAs Protect the Germ Line from Transposable Elements	466
Transcription Activators Work Synergistically	419	RNA Interference Has Become a Powerful Experimental Tool	467
Condensate Formation Likely Increases the Efficiency of Transcription Initiation	420	Cells Have Additional Mechanisms to Hold Transposons and Integrated Viral Genomes in Check	467
Eukaryotic Transcription Repressors Can Inhibit Transcription in Several Ways	420	Bacteria Use Small Noncoding RNAs to Protect Themselves from Viruses	468
Insulator DNA Sequences Prevent Eukaryotic Transcription	422	Long Noncoding RNAs Have Diverse Functions in the Cell	469
Regulators from Influencing Distant Genes	422	Summary	471
Summary	422	Problems	472
MOLECULAR GENETIC MECHANISMS THAT CREATE AND MAINTAIN SPECIALIZED CELL TYPES	423	References	474
Complex Genetic Switches That Regulate <i>Drosophila</i> Development Are Built Up from Smaller Modules	423	Chapter 8 Analyzing Cells, Molecules, and Systems	475
The <i>Drosophila</i> <i>Eve</i> Gene Is Regulated by Combinatorial Controls	424	ISOLATING CELLS AND GROWING THEM IN CULTURE	476
Transcription Regulators Are Brought into Play by Extracellular Signals	426	Cells Can Be Isolated from Tissues and Grown in Culture	476
Combinatorial Gene Control Creates Many Different Cell Types	427	Eukaryotic Cell Lines Are a Widely Used Source of Homogeneous Cells	478
Specialized Cell Types Can Be Experimentally Reprogrammed to Become Pluripotent Stem Cells	428	Hybridoma Cell Lines Are Factories That Produce Monoclonal Antibodies	478
Combinations of Master Transcription Regulators Specify Cell Types by Controlling the Expression of Many Genes	429	Summary	480
Specialized Cells Must Rapidly Turn Some Genes On and Off	430	PURIFYING PROTEINS	480
Differentiated Cells Maintain Their Identity	431	Cells Can Be Separated into Their Component Fractions	480
		Cell Extracts Provide Accessible Systems to Study Cell Functions	482
		Proteins Can Be Separated by Chromatography	483

Immunoprecipitation Is a Rapid Affinity Purification Method	486	Expression of Individual Genes Can Be Measured Using	536
Genetically Engineered Tags Provide an Easy Way to Purify Proteins	486	Quantitative RT-PCR	536
Purified Cell-free Systems Are Required for the Precise Dissection of Molecular Functions	486	Global Analysis of mRNAs by RNA-seq Provides a Snapshot of Gene Expression	538
Summary	487	Genome-wide Chromatin Immunoprecipitation Identifies Sites on the Genome Occupied by Transcription Regulators	538
ANALYZING PROTEINS	487	Ribosome Profiling Reveals Which mRNAs Are Being Translated in the Cell	538
Proteins Can Be Separated by SDS Polyacrylamide-Gel Electrophoresis	487	Recombinant DNA Methods Have Revolutionized Human Health	539
Two-dimensional Gel Electrophoresis Provides Greater Protein Separation	489	Transgenic Plants Are Important for Agriculture	540
Specific Proteins Can Be Detected by Blotting with Antibodies	490	Summary	542
Hydrodynamic Measurements Reveal the Size and Shape of a Protein Complex	490	MATHEMATICAL ANALYSIS OF CELL FUNCTION	542
Mass Spectrometry Provides a Highly Sensitive Method for Identifying Unknown Proteins	491	Regulatory Networks Depend on Molecular Interactions	543
Sets of Interacting Proteins Can Be Identified by Biochemical Methods	493	Differential Equations Help Us Predict Transient Behavior	545
Optical Methods Can Monitor Protein Interactions	493	Promoter Activity and Protein Degradation Affect the Rate of Change of Protein Concentration	546
Protein Structure Can Be Determined Using X-ray Diffraction	494	The Time Required to Reach Steady State Depends on Protein Lifetime	547
NMR Can Be Used to Determine Protein Structure in Solution	496	Quantitative Methods Are Similar for Transcription Repressors and Activators	548
Protein Sequence and Structure Provide Clues About Protein Function	497	Negative Feedback Is a Powerful Strategy in Cell Regulation	549
Summary	498	Delayed Negative Feedback Can Induce Oscillations	549
ANALYZING AND MANIPULATING DNA	498	DNA Binding by a Repressor or an Activator Can Be Cooperative	551
Restriction Nucleases Cut Large DNA Molecules into Specific Fragments	498	Positive Feedback Is Important for Switchlike Responses and Bistability	551
Gel Electrophoresis Separates DNA Molecules of Different Sizes	499	Robustness Is an Important Characteristic of Biological Networks	553
Purified DNA Molecules Can Be Specifically Labeled with Radioisotopes or Chemical Markers <i>in Vitro</i>	501	Two Transcription Regulators That Bind to the Same Gene Promoter Can Exert Combinatorial Control	554
Genes Can Be Cloned Using Bacteria	501	An Incoherent Feed-forward Interaction Generates Pulses	555
An Entire Genome Can Be Represented in a DNA Library	503	A Coherent Feed-forward Interaction Detects Persistent Inputs	556
Hybridization Provides a Powerful but Simple Way to Detect Specific Nucleotide Sequences	505	The Same Network Can Behave Differently in Different Cells Because of Stochastic Effects	557
Genes Can Be Cloned <i>in Vitro</i> Using PCR	506	Several Computational Approaches Can Be Used to Model the Reactions in Cells	557
PCR Is Also Used for Diagnostic and Forensic Applications	507	Statistical Methods Are Critical for the Analysis of Biological Data	558
PCR and Synthetic DNA Are Ideal Sources of Specific Gene Sequences for Cloning	510	Summary	558
DNA Cloning Allows Any Protein to Be Produced in Large Amounts	511	Problems	559
DNA Can Be Sequenced Rapidly by Dideoxy Sequencing	512	References	561
Next-Generation Sequencing Methods Have Revolutionized DNA and RNA Analysis	514	Chapter 9 Visualizing Cells and Their Molecules	563
To Be Useful, Genome Sequences Must Be Annotated	516	LOOKING AT CELLS AND MOLECULES IN THE LIGHT	563
Summary	518	MICROSCOPE	563
STUDYING GENE FUNCTION AND EXPRESSION	518	The Conventional Light Microscope Can Resolve Details 0.2 μm Apart	564
Classical Genetic Screens Identify Random Mutants with Specific Abnormalities	519	Photon Noise Creates Additional Limits to Resolution When Light Levels Are Low	567
Mutations Can Cause Loss or Gain of Protein Function	522	Living Cells Are Seen Clearly in a Phase-Contrast or a Differential-Interference-Contrast Microscope	567
Complementation Tests Reveal Whether Two Mutations Are in the Same Gene or Different Genes	523	Images Can Be Enhanced and Analyzed by Digital Techniques	568
Gene Products Can Be Ordered in Pathways by Epistasis Analysis	523	Intact Tissues Are Usually Fixed and Sectioned Before Microscopy	569
Mutations Responsible for a Phenotype Can Be Identified Through DNA Analysis	524	Specific Molecules Can Be Located in Cells by Fluorescence Microscopy	570
Rapid and Cheap DNA Sequencing Has Revolutionized Human Genetic Studies	524	Antibodies Can Be Used to Detect Specific Proteins	572
Linked Blocks of Polymorphisms Have Been Passed Down from Our Ancestors	525	Individual Proteins Can Be Fluorescently Tagged in Living Cells and Organisms	573
Sequence Variants Can Aid the Search for Mutations Associated with Disease	526	Protein Dynamics Can Be Followed in Living Cells	575
Genomics Is Accelerating the Discovery of Rare Mutations That Predispose Us to Serious Disease	527	Fluorescent Biosensors Can Monitor Cell Signaling	576
The Cellular Functions of a Known Gene Can Be Studied with Genome Engineering	527	Imaging of Complex Three-dimensional Objects Is Possible with the Optical Microscope	577
Animals and Plants Can Be Genetically Altered	528	The Confocal Microscope Produces Optical Sections by Excluding Out-of-Focus Light	578
The Bacterial CRISPR System Has Been Adapted to Edit Genomes in a Wide Variety of Species	530	Superresolution Fluorescence Techniques Can Overcome Diffraction-limited Resolution	580
Large Collections of Engineered Mutations Provide a Tool for Examining the Function of Every Gene in an Organism	531	Single-Molecule Localization Microscopy Also Delivers Superresolution	583
RNA Interference Is a Simple and Rapid Way to Test Gene Function	533	Expanding the Specimen Can Offer Higher Resolution, but with a Conventional Microscope	585
Reporter Genes Reveal When and Where a Gene Is Expressed	534	Large Multicellular Structures Can Be Imaged Over Time	586
<i>In Situ</i> Hybridization Can Reveal the Location of mRNAs and Noncoding RNAs	535	Single Molecules Can Be Visualized by Total Internal Reflection Fluorescence Microscopy	587
		Summary	588

LOOKING AT CELLS AND MOLECULES IN THE ELECTRON MICROSCOPE

The Electron Microscope Resolves the Fine Structure of the Cell	588
Biological Specimens Require Special Preparation for Electron Microscopy	589
Heavy Metals Can Provide Additional Contrast	590
Images of Surfaces Can Be Obtained by Scanning Electron Microscopy	591
Electron Microscope Tomography Allows the Molecular Architecture of Cells to Be Seen in Three Dimensions	593
Cryo-electron Microscopy Can Determine Molecular Structures at Atomic Resolution	595
Light Microscopy and Electron Microscopy Are Mutually Beneficial	597
Using Microscopy to Study Cells Always Involves Trade-Offs	598
Summary	599
Problems	600
References	601

Chapter 10 Membrane Structure **603****THE LIPID BILAYER** **604**

Glycerophospholipids, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes	605
Phospholipids Spontaneously Form Bilayers	606
The Lipid Bilayer Is a Two-dimensional Fluid	608
The Fluidity of a Lipid Bilayer Depends on Its Composition	609
Despite Their Fluidity, Lipid Bilayers Can Form Domains of Different Compositions	610
Lipid Droplets Are Surrounded by a Phospholipid Monolayer	611
The Asymmetry of the Lipid Bilayer Is Functionally Important	612
Glycolipids Are Found on the Surface of All Eukaryotic Plasma Membranes	613
Summary	614
MEMBRANE PROTEINS	615
Membrane Proteins Can Be Associated with the Lipid Bilayer in Various Ways	615
Lipid Anchors Control the Membrane Localization of Some Signaling Proteins	616
In Most Transmembrane Proteins, the Polypeptide Chain Crosses the Lipid Bilayer in an α -Helical Conformation	617
Transmembrane α Helices Often Interact with One Another	619
Some β Barrels Form Large Channels	619
Many Membrane Proteins Are Glycosylated	621
Membrane Proteins Can Be Solubilized and Purified in Detergents	622
Bacteriorhodopsin Is a Light-driven Proton (H^+) Pump That Traverses the Lipid Bilayer as Seven α Helices	625
Membrane Proteins Often Function as Large Complexes	627
Many Membrane Proteins Diffuse in the Plane of the Membrane	627
Cells Can Confine Proteins and Lipids to Specific Domains Within a Membrane	629
The Cortical Cytoskeleton Gives Membranes Mechanical Strength and Restricts Membrane Protein Diffusion	630
Membrane-bending Proteins Deform Bilayers	632
Summary	633
Problems	634
References	635

Chapter 11 Small-Molecule Transport and Electrical Properties of Membranes **637****PRINCIPLES OF MEMBRANE TRANSPORT** **637**

Protein-free Lipid Bilayers Are Impermeable to Ions	638
There Are Two Main Classes of Membrane Transport Proteins: Transporters and Channels	638
Active Transport Is Mediated by Transporters Coupled to an Energy Source	639
Summary	640
TRANSPORTERS AND ACTIVE MEMBRANE TRANSPORT	640
Active Transport Can Be Driven by Ion-Concentration Gradients	642
Transporters in the Plasma Membrane Regulate Cytosolic pH	644
An Asymmetric Distribution of Transporters in Epithelial Cells Underlies the Transcellular Transport of Solutes	645
There Are Three Classes of ATP-driven Pumps	646

A P-type ATPase Pumps Ca^{2+} into the Sarcoplasmic Reticulum in Muscle Cells	647
The Plasma Membrane Na^+ - K^+ Pump Establishes Na^+ and K^+ Gradients Across the Plasma Membrane	648
ABC Transporters Constitute the Largest Family of Membrane Transport Proteins	649
Summary	651
CHANNELS AND THE ELECTRICAL PROPERTIES OF MEMBRANES	651
Aquaporins Are Permeable to Water but Impermeable to Ions	652
Ion Channels Are Ion-selective and Fluctuate Between Open and Closed States	653
The Membrane Potential in Animal Cells Depends Mainly on K^+ Leak Channels and the K^+ Gradient Across the Plasma Membrane	655
The Resting Potential Decays Only Slowly When the Na^+ - K^+ Pump Is Stopped	655
The Three-dimensional Structure of a Bacterial K^+ Channel Shows How an Ion Channel Can Work	657
Mechanosensitive Channels Allow Cells to Sense Their Physical Environment	659
The Function of a Neuron Depends on Its Elongated Structure	661
Voltage-gated Cation Channels Generate Action Potentials in Electrically Excitable Cells	662
Myelination Increases the Speed and Efficiency of Action Potential Propagation in Nerve Cells	666
Patch-Clamp Recording Indicates That Individual Ion Channels Open in an All-or-Nothing Fashion	666
Voltage-gated Cation Channels Are Evolutionarily and Structurally Related	668
Different Neuron Types Display Characteristic Stable Firing Properties	668
Transmitter-gated Ion Channels Convert Chemical Signals into Electrical Ones at Chemical Synapses	669
Chemical Synapses Can Be Excitatory or Inhibitory	670
The Acetylcholine Receptors at the Neuromuscular Junction Are Excitatory Transmitter-gated Cation Channels	671
Neurons Contain Many Types of Transmitter-gated Channels	672
Many Psychoactive Drugs Act at Synapses	673
Neuromuscular Transmission Involves the Sequential Activation of Five Different Sets of Ion Channels	673
Single Neurons Are Complex Computation Devices	674
Neuronal Computation Requires a Combination of at Least Three Kinds of K^+ Channels	675
Long-term Potentiation in the Mammalian Hippocampus Depends on Ca^{2+} Entry Through NMDA-Receptor Channels	677
The Use of Channelrhodopsins Has Revolutionized the Study of Neural Circuits	678
Summary	679
Problems	680
References	681

Chapter 12 Intracellular Organization and Protein Sorting **683****THE COMPARTMENTALIZATION OF CELLS** **683**

All Eukaryotic Cells Have the Same Basic Set of Membrane-enclosed Organelles	683
Evolutionary Origins Explain the Topological Relationships of Organelles	686
Macromolecules Can Be Segregated Without a Surrounding Membrane	688
Multivalent Interactions Mediate Formation of Biomolecular Condensates	690
Biomolecular Condensates Create Biochemical Factories	690
Biomolecular Condensates Form and Disassemble in Response to Need	693
Proteins Can Move Between Compartments in Different Ways	694
Sorting Signals and Sorting Receptors Direct Proteins to the Correct Cell Address	695
Construction of Most Organelles Requires Information in the Organelle Itself	697
Summary	697

THE ENDOPLASMIC RETICULUM	698	The Assembly of a Clathrin Coat Drives Vesicle Formation	752
The ER Is Structurally and Functionally Diverse	698	Adaptor Proteins Select Cargo into Clathrin-coated Vesicles	753
Signal Sequences Were First Discovered in Proteins Imported into the Rough ER	701	Phosphoinositides Mark Organelles and Membrane Domains	754
A Signal-Recognition Particle (SRP) Directs the ER Signal Sequence to a Specific Receptor at the ER	702	Membrane-bending Proteins Help Deform the Membrane During Vesicle Formation	755
The Polypeptide Chain Passes Through a Signal Sequence-gated Aqueous Channel in the Translocator	705	Cytoplasmic Proteins Regulate the Pinching off and Uncoating of Coated Vesicles	756
Translocation Across the ER Membrane Does Not Always Require Ongoing Polypeptide Chain Elongation	707	Monomeric GTPases Control Coat Assembly	756
Transmembrane Proteins Contain Hydrophobic Segments That Are Recognized Like Signal Sequences	709	Coat-recruitment GTPases Participate in Coat Disassembly	758
Hydrophobic Segments of Multipass Transmembrane Proteins Are Interpreted Contextually to Determine Their Orientation	710	The Shape and Size of Transport Vesicles Are Diverse	759
Some Proteins Are Integrated into the ER Membrane by a Post-translational Mechanism	711	Rab Proteins Guide Transport Vesicles to Their Target Membrane	760
Some Membrane Proteins Acquire a Covalently Attached Glycosylphosphatidylinositol (GPI) Anchor	712	Rab Proteins Create and Change the Identity of an Organelle	761
Translocated Polypeptide Chains Fold and Assemble in the Lumen of the Rough ER	712	SNAREs Mediate Membrane Fusion	762
Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common <i>N</i> -Linked Oligosaccharide	714	Interacting SNAREs Need to Be Pried Apart Before They Can Function Again	763
Oligosaccharides Are Used as Tags to Mark the State of Protein Folding	715	Viruses Encode Specialized Membrane Fusion Proteins Needed for Cell Entry	764
Improperly Folded Proteins Are Exported from the ER and Degraded in the Cytosol	716	Summary	764
Misfolded Proteins in the ER Activate an Unfolded Protein Response	717	TRANSPORT FROM THE ENDOPLASMIC RETICULUM THROUGH THE GOLGI APPARATUS	765
The ER Assembles Most Lipid Bilayers	720	Proteins Leave the ER in COPII-coated Transport Vesicles	765
Membrane Contact Sites Between the ER and Other Organelles Facilitate Selective Lipid Transfer	722	Only Proteins That Are Properly Folded and Assembled Can Leave the ER	766
Summary	723	Vesicular Tubular Clusters Mediate Transport from the ER to the Golgi Apparatus	766
PEROXISOMES	723	The Retrieval Pathway to the ER Uses Sorting Signals	768
Peroxisomes Use Molecular Oxygen and Hydrogen Peroxide to Perform Oxidation Reactions	724	Many Proteins Are Selectively Retained in the Compartments in Which They Function	768
Short Signal Sequences Direct the Import of Proteins into Peroxisomes	724	The Golgi Apparatus Consists of an Ordered Series of Compartments	769
Summary	726	Oligosaccharide Chains Are Processed in the Golgi Apparatus	771
THE TRANSPORT OF PROTEINS INTO MITOCHONDRIA AND CHLOROPLASTS	726	Proteoglycans Are Assembled in the Golgi Apparatus	772
Translocation into Mitochondria Depends on Signal Sequences and Protein Translocators	727	What Is the Purpose of Glycosylation?	773
Mitochondrial Proteins Are Imported Post-translationally as Unfolded Polypeptide Chains	728	Transport Through the Golgi Apparatus Occurs by Multiple Mechanisms	774
Protein Import Is Powered by ATP Hydrolysis, a Membrane Potential, and Redox Potential	730	Golgi Matrix Proteins Help Organize the Stack	775
Transport into the Inner Mitochondrial Membrane Occurs Via Several Routes	731	Summary	776
Bacteria and Mitochondria Use Similar Mechanisms to Insert β Barrels into Their Outer Membrane	733	TRANSPORT FROM THE TRANS GOLGI NETWORK TO THE CELL EXTERIOR AND ENDOSOMES	776
Two Signal Sequences Direct Proteins to the Thylakoid Membrane in Chloroplasts	733	Many Proteins and Lipids Are Carried Automatically from the <i>Trans</i> Golgi Network to the Cell Surface	777
Summary	735	A Mannose 6-Phosphate Receptor Sorts Lysosomal Hydrolases in the <i>Trans</i> Golgi Network	777
THE TRANSPORT OF MOLECULES BETWEEN THE NUCLEUS AND THE CYTOSOL	735	Defects in the GlcNAc Phosphotransferase Cause a Lysosomal Storage Disease in Humans	779
Nuclear Pore Complexes Perforate the Nuclear Envelope	736	Secretory Vesicles Bud from the <i>Trans</i> Golgi Network	780
Nuclear Localization Signals Direct Proteins to the Nucleus	738	Precursors of Secretory Proteins Are Proteolytically Processed During the Formation of Secretory Vesicles	781
Nuclear Import Receptors Bind to Both Nuclear Localization Signals and NPC Proteins	739	Secretory Vesicles Wait Near the Plasma Membrane Until Signaled to Release Their Contents	782
The Ran GTPase Imposes Directionality on Nuclear Import Through NPCs	740	For Rapid Exocytosis, Synaptic Vesicles Are Primed at the Presynaptic Plasma Membrane	782
Nuclear Export Works Like Nuclear Import, but in Reverse	741	Synaptic Vesicles Can Be Recycled Locally After Exocytosis	783
Transport Through NPCs Can Be Regulated by Controlling Access to the Transport Machinery	742	Secretory Vesicle Membrane Components Are Quickly Removed from the Plasma Membrane	784
The Nuclear Envelope Disassembles and Reassembles During Mitosis	743	Some Regulated Exocytosis Events Serve to Enlarge the Plasma Membrane	785
Summary	745	Polarized Cells Direct Proteins from the <i>Trans</i> Golgi Network to the Appropriate Domain of the Plasma Membrane	786
Problems	746	Summary	787
References	748	TRANSPORT INTO THE CELL FROM THE PLASMA MEMBRANE: ENDOCYTOSIS	788
Chapter 13 Intracellular Membrane Traffic	749	Pinocytic Vesicles Form from Coated Pits in the Plasma Membrane	789
MECHANISMS OF MEMBRANE TRANSPORT AND COMPARTMENT IDENTITY	751	Not All Membrane Invaginations and Pinocytic Vesicles Are Clathrin Coated	789
There Are Various Types of Coated Vesicles	751	Cells Use Receptor-mediated Endocytosis to Import Selected Extracellular Macromolecules	791
		Specific Proteins Are Retrieved from Early Endosomes and Returned to the Plasma Membrane	792
		Recycling Endosomes Regulate Plasma Membrane Composition	793
		Plasma Membrane Signaling Receptors Are Down-regulated by Degradation in Lysosomes	794

Early Endosomes Mature into Late Endosomes	795	CHLOROPLASTS AND PHOTOSYNTHESIS	843
ESCRT Protein Complexes Mediate the Formation of Intraluminal Vesicles in Multivesicular Bodies	796	Chloroplasts Resemble Mitochondria but Have a Separate Thylakoid Compartment	843
Summary	798	Chloroplasts Capture Energy from Sunlight and Use It to Fix Carbon	844
THE DEGRADATION AND RECYCLING OF MACROMOLECULES IN LYSOSOMES	798	Carbon Fixation Uses ATP and NADPH to Convert CO ₂ into Sugars	845
Lysosomes Are the Principal Sites of Intracellular Digestion	798	Carbon Fixation in Some Plants Is Compartmentalized to Facilitate Growth at Low CO ₂ Concentrations	846
Lysosomes Are Heterogeneous	799	The Sugars Generated by Carbon Fixation Can Be Stored as Starch or Consumed to Produce ATP	849
Plant and Fungal Vacuoles Are Remarkably Versatile Lysosomes	800	The Thylakoid Membranes of Chloroplasts Contain the Protein Complexes Required for Photosynthesis and ATP Generation	849
Multiple Pathways Deliver Materials to Lysosomes	801	Chlorophyll-Protein Complexes Can Transfer Either Excitation Energy or Electrons	850
Cells Can Acquire Nutrients from the Extracellular Fluid by Macropinocytosis	802	A Photosystem Contains Chlorophylls in Antennae and a Reaction Center	851
Specialized Phagocytic Cells Can Ingest Large Particles	802	The Thylakoid Membrane Contains Two Different Photosystems Working in Series	852
Cargo Recognition by Cell-surface Receptors Initiates Phagocytosis	803	Photosystem II Uses a Manganese Cluster to Withdraw Electrons from Water	853
Autophagy Degrades Unwanted Proteins and Organelles	804	The Cytochrome <i>b₆-f</i> Complex Connects Photosystem II to Photosystem I	854
The Rate of Nonselective Autophagy Is Regulated by Nutrient Availability	805	Photosystem I Carries Out the Second Charge-Separation Step in the Z Scheme	855
A Family of Cargo-specific Receptors Mediates Selective Autophagy	806	The Chloroplast ATP Synthase Uses the Proton Gradient Generated by the Photosynthetic Light Reactions to Produce ATP	855
Some Lysosomes and Multivesicular Bodies Undergo Exocytosis	807	The Proton-Motive Force for ATP Production in Mitochondria and Chloroplasts Is Essentially the Same	856
Summary	807	Chemiosmotic Mechanisms Evolved in Stages By Providing an Inexhaustible Source of Reducing Power, Photosynthetic Bacteria Overcame a Major Evolutionary Obstacle	857
Problems	808	The Photosynthetic Electron-Transport Chains of Cyanobacteria Produced Atmospheric Oxygen and Permitted New Life-Forms	857
References	810	Summary	860
Chapter 14 Energy Conversion and Metabolic Compartmentation: Mitochondria and Chloroplasts	811	THE GENETIC SYSTEMS OF MITOCHONDRIA AND CHLOROPLASTS	861
THE MITOCHONDRION	813	The Genetic Systems of Mitochondria and Chloroplasts Resemble Those of Prokaryotes	861
The Mitochondrion Has an Outer Membrane and an Inner Membrane	814	Over Time, Mitochondria and Chloroplasts Have Exported Most of Their Genes to the Nucleus by Gene Transfer	862
Fission, Fusion, Distribution, and Degradation of Mitochondria	815	Mitochondria Have a Relaxed Codon Usage and Can Have a Variant Genetic Code	864
The Inner Membrane Cristae Contain the Machinery for Electron Transport and ATP Synthesis	817	Chloroplasts and Bacteria Share Many Striking Similarities	865
The Citric Acid Cycle in the Matrix Produces NADH	817	Organelle Genes Are Maternally Inherited in Animals and Plants	866
Mitochondria Have Many Essential Roles in Cellular Metabolism	818	Mutations in Mitochondrial DNA Can Cause Severe Inherited Diseases	866
A Chemiosmotic Process Couples Oxidation Energy to ATP Production	821	Why Do Mitochondria and Chloroplasts Maintain a Costly Separate System for DNA Transcription and Translation?	867
The Energy Derived from Oxidation Is Stored as an Electrochemical Gradient	822	Summary	868
Summary	823	Problems	869
THE PROTON PUMPS OF THE ELECTRON-TRANSPORT CHAIN	823	References	871
The Redox Potential Is a Measure of Electron Affinities	823	Chapter 15 Cell Signaling	873
Electron Transfers Release Large Amounts of Energy	824	PRINCIPLES OF CELL SIGNALING	873
Transition Metal Ions and Quinones Accept and Release Electrons Readily	824	Extracellular Signals Can Act Over Short or Long Distances	874
NADH Transfers Its Electrons to Oxygen Through Three Large Enzyme Complexes Embedded in the Inner Membrane	827	Extracellular Signal Molecules Bind to Specific Receptors	875
The NADH Dehydrogenase Complex Contains Separate Modules for Electron Transport and Proton Pumping	828	Each Cell Is Programmed to Respond to Specific Combinations of Extracellular Signals	876
Cytochrome <i>c</i> Reductase Takes Up and Releases Protons on Opposite Sides of the Crista Membrane, Thereby Pumping Protons	829	There Are Three Major Classes of Cell-Surface Receptor Proteins	878
The Cytochrome <i>c</i> Oxidase Complex Pumps Protons and Reduces O ₂ Using a Catalytic Iron-Copper Center	831	Cell-Surface Receptors Relay Signals Via Intracellular Signaling Molecules	879
Succinate Dehydrogenase Acts in Both the Electron-Transport Chain and the Citric Acid Cycle	832	Intracellular Signals Must Be Specific and Robust in a Noisy Cytoplasm	881
The Respiratory Chain Forms a Supercomplex in the Crista Membrane	833	Intracellular Signaling Complexes Form at Activated Cell-Surface Receptors	882
Protons Can Move Rapidly Through Proteins Along Predefined Pathways	834	Modular Interaction Domains Mediate Interactions Between Intracellular Signaling Proteins	883
Summary	835	The Relationship Between Signal and Response Varies in Different Signaling Pathways	885
ATP PRODUCTION IN MITOCHONDRIA	835	The Speed of a Response Depends on the Turnover of Signaling Molecules	886
The Large Negative Value of ΔG for ATP Hydrolysis Makes ATP Useful to the Cell	835		
The ATP Synthase Is a Nanomachine That Produces ATP by Rotary Catalysis	837		
Proton-driven Turbines Are Ancient and Critical for Energy Conversion	839		
Mitochondrial Cristae Help to Make ATP Synthesis Efficient	840		
Special Transport Proteins Move Solutes Through the Inner Membrane	841		
Chemiosmotic Mechanisms First Arose in Bacteria	842		
Summary	842		

Cells Can Respond Abruptly to a Gradually Increasing Signal	887
Positive Feedback Can Generate an All-or-None Response	888
Negative Feedback Is a Common Feature of Intracellular Signaling Systems	890
Cells Can Adjust Their Sensitivity to a Signal	890
Summary	892
SIGNALING THROUGH G-PROTEIN-COUPLED RECEPTORS	892
Heterotrimeric G Proteins Relay Signals from GPCRs	893
Some G Proteins Regulate the Production of Cyclic AMP	895
Cyclic-AMP-dependent Protein Kinase (PKA) Mediates Most of the Effects of Cyclic AMP	896
Some G Proteins Signal Via Phospholipids	898
Ca ²⁺ Functions as a Ubiquitous Intracellular Mediator	899
Feedback Generates Ca ²⁺ Waves and Oscillations	900
Ca ²⁺ /Calmodulin-dependent Protein Kinases Mediate Many Responses to Ca ²⁺ Signals	902
Some G Proteins Directly Regulate Ion Channels	904
Smell and Vision Depend on GPCRs That Regulate Ion Channels	905
Nitric Oxide Gas Can Mediate Signaling Between Cells	908
Second Messengers and Enzymatic Cascades Amplify Signals	909
GPCR Desensitization Depends on Receptor Phosphorylation	909
Summary	910
SIGNALING THROUGH ENZYME-COUPLED RECEPTORS	911
Activated Receptor Tyrosine Kinases (RTKs) Phosphorylate Themselves	911
Phosphorylated Tyrosines on RTKs Serve as Docking Sites for Intracellular Signaling Proteins	913
Proteins with SH2 Domains Bind to Phosphorylated Tyrosines	913
The Monomeric GTPase Ras Mediates Signaling by Most RTKs	915
Ras Activates a MAP Kinase Signaling Module	916
Scaffold Proteins Reduce Cross-Talk Between Different MAP Kinase Modules	918
Rho Family GTPases Functionally Couple Cell-Surface Receptors to the Cytoskeleton	919
PI 3-Kinase Produces Lipid Docking Sites in the Plasma Membrane	920
The PI-3-Kinase-Akt Signaling Pathway Stimulates Animal Cells to Survive and Grow	921
RTKs and GPCRs Activate Overlapping Signaling Pathways	923
Some Enzyme-coupled Receptors Associate with Cytoplasmic Tyrosine Kinases	923
Cytokine Receptors Activate the JAK-STAT Signaling Pathway	924
Extracellular Signal Proteins of the TGF β Superfamily Act Through Receptor Serine/Threonine Kinases and Smads	926
Summary	927
ALTERNATIVE SIGNALING ROUTES IN GENE REGULATION	928
The Receptor Notch Is a Latent Transcription Regulator	928
Wnt Proteins Activate Frizzled and Thereby Inhibit β -Catenin Degradation	930
Hedgehog Proteins Initiate a Complex Signaling Pathway in the Primary Cilium	932
Many Inflammatory and Stress Signals Act Through an NF κ B-dependent Signaling Pathway	934
Nuclear Receptors Are Ligand-modulated Transcription Regulators	935
Circadian Clocks Use Negative Feedback Loops to Control Gene Expression	937
Three Purified Proteins Can Reconstitute a Cyanobacterial Circadian Clock in a Test Tube	938
Summary	939
SIGNALING IN PLANTS	940
Multicellularity and Cell Communication Evolved Independently in Plants and Animals	940
Receptor Serine/Threonine Kinases Are the Largest Class of Cell-Surface Receptors in Plants	941
Ethylene Blocks the Degradation of Specific Transcription Regulatory Proteins in the Nucleus	941
Regulated Positioning of Auxin Transporters Patterns Plant Growth	943
Phytochromes Detect Red Light, and Cryptochromes Detect Blue Light	944
Summary	945
Problems	946
References	948

Chapter 16 The Cytoskeleton	949
FUNCTION AND DYNAMICS OF THE CYTOSKELETON	949
Cytoskeletal Filaments Are Dynamic, but Can Nevertheless Form Stable Structures	951
The Cytoskeleton Determines Cellular Organization and Polarity	952
Filaments Assemble from Protein Subunits That Impart Specific Physical and Dynamic Properties	953
Accessory Proteins and Motors Act on Cytoskeletal Filaments	955
Molecular Motors Operate in a Cellular Environment Dominated by Brownian Motion	956
Summary	957
ACTIN	957
Actin Subunits Assemble Head-to-Tail to Create Flexible, Polar Filaments	958
Nucleation Is the Rate-limiting Step in the Formation of Actin Filaments	958
Actin Filaments Have Two Distinct Ends That Grow at Different Rates	962
ATP Hydrolysis Within Actin Filaments Leads to Treadmilling at Steady State	962
The Functions of Actin Filaments Are Inhibited by Both Polymer-stabilizing and Polymer-destabilizing Chemicals	963
Actin-binding Proteins Influence Filament Dynamics and Organization	964
Actin Nucleation Is Tightly Regulated and Generates Branched or Straight Filaments	964
Actin Filament Elongation Is Regulated by Monomer-binding Proteins	967
Actin Filament-binding Proteins Alter Filament Dynamics and Organization	968
Severing Proteins Regulate Actin Filament Depolymerization	970
Bacteria Can Hijack the Host Actin Cytoskeleton	971
Actin at the Cell Cortex Determines Cell Shape	971
Distinct Modes of Cell Migration Rely on the Actin Cytoskeleton	972
Cells Migrating in Three Dimensions Can Navigate Around Barriers	974
Summary	975
MYOSIN AND ACTIN	976
Actin-based Motor Proteins Are Members of the Myosin Superfamily	976
Myosin Generates Force by Coupling ATP Hydrolysis to Conformational Changes	977
Sliding of Myosin II Along Actin Filaments Causes Muscles to Contract	977
A Sudden Rise in Cytosolic Ca ²⁺ Concentration Initiates Muscle Contraction	981
Heart Muscle Is a Precisely Engineered Machine	984
Actin and Myosin Perform a Variety of Functions in Non-Muscle Cells	984
Summary	986
MICROTUBULES	987
Microtubules Are Hollow Tubes Made of Protofilaments	988
Microtubules Undergo a Process Called Dynamic Instability	988
Microtubule Functions Are Inhibited by Both Polymer-stabilizing and Polymer-destabilizing Drugs	991
A Protein Complex Containing γ -Tubulin Nucleates Microtubules	991
The Centrosome Is a Prominent Microtubule Nucleation Site	991
Microtubule Organization Varies Widely Among Cell Types	993
Microtubule-binding Proteins Modulate Filament Dynamics and Organization	995
Microtubule Plus End-binding Proteins Modulate Microtubule Dynamics and Attachments	996
Tubulin-sequestering and Microtubule-severing Proteins Modulate Microtubule Dynamics	998
Two Types of Motor Proteins Move Along Microtubules	999
Microtubules and Motors Move Organelles and Vesicles	1002
Motile Cilia and Flagella Are Built from Microtubules and Dyneins	1004
Primary Cilia Perform Important Signaling Functions in Animal Cells	1005
Summary	1006
INTERMEDIATE FILAMENTS AND OTHER CYTOSKELETAL POLYMERS	1007
Intermediate Filament Structure Depends on the Lateral Bundling and Twisting of Coiled-Coils	1007
Intermediate Filaments Impart Mechanical Stability to Animal Cells	1009
Linker Proteins Connect Cytoskeletal Filaments and Bridge the Nuclear Envelope	1011

Septins Form Filaments That Contribute to Subcellular Organization	1012	Actin and Myosin II in the Contractile Ring Guide the Process of Cytokinesis	1065
Bacterial Cell Shape and Division Depend on Homologs of Eukaryotic Cytoskeletal Proteins	1013	Local Activation of RhoA Triggers Assembly and Contraction of the Contractile Ring	1065
Summary	1016	The Microtubules of the Mitotic Spindle Determine the Plane of Animal Cell Division	1066
CELL POLARITY AND COORDINATION OF THE CYTOSKELETON	1016	The Phragmoplast Guides Cytokinesis in Higher Plants	1068
Cell Polarity Is Governed by Small GTPases in Budding Yeast	1016	Membrane-enclosed Organelles Must Be Distributed to Daughter Cells During Cytokinesis	1069
PAR Proteins Generate Anterior–Posterior Polarity in Embryos	1018	Some Cells Reposition Their Spindle to Divide Asymmetrically	1069
Conserved Complexes Polarize Epithelial Cells and Control Their Growth	1019	Mitosis Can Occur Without Cytokinesis	1070
Cell Migration Requires Dynamic Cell Polarity	1020	Summary	1070
External Signals Can Dictate the Direction of Cell Migration	1022	MEIOSIS	1071
Communication Among Cytoskeletal Elements Supports Whole-Cell Polarity and Locomotion	1023	Meiosis Includes Two Rounds of Chromosome Segregation	1071
Summary	1023	Duplicated Homologs Pair During Meiotic Prophase	1073
Problems	1024	Homolog Pairing Culminates in the Formation of a Synaptonemal Complex	1073
References	1025	Homolog Segregation Depends on Several Unique Features of Meiosis I	1075
Chapter 17 The Cell Cycle	1027	Crossing-Over Is Highly Regulated	1076
OVERVIEW OF THE CELL CYCLE	1027	Meiosis Frequently Goes Wrong	1077
The Eukaryotic Cell Cycle Usually Consists of Four Phases	1028	Summary	1077
Cell-Cycle Control Is Similar in All Eukaryotes	1030	CONTROL OF CELL DIVISION AND CELL GROWTH	1077
Cell-Cycle Progression Can Be Studied in Various Ways	1030	Mitogens Stimulate Cell Division	1078
Summary	1031	Cells Can Enter a Specialized Nondividing State	1078
THE CELL-CYCLE CONTROL SYSTEM	1031	Mitogens Stimulate G ₁ -Cdk and G ₁ /S-Cdk Activities	1079
The Cell-Cycle Control System Triggers the Major Events of the Cell Cycle	1032	DNA Damage Blocks Cell Division	1080
The Cell-Cycle Control System Depends on Cyclically Activated Cyclin-dependent Protein Kinases	1033	Many Human Cells Have a Built-In Limitation on the Number of Times They Can Divide	1082
Protein Phosphatases Reverse the Effects of Cdks	1035	Cell Proliferation Is Accompanied by Cell Growth	1083
Hundreds of Cdk Substrates Are Phosphorylated in a Defined Order	1035	Proliferating Cells Usually Coordinate Their Growth and Division	1084
Positive Feedback Generates the Switchlike Behavior of Cell-Cycle Transitions	1036	Summary	1084
The Anaphase-promoting Complex/Cyclosome (APC/C) Triggers the Metaphase-to-Anaphase Transition	1038	Problems	1085
The G ₁ Phase Is a Stable State of Cdk Inactivity	1040	References	1087
The Cell-Cycle Control System Functions as a Linked Series of Biochemical Switches	1041	Chapter 18 Cell Death	1089
Summary	1042	Apoptosis Eliminates Unwanted Cells	1090
S PHASE	1042	Apoptosis Depends on an Intracellular Proteolytic Cascade Mediated by Caspases	1091
S-Cdk Initiates DNA Replication Once Per Cell Cycle	1043	Activation of Cell-Surface Death Receptors Initiates the Extrinsic Pathway of Apoptosis	1093
Chromosome Duplication Requires Duplication of Chromatin Structure	1045	The Intrinsic Pathway of Apoptosis Depends on Proteins Released from Mitochondria	1094
Cohesins Hold Sister Chromatids Together	1045	Bcl2 Proteins Are the Critical Controllers of the Intrinsic Pathway of Apoptosis	1095
Summary	1046	An Inhibitor of Apoptosis (an IAP) and Two Anti-IAP Proteins Help Control Caspase Activation in the Cytosol of Some Mammalian Cells	1098
MITOSIS	1046	Extracellular Survival Factors Inhibit Apoptosis in Various Ways	1098
M-Cdk and Other Protein Kinases Drive Entry into Mitosis	1047	Healthy Neighbors Phagocytose and Digest Apoptotic Cells	1100
Condensin Helps Configure Duplicated Chromosomes for Separation	1047	Either Excessive or Insufficient Apoptosis Can Contribute to Disease	1100
The Mitotic Spindle Is a Dynamic Microtubule-based Machine	1050	Summary	1102
Microtubules Are Nucleated in Multiple Regions of the Spindle	1051	Problems	1103
Microtubule Instability Increases Greatly in Mitosis	1052	References	1104
Microtubule-based Motor Proteins Govern Spindle Assembly and Function	1052	Chapter 19 Cell Junctions and the Extracellular Matrix	1105
Bipolar Spindle Assembly in Most Animal Cells Begins with Centrosome Duplication	1053	CELL–CELL JUNCTIONS	1108
Spindle Assembly in Animal Cells Requires Nuclear-Envelope Breakdown	1054	Cadherins Form a Diverse Family of Adhesion Molecules	1108
Mitotic Chromosomes Promote Bipolar Spindle Assembly	1055	Cadherins Mediate Homophilic Adhesion	1108
Kinetochores Attach Sister Chromatids to the Spindle	1056	Cadherin-dependent Cell–Cell Adhesion Guides the Organization of Developing Tissues	1110
Bi-orientation Is Achieved by Trial and Error	1057	Assembly of Strong Cell–Cell Adhesions Requires Changes in the Actin Cytoskeleton	1112
Multiple Forces Act on Chromosomes in the Spindle	1059	Catenins Link Classical Cadherins to the Actin Cytoskeleton	1113
The APC/C Triggers Sister-Chromatid Separation and the Completion of Mitosis	1060	Adherens Junctions Respond to Tension from Inside and Outside the Tissue	1113
Unattached Chromosomes Block Sister-Chromatid Separation: The Spindle Assembly Checkpoint	1062	Tissue Remodeling Depends on the Coordination of Actin-mediated Contraction with Cell–Cell Adhesion	1114
Chromosomes Segregate in Anaphase A and B	1062	Desmosomes Give Epithelia Mechanical Strength	1116
Segregated Chromosomes Are Packaged in Daughter Nuclei at Telophase	1063	Tight Junctions Form a Seal Between Cells and a Fence Between Plasma Membrane Domains	1116
Summary	1064		
CYTOKINESIS	1064		

Tight Junctions Contain Strands of Transmembrane Adhesion Proteins	1119	Cancer Cells Contain Somatic Mutations	1166
Scaffold Proteins Organize Junctional Protein Complexes	1120	A Single Mutation Is Not Enough to Change a Normal Cell into a Cancer Cell	1166
Gap Junctions Couple Cells Both Electrically and Metabolically	1121	Many Cancers Develop Gradually Through Successive Rounds of Random Inherited Change Followed by Natural Selection	1167
A Gap-Junction Connexon Is Made of Six Transmembrane Connexin Subunits	1122	Cancers Can Evolve Abruptly Due to Genetic Instability	1168
In Plants, Plasmodesmata Perform Many of the Same Functions as Gap Junctions	1123	Some Cancers May Harbor a Small Population of Stem Cells	1170
Selectins Mediate Transient Cell–Cell Adhesions in the Bloodstream	1125	A Common Set of Hallmarks Typically Characterizes Cancerous Growth	1171
Members of the Immunoglobulin Superfamily Mediate Ca ²⁺ -independent Cell–Cell Adhesion	1126	Cancer Cells Display an Altered Control of Growth and Homeostasis	1172
Summary	1127	Human Cancer Cells Escape a Built-in Limit to Cell Proliferation	1173
THE EXTRACELLULAR MATRIX OF ANIMALS	1127	Cancer Cells Have an Abnormal Ability to Bypass Death Signals	1174
The Extracellular Matrix Is Made and Oriented by the Cells Within It	1128	Cancer Cells Have Altered Sugar Metabolism	1175
Glycosaminoglycan (GAG) Chains Occupy Large Amounts of Space and Form Hydrated Gels	1129	The Tumor Microenvironment Influences Cancer Development	1175
Hyaluronan Acts as a Space Filler During Tissue Morphogenesis and Repair	1129	Cancer Cells Must Survive and Proliferate in a Foreign Environment	1176
Proteoglycans Are Composed of GAG Chains Covalently Linked to a Core Protein	1130	Summary	1178
Collagens Are the Major Proteins of the Extracellular Matrix	1132	CANCER-CRITICAL GENES: HOW THEY ARE FOUND AND WHAT THEY DO	1178
Collagen Chains Undergo a Series of Post-translational Modifications	1133	The Identification of Gain-of-Function and Loss-of-Function Cancer Mutations Has Traditionally Required Different Methods	1179
Secreted Fibril-associated Collagens Help Organize the Fibrils	1135	Retroviruses Led to the Identification of Oncogenes	1180
Elastin Gives Tissues Their Elasticity	1136	Genes Mutated in Cancer Can Be Made Overactive in Many Ways	1181
Cells Govern and Respond to the Mechanical Properties of the Matrix	1137	Studies of Rare Hereditary Cancer Syndromes First Identified Tumor Suppressor Genes	1182
Fibronectin and Other Multidomain Glycoproteins Help Organize the Matrix	1138	Both Genetic and Epigenetic Mechanisms Can Inactivate Tumor Suppressor Genes	1183
Fibronectin Binds to Integrins	1139	Systematic Sequencing of Cancer Cell Genomes Has Transformed Our Understanding of the Disease	1184
Tension Exerted by Cells Regulates the Assembly of Fibronectin Fibrils	1140	Many Cancers Have an Extraordinarily Disrupted Genome	1185
The Basal Lamina Is a Specialized Form of Extracellular Matrix	1141	Epigenetic and Chromatin Changes Contribute to Most Cancers	1185
Laminin and Type IV Collagen Are Major Components of the Basal Lamina	1141	Hundreds of Human Genes Contribute to Cancer	1186
Basal Laminae Have Diverse Functions	1143	Disruptions in a Handful of Key Pathways Are Common to Many Cancers	1187
Cells Have to Be Able to Degrade Matrix, as Well as Make It	1144	Mutations in the PI 3-kinase/Akt/mTOR Pathway Drive Cancer Cells to Grow	1188
Matrix Proteoglycans and Glycoproteins Regulate the Activities of Secreted Proteins	1145	Mutations in the p53 Pathway Enable Cancer Cells to Survive and Proliferate Despite Stress and DNA Damage	1189
Summary	1146	Studies Using Mice Help to Define the Functions of Cancer-critical Genes	1190
CELL–MATRIX JUNCTIONS	1147	Cancers Become More and More Heterogeneous as They Progress	1192
Integrins Are Transmembrane Heterodimers That Link the Extracellular Matrix to the Cytoskeleton	1147	Colorectal Cancers Evolve Slowly Via a Succession of Visible Changes	1192
Integrin Defects Are Responsible for Many Genetic Diseases	1148	A Few Key Genetic Lesions Are Common to a Large Fraction of Colorectal Cancers	1194
Integrins Can Switch Between an Active and an Inactive Conformation	1149	Some Colorectal Cancers Have Defects in DNA Mismatch Repair	1195
Integrins Cluster to Form Strong Adhesions	1151	The Steps of Tumor Progression Can Often Be Correlated with Specific Mutations	1196
Extracellular Matrix Attachments Act Through Integrins to Control Cell Proliferation and Survival	1151	The Changes in Tumor Cells That Lead to Metastasis Are Still Largely a Mystery	1197
Integrins Recruit Intracellular Signaling Proteins at Sites of Cell–Matrix Adhesion	1152	Summary	1197
Cell–Matrix Adhesions Respond to Mechanical Forces	1153	CANCER PREVENTION AND TREATMENT: PRESENT AND FUTURE	1198
Summary	1154	Epidemiology Reveals That Many Cases of Cancer Are Preventable	1198
THE PLANT CELL WALL	1154	Sensitive Assays Can Detect Those Cancer-causing Agents That Damage DNA	1199
The Composition of the Cell Wall Depends on the Cell Type	1155	Fifty Percent of Cancers Could Be Prevented by Changes in Lifestyle	1200
The Tensile Strength of the Cell Wall Allows Plant Cells to Develop Turgor Pressure	1155	Viruses and Other Infections Contribute to a Significant Proportion of Human Cancers	1201
The Primary Cell Wall Is Built from Cellulose Microfibrils Interwoven with a Network of Pectic Polysaccharides	1156	Cancers of the Uterine Cervix Can Be Prevented by Vaccination Against Human Papillomavirus	1202
Oriented Cell Wall Deposition Controls Plant Cell Growth	1157	Infectious Agents Can Cause Cancer in a Variety of Ways	1203
Microtubules Orient Cell Wall Deposition	1158	The Search for Cancer Cures Is Difficult but Not Hopeless	1204
Summary	1159	Traditional Therapies Exploit the Genetic Instability and Loss of Cell–Cycle Checkpoint Responses in Cancer Cells	1204
Problems	1160	New Drugs Can Kill Cancer Cells Selectively by Targeting Specific Mutations	1204
References	1162	PARP Inhibitors Kill Cancer Cells That Have Defects in <i>Brca1</i> or <i>Brca2</i> Genes	1205
Chapter 20 Cancer	1163		
CANCER AS A MICROEVOLUTIONARY PROCESS	1163		
Cancer Cells Bypass Normal Proliferation Controls and Colonize Other Tissues	1164		
Most Cancers Derive from a Single Abnormal Cell	1165		

Small Molecules Can Be Designed to Inhibit Specific Oncogenic Proteins	1207	A Gene Expression Oscillator Acts as a Clock to Control Vertebrate Segmentation	1249
Many Cancers May Be Treatable by Enhancing Immune Responses	1209	Cell-intrinsic Timing Mechanisms Can Lead to Different Cell Fates	1251
Immunosuppression Is a Major Hurdle for Cancer Immunotherapy	1210	Cells Rarely Count Cell Divisions to Time Their Development	1252
Cancers Evolve Resistance to Therapies	1212	MicroRNAs Can Regulate Developmental Transitions	1252
We Now Have the Tools to Devise Combination Therapies Tailored to the Individual	1212	Cell and Nuclear Size Relationships Schedule the Onset of Zygotic Gene Expression	1254
Summary	1213	Hormonal Signals Coordinate the Timing of Developmental Transitions	1255
Problems	1214	Environmental Cues Determine the Time of Flowering	1256
References	1216	Summary	1257
Chapter 21 Development of Multicellular Organisms	1217	MORPHOGENESIS	1257
OVERVIEW OF DEVELOPMENT	1218	Imbalance in Physical Forces Acting on Cells Drives Morphogenesis	1258
Conserved Mechanisms Establish the Core Tissues of Animals	1218	Tension and Adhesion Determine Cell Packing Within Epithelial Sheets	1258
The Developmental Potential of Cells Becomes Progressively Restricted	1219	Changing Patterns of Cell Adhesion Molecules Force Cells into New Arrangements	1259
Cell Memory Underlies Cell Decision-Making	1220	Repulsive Interactions Help Maintain Tissue Boundaries	1259
Several Model Organisms Have Been Crucial for Understanding Development	1220	Groups of Similar Cells Can Perform Dramatic Collective Rearrangements	1261
Regulatory DNA Seems Largely Responsible for the Differences Between Animal Species	1220	Planar Cell Polarity Orients Cell Behaviors Within an Embryo	1261
Small Numbers of Conserved Cell-Cell Signaling Pathways Coordinate Spatial Patterning	1221	An Epithelium Can Bend During Development to Form a Tube	1263
Through Combinatorial Control and Cell Memory, Simple Signals Can Generate Complex Patterns	1221	Interactions Between an Epithelium and Mesenchyme Generate Branching Tubular Structures	1264
Morphogens Are Diffusible Inductive Signals That Exert Graded Effects	1222	The Extracellular Matrix Also Influences Tissue Shape	1265
Lateral Inhibition Can Generate Patterns of Different Cell Types	1223	Cell Migration Is Guided by Environmental Signals	1266
Asymmetric Cell Division Can Also Generate Diversity	1224	The Distribution of Migrant Cells Depends on Survival Factors	1267
Initial Patterns Are Established in Small Fields of Cells and Refined by Sequential Induction as the Embryo Grows	1225	Cells Migrate in Groups to Achieve Large-Scale Morphogenetic Movements	1268
Developmental Biology Provides Insights into Disease and Tissue Maintenance	1225	Summary	1269
Summary	1226	GROWTH	1269
MECHANISMS OF PATTERN FORMATION	1226	The Proliferation, Death, and Size of Cells Determine Organ and Organism Size	1270
Different Animals Use Different Mechanisms to Establish Their Primary Axes of Polarization	1226	Changes in Cell Size Usually Result from Modified Cell Cycles	1271
Studies in <i>Drosophila</i> Have Revealed Many Genetic Control Mechanisms Underlying Development	1228	Animals and Organs Can Assess and Regulate Total Cell Mass	1272
Gene Products Deposited in the Egg Organize the Axes of the Early <i>Drosophila</i> Embryo	1228	Various Extracellular Signals Stimulate or Inhibit Growth	1273
Three Groups of Genes Control <i>Drosophila</i> Segmentation Along the A-P Axis	1230	The Hippo Pathway Relays Mechanical Signals Regulating Growth	1273
A Hierarchy of Gene Regulatory Interactions Subdivides the <i>Drosophila</i> Embryo	1231	Hormones Coordinate Growth Throughout the Body	1274
Egg-Polarity, Gap, and Pair-Rule Genes Create a Transient Pattern That Is Remembered by Segment-Polarity and <i>Hox</i> Genes	1233	The Duration of Growth Influences Organism Size	1275
<i>Hox</i> Genes Permanently Pattern the A-P Axis	1233	Summary	1275
<i>Hox</i> Proteins Give Each Segment Its Individuality	1234	Problems	1276
<i>Hox</i> Genes Are Expressed According to Their Order in the <i>Hox</i> Complex	1234	References	1278
Trithorax and Polycomb Group Proteins Regulate <i>Hox</i> Expression to Maintain a Permanent Record of Positional Information	1235	Chapter 22 Stem Cells in Tissue Homeostasis and Regeneration	1279
The D-V Signaling Genes Create a Gradient of the Transcription Regulator Dorsal	1236	STEM CELLS AND TISSUE HOMEOSTASIS	1279
A Hierarchy of Inductive Interactions Subdivides the Vertebrate Embryo	1238	Stem Cells Are Defined by Their Ability to Self-renew and Produce Differentiated Cells	1280
A Competition Between Secreted Signaling Proteins Patterns the Vertebrate Embryonic Axes	1239	The Epithelial Lining of the Small Intestine Is Continually Renewed Through Cell Proliferation in Crypts	1281
<i>Hox</i> Genes Control the Vertebrate A-P Axis	1240	Epidermal Stem Cells Maintain a Self-renewing, Waterproof, Epithelial Barrier on the Body Surface	1282
Some Transcription Regulators Can Activate a Program That Defines a Cell Type or Creates an Entire Organ	1241	Cell Lineage Tracing Reveals the Location of Stem Cells and Their Progeny	1284
Notch-mediated Lateral Inhibition Refines Cellular Spacing Patterns	1242	Quiescent Stem Cells Are Difficult to Identify by Lineage Tracing	1285
Cell-fate Determinants Can Be Asymmetrically Inherited	1244	Hematopoietic Stem Cells Can Be Identified by Transplantation	1286
Evolution of Regulatory DNA Explains Many Morphological Differences	1245	Some Tissues Do Not Require Stem Cells for Their Maintenance	1289
Summary	1247	In Response to Injury, Some Differentiated Cells Can Revert to Progenitor Cells and Some Progenitor Cells Can Revert to Stem Cells	1289
DEVELOPMENTAL TIMING	1248	Some Tissues Lack Stem Cells and Are Not Renewable	1290
Molecular Lifetimes Play a Critical Part in Developmental Timing	1248	Summary	1290
		CONTROL OF STEM-CELL FATE AND SELF-RENEWAL	1291
		The Stem-Cell Niche Maintains Stem-Cell Self-Renewal	1291
		The Size of the Niche Can Determine the Number of Stem Cells	1292
		Asymmetric Stem-Cell Division Can Maintain Stem-Cell Number	1293
		In Many Symmetric Stem-Cell Divisions, Daughter Cells Choose Their Fates Independently and Stochastically	1294
		A Decline in Stem-Cell Function Contributes to Tissue Aging	1294

Summary	1296
REGENERATION AND REPAIR	1296
Planarian Flatworms Contain Stem Cells That Can Regenerate a Whole New Body	1297
Some Vertebrates Can Regenerate Entire Limbs and Organs	1298
Stem Cells Can Be Used Clinically to Replace Lost Hematopoietic or Skin Cells	1299
Neural Stem Cells Can Be Manipulated in Culture and Used to Repopulate a Diseased Central Nervous System	1299
Summary	1300
CELL REPROGRAMMING AND PLURIPOTENT STEM CELLS	1300
Nuclei Can Be Reprogrammed by Transplantation into Foreign Cytoplasm	1301
Reprogramming of a Transplanted Nucleus Involves Drastic Changes in Chromatin	1301
Embryonic Stem (ES) Cells Can Generate Any Part of the Body	1302
A Core Set of Transcription Regulators Defines and Maintains the ES-Cell State	1303
Fibroblasts Can Be Reprogrammed to Create Induced Pluripotent Stem (iPS) Cells	1303
Reprogramming Involves a Massive Upheaval of the Gene Control System	1304
An Experimental Manipulation of Factors That Modify Chromatin Can Increase Reprogramming Efficiencies	1305
ES and iPS Cells Can Be Guided to Generate Specific Adult Cell Types and Even Organoids	1306
Cells of One Specialized Type Can Be Forced to Transdifferentiate Directly into Another	1306
ES and iPS Cells Are Also Useful for Drug Discovery and Analysis of Disease	1308
Summary	1309
Problems	1310
References	1312

Chapter 23 Pathogens and Infection 1313

INTRODUCTION TO PATHOGENS	1313
Pathogens Can Be Viruses, Bacteria, or Eukaryotes	1314
Pathogens Interact with Their Hosts in Different Ways	1314
Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches	1315
Bacterial Pathogens Carry Specialized Virulence Genes	1317
Bacterial Virulence Genes Encode Toxins and Secretion Systems That Deliver Effector Proteins to Host Cells	1319
Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms	1321
All Aspects of Viral Propagation Depend on Host-Cell Machinery	1322
Summary	1325
CELL BIOLOGY OF PATHOGEN INFECTION	1325
Pathogens Breach Epithelial Barriers to Infect the Host	1326
Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms	1326
Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them	1328
Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells	1329
Viruses Bind to Virus Receptors at the Host-Cell Surface	1329
Viruses Enter Host Cells by Membrane Fusion, Pore Formation, or Membrane Disruption	1330
Bacteria Enter Host Cells by Phagocytosis	1331
Intracellular Eukaryotic Parasites Actively Invade Host Cells	1333
Some Intracellular Pathogens Escape from the Phagosome into the Cytosol	1334
Many Pathogens Alter Membrane Traffic in the Host Cell to Survive and Replicate	1335
Bacteria and Viruses Use the Host-Cell Cytoskeleton for Intracellular Movement	1338
Many Microbes Manipulate Autophagy	1340
Viruses Can Take Over the Metabolism of the Host Cell	1340
Pathogens Can Evolve Rapidly by Antigenic Variation	1341
Error-prone Replication Dominates Viral Evolution	1343
Drug-resistant Pathogens Are a Growing Problem	1344
Summary	1346

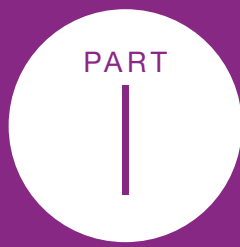
THE HUMAN MICROBIOTA	1347
The Human Microbiota Is a Complex Ecological System	1347
The Microbiota Influences Our Development and Health	1348
Summary	1349
Problems	1350
References	1351

Chapter 24 The Innate and Adaptive Immune Systems 1353

THE INNATE IMMUNE SYSTEM	1354
Epithelial Surfaces Serve as Barriers to Infection	1354
Pattern Recognition Receptors (PRRs) Recognize Conserved Features of Pathogens	1354
There Are Multiple Families of PRRs	1355
Activated PRRs Trigger an Inflammatory Response at Sites of Infection	1356
Phagocytic Cells Seek, Engulf, and Destroy Pathogens	1358
Complement Activation Targets Pathogens for Phagocytosis or Lysis	1358
Virus-infected Cells Take Drastic Measures to Prevent Viral Replication	1360
Natural Killer Cells Induce Virus-infected Cells to Kill Themselves	1361
Dendritic Cells Provide the Link Between the Innate and Adaptive Immune Systems	1362
Summary	1362
OVERVIEW OF THE ADAPTIVE IMMUNE SYSTEM	1364
B Cells Develop in the Bone Marrow, T Cells in the Thymus	1365
Immunological Memory Depends on Both Clonal Expansion and Lymphocyte Differentiation	1366
Most B and T Cells Continually Recirculate Through Peripheral Lymphoid Organs	1368
Immunological Self-tolerance Ensures That B and T Cells Do Not Attack Normal Host Cells and Molecules	1370
Summary	1372
B CELLS AND IMMUNOGLOBULINS	1372
B Cells Make Immunoglobulins (Igs) as Both Cell-Surface Antigen Receptors and Secreted Antibodies	1373
Mammals Make Five Classes of Igs	1373
Ig Light and Heavy Chains of Antibodies Consist of Constant and Variable Regions	1375
Ig Genes Are Assembled from Separate Gene Segments During B Cell Development	1377
Antigen-driven Somatic Hypermutation Fine-Tunes Antibody Responses	1379
B Cells Can Switch the Class of Ig They Make	1379
Summary	1381
T CELLS AND MHC PROTEINS	1382
T Cell Receptors (TCRs) Are Ig-like Heterodimers	1382
Activated Dendritic Cells Activate Naïve T Cells	1383
T Cells Recognize Foreign Peptides Bound to MHC Proteins	1384
MHC Proteins Are the Most Polymorphic Human Proteins Known	1388
CD4 and CD8 Co-receptors on T Cells Bind to Invariant Parts of MHC Proteins	1389
Developing Thymocytes Undergo Positive and Negative Selection	1389
Cytotoxic T Cells Induce Infected Target Cells to Undergo Apoptosis	1391
Effector Helper T Cells Help Activate Other Cells of the Innate and Adaptive Immune Systems	1392
Naïve Helper T Cells Can Differentiate into Different Types of Effector T Cells	1393
Both T and B Cells Require Multiple Extracellular Signals for Activation	1394
Many Cell-Surface Proteins Belong to the Ig Superfamily	1396
Vaccination Against Pathogens Has Been Immunology's Greatest Contribution to Human Health	1396
Summary	1400
Problems	1402
References	1404

Glossary G:1

Index I:1



INTRODUCTION TO THE CELL

Cells, Genomes, and the Diversity of Life

CHAPTER

1

The surface of our planet is populated by living things—*organisms*—curious, intricately organized chemical factories that take in matter from their surroundings and use these raw materials to generate copies of themselves. These organisms appear extraordinarily diverse. What could be more different than a tiger and a piece of seaweed or a butterfly and a tree? Yet our ancestors, knowing nothing of cells or DNA, saw that all these things had something in common. They called that something “life,” marveled at it, struggled to define it, and despaired of explaining what it was or how it worked in terms that relate to non-living matter.

The remarkable discoveries of the past 100 years or so have not diminished the marvel—quite the contrary. But they have removed the central mystery regarding the nature of life. We can now see that all living things are made of 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.

Because cells are the fundamental units of life, it is to *cell biology*—the study of the structure, function, and behavior of cells—that we must look for answers to the questions of what life is and how it works. With a deeper understanding of cells and their evolution, we can begin to tackle the grand historical problems of life on Earth: its mysterious origins, its stunning diversity, and its invasion of every conceivable habitat. Indeed, as emphasized long ago by the pioneering cell biologist E. B. Wilson, “the key to every biological problem must finally be sought in the cell; for every living organism is, or at some time has been, a cell.”

Despite their apparent diversity, living things are fundamentally similar inside. The whole of biology is thus a counterpoint between two themes: astonishing variety in individual particulars and astonishing constancy in fundamental mechanisms. In this chapter, we begin by outlining the universal features common to all life on our planet, along with some of the fundamental properties of their cells. We then discuss how an analysis of DNA *genomes* allows scientists to position the wide variety of organisms in an evolutionary “tree of life.” This

IN THIS CHAPTER

The Universal Features of Life on Earth

Genome Diversification and the Tree of Life

Eukaryotes and the Origin of the Eukaryotic Cell

Model Organisms

approach, which quantifies how closely organisms are related to one another, allows us to identify the three major branches of life on Earth, *eukaryotes*, *bacteria*, and *archaea*—each with unique qualities. We shall see that the familiar world of plants and animals—the focus of scientists for many centuries—makes up only a small slice of the complete diversity of life, the vast majority of which is invisible to the unaided human eye.

After exploring some of the ways that genomes change over evolutionary times, we highlight the handful of *model organisms* that biologists have chosen to focus on to dissect the molecular mechanisms underlying life. A few specific viruses, including SARS-CoV-2, pose grave threats to humans, so they too have become objects of intensive study. For this reason, this section also includes an introduction to viruses, the ubiquitous parasites that have evolved to feed on cells. Viruses are now recognized to be the most abundant biological entities on the planet.

THE UNIVERSAL FEATURES OF LIFE ON EARTH

There are more than 2 million described species living on Earth today, but many, many more are yet to be discovered. Each species is different, and each reproduces itself faithfully, yielding progeny that are unique to that species. Thus, the parent organism hands down information specifying, in extraordinary detail, the characteristics that the offspring will have. This phenomenon of *heredity* is central to the definition of life: it distinguishes life from other processes, such as the growth of a crystal, or the burning of a candle, or the formation of waves on water, in which structures are generated without the same type of link between the peculiarities of parents and offspring. A living organism must consume free energy to exist, as does a candle flame. But life employs this *free energy* to drive a very complex system of chemical reactions that create and maintain the intricate organization of its cells, all as specified by the hereditary information in those cells.

Most living organisms are single cells. Others, such as us, are like vast multicellular cities in which groups of cells perform specialized functions that are linked by intricate systems of intercellular communication. But even for the aggregate of more than 10^{13} cells that makes up a human body, the whole organism has been generated by cell divisions from a single cell. The single cell therefore contains all of the hereditary information that defines a species (**Figure 1-1**). The cell must also contain all of the machinery needed to gather raw materials from the environment and to construct from them a new cell in its own image, complete with a new copy of the hereditary information of its parent. Every cell on Earth is truly amazing.

All Cells Store Their Hereditary Information in the Form of Double-Strand DNA Molecules

Computers have made us familiar with the concept of information as a measurable quantity— 10^6 bytes to record a few hundred pages of text or an image from a digital camera, 10^9 bytes for a 60-minute video streamed from the Internet, and so on. Computers have also made us well aware that the same information can be recorded in many different physical forms: the discs and tapes that we used 25 years ago for our electronic archives have become unreadable on present-day machines. Living cells, like computers, store information, and it is estimated that they have been evolving and diversifying for more than 3.5 billion years. One might not expect that they would all store their information in the same form or that the hereditary information carried by one type of cell should be readable by the information-handling machinery of another. And yet it is so. This fact provides compelling evidence that all living things on Earth have inherited the form of their genetic instructions, as well as how to use them, from a *universal common ancestral cell*. This ancestor is thought to have existed roughly 3.5–3.8 billion years ago.

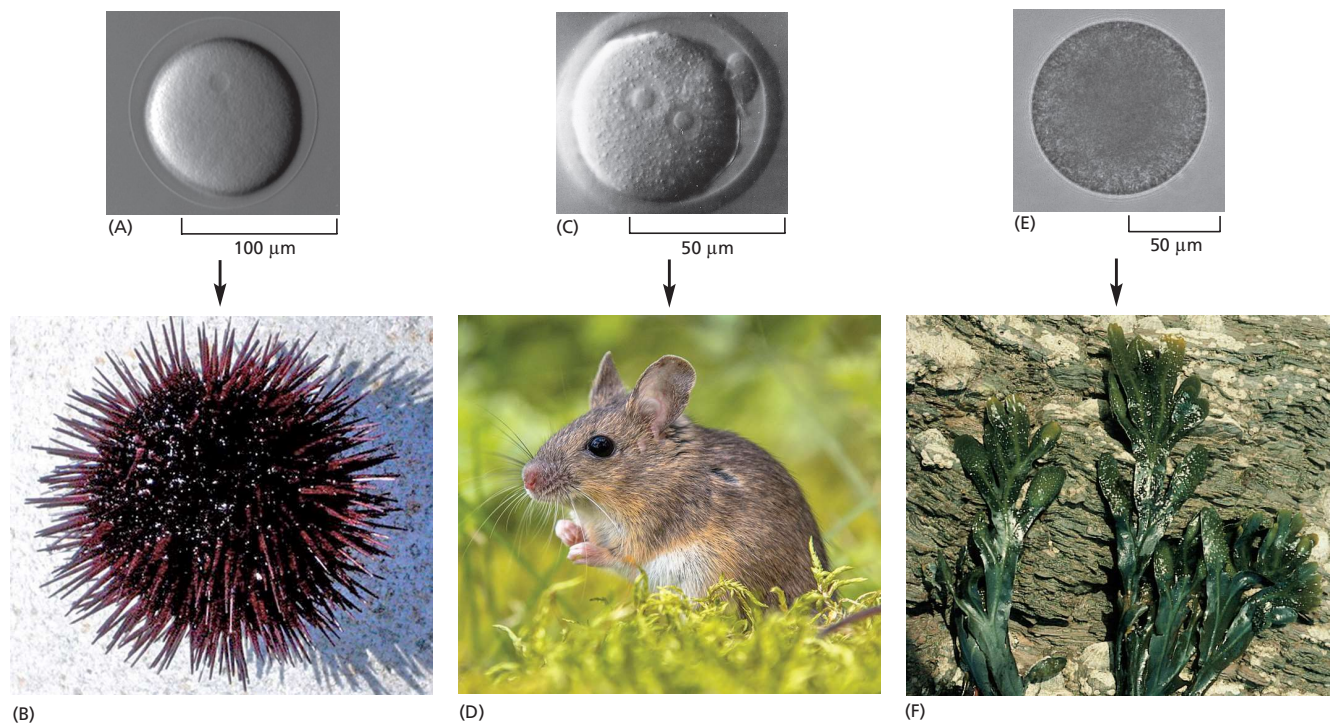


Figure 1–1 The hereditary information in the fertilized egg cell determines the nature of the whole multicellular organism that will develop from it. As indicated, although their starting cells look superficially similar, the egg of a sea urchin gives rise to a sea urchin (A and B), the egg of a mouse gives rise to a mouse (C and D), and the egg of the seaweed *Fucus* gives rise to a *Fucus* seaweed (E and F). (A, courtesy of David McClay; B, courtesy of Tim Hunt; C, courtesy of Patricia Calarco, from G. Martin, *Science* 209:768–776, 1980. With permission from AAAS; D, Rudmer Zwerver/Alamy Stock Photo; E and F, courtesy of Colin Brownlee.)

All cells on Earth today store their hereditary information in the form of double-strand molecules of DNA—long, unbranched, paired *polymer* chains, which are always composed of the same four types of *monomers*. These monomers, chemical compounds known as *nucleotides*, have nicknames drawn from a four-letter alphabet—A, T, C, G—and they are strung together in a long linear sequence that encodes the hereditary information, just as the sequence of 1's and 0's encodes the information in a computer file. We can take a piece of DNA from a human cell and insert it into a bacterium or a piece of bacterial DNA and insert it into a human cell, and, with only a few minor modifications, the information will be successfully read, interpreted, and copied. As we describe in Chapter 8, scientists can now rapidly read out the sequence of nucleotides in any DNA molecule and thereby determine the complete DNA sequence of any cell's **genome**—the totality of its hereditary information embodied in the linear sequence of nucleotides in its DNA. As a result, we now know the complete genome sequences for tens of thousands of species, ranging from the smallest bacterium to the largest plants and animals on Earth.

All Cells Replicate Their Hereditary Information by Templated Polymerization

The mechanisms that make life possible depend on the structure of the double-strand DNA molecule. We discuss this remarkable molecule in detail in Chapters 4 and 5; here we provide only an overview of its structure and means of reproduction. Each monomer in a single DNA strand—that is, each **nucleotide**—consists of two parts: a sugar (deoxyribose) with a phosphate group attached to it, and a *base*, which may be either adenine (A), guanine (G),

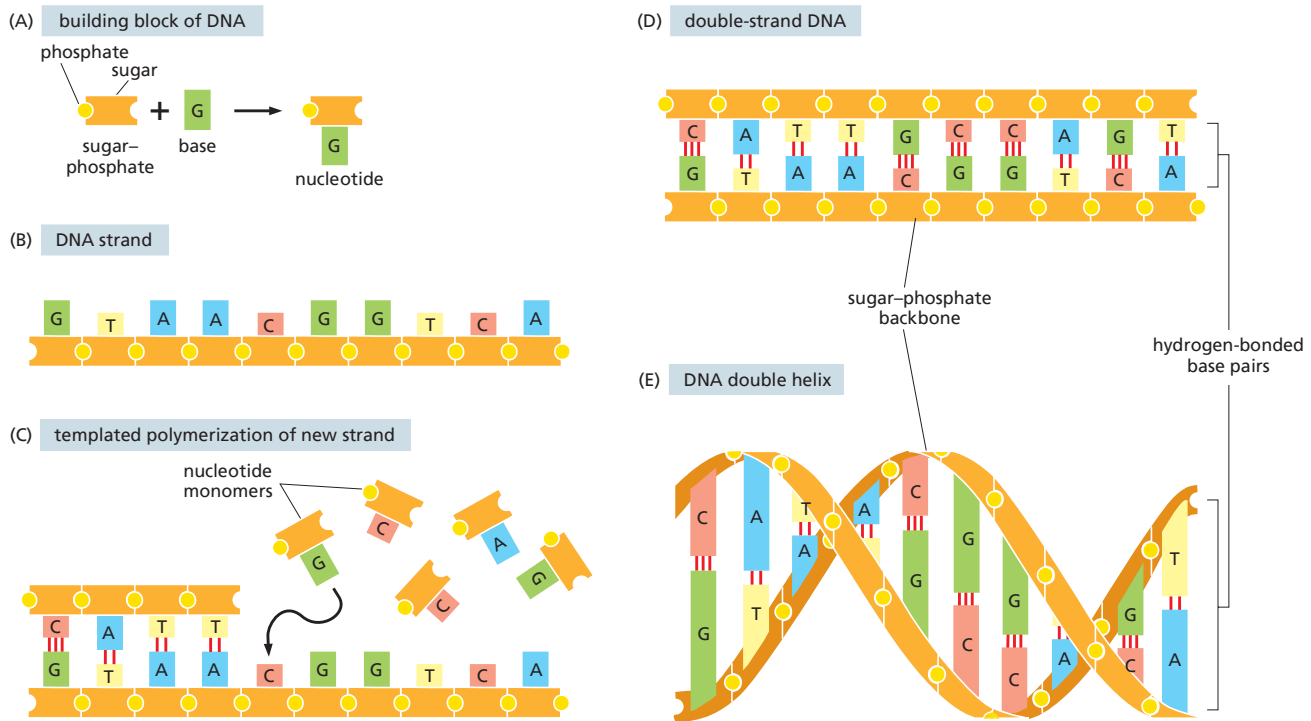


Figure 1-2 DNA and its building blocks. (A) DNA is made from simple subunits, called nucleotides. Each nucleotide consists of a specific arrangement of about 35 covalently linked atoms, forming a sugar-phosphate molecule with a nitrogen-containing side group, or base, attached to it. The bases are of four types (adenine, guanine, cytosine, and thymine), corresponding to four distinct nucleotides, labeled A, G, C, and T. (B) A single strand of DNA consists of nucleotides joined together by sugar-phosphate linkages. Note that the individual sugar-phosphate units are asymmetric, giving the backbone of the strand a definite directionality, or polarity. This directionality guides the molecular processes by which the information in DNA is both interpreted and copied (*replicated*) in cells: the information is always “read” in a consistent order, just as written English text is read from left to right. (C) Through templated polymerization, the sequence of nucleotides in an existing DNA strand controls the sequence in which nucleotides are joined together in a new DNA strand; T in one strand pairs with A in the other, and G in one strand with C in the other. The new strand therefore has a nucleotide sequence *complementary* to that of the old strand and a backbone with opposite directionality: thus, GTAA... in the original strand, is ...TTAC in the new strand. (D) A normal DNA molecule consists of two such complementary strands. The nucleotides within each strand are linked by strong (covalent) chemical bonds; the complementary nucleotides on opposite strands are held together more weakly, by hydrogen bonds. (E) The two strands twist around each other to form a double helix—a robust structure that can accommodate any sequence of nucleotides without altering its basic double-helical structure (see Movie 4.1).

cytosine (C), or thymine (T) (Figure 1-2). Each sugar is linked to the next via the phosphate group, creating a polymer chain composed of a repetitive sugar-phosphate backbone with a series of bases protruding from it. The DNA polymer is extended by adding monomers at one end. For a single isolated strand, these monomers can, in principle, be added in any order, because each one links to the next in the same way, through the part of the molecule that is the same for all of them. In the living cell, however, DNA is not synthesized as a free strand in isolation, but on a template formed by a preexisting DNA strand. The bases that protrude from this template can bind to bases of the strand being synthesized, according to a strict rule defined by the complementary structures of the bases: A binds to T, and C binds to G. This *base-pairing* holds fresh monomers in place and thereby controls the selection of which one of the four monomers will next be added to a growing strand. In this way, a double-strand structure is created, consisting of two exactly complementary sequences of A's, C's, T's, and G's. These two strands twist around each other, forming a DNA double helix (see Figure 1-2E).

Compared with the covalent sugar-phosphate bonds, the hydrogen bonds between the base pairs are weak, which allows the two DNA strands to be

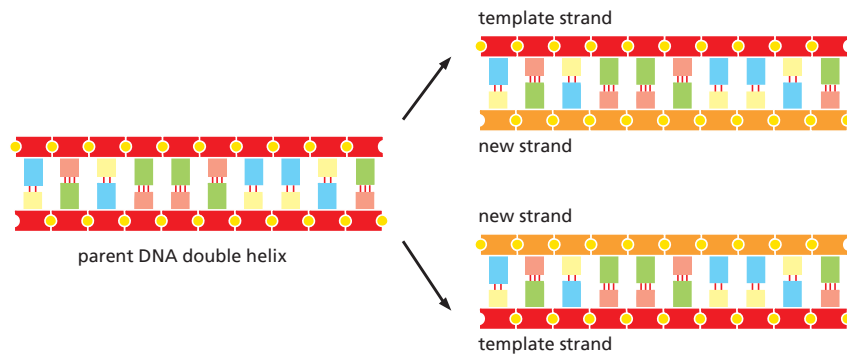


Figure 1–3 The copying of genetic information by DNA replication. In this process, the two strands of a DNA double helix are pulled apart, and each serves as a template for the synthesis of a new complementary strand. The end result is two daughter DNA double helices that are identical in sequence to the parent double helix.

pulled apart without breakage of their backbones. Each strand then can serve as a template, in the way just described, for the synthesis of a fresh DNA strand complementary to itself—a fresh copy, that is, of the hereditary information (**Figure 1–3**). In different types of cells, this process of **DNA replication** occurs at different rates, with different controls to start it or stop it, and with different auxiliary molecules to help the process along (discussed in Chapters 5 and 17). But the basics are universal: DNA is the information store for heredity, and *templated polymerization* is the way in which this information is copied throughout the living world.

All Cells Transcribe Portions of Their DNA into RNA Molecules

To carry out its information-bearing function, DNA must do more than copy itself. It must also *express* its information, by letting the information guide the synthesis of other molecules in the cell. This expression occurs by a mechanism that is the same in all living organisms, leading first and foremost to the production of two other crucial classes of biological polymers: RNA molecules and protein molecules. The process begins with a templated polymerization called **transcription**, in which segments of the DNA sequence are used as templates for the synthesis of shorter molecules of the closely related polymer **ribonucleic acid, or RNA**. Subsequently, in a process called **translation**, many of these RNA molecules direct the synthesis of polymers of a radically different chemical class—the *proteins* (**Figure 1–4**). The detailed chemical reactions involved are presented in Chapter 6; here they will only be briefly outlined.

The backbone of an RNA molecule is formed by a slightly different sugar from that in DNA—ribose instead of deoxyribose; in addition, one of the four bases is slightly different—uracil (U) replaces thymine (T). Most important, however, the other three bases—A, C, and G—are identical to those in DNA, and all four bases will pair with their complementary counterparts in DNA—the A, U, C, and G of RNA with the T, A, G, and C of DNA, respectively. During transcription, this pairing allows the RNA monomers to be lined up and selected for polymerization on a template strand of DNA, just as DNA monomers are selected during replication. The outcome is a single-strand polymer molecule whose sequence of nucleotides faithfully represents a portion of the cell's genetic information, even though it is written in a slightly different alphabet—consisting of the four RNA monomers instead of the four DNA monomers.

The same segment of DNA can be used repeatedly to guide the synthesis of many identical RNA molecules. Thus, whereas the cell's archive of genetic information in the form of DNA is fixed and sacrosanct, *RNA transcripts* are mass-produced and disposable. Most of these transcripts function as intermediates in the transfer of genetic information by serving as *messenger RNA (mRNA)* molecules that guide the synthesis of proteins according to the genetic instructions stored in the DNA. But as we discuss in Chapter 6, some RNA transcripts do not serve as information carriers; instead, they function directly in the cell to carry out a variety of other functions.

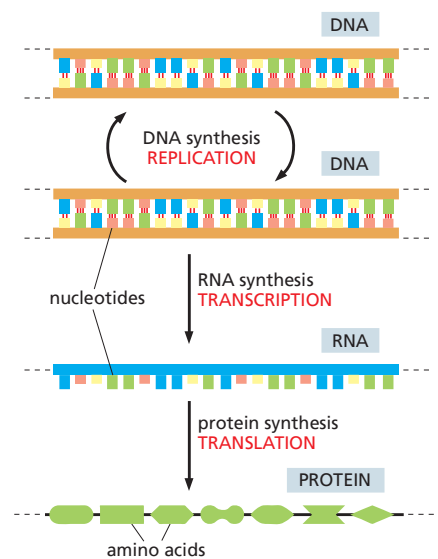


Figure 1–4 From DNA to protein. In addition to DNA replication (shown at the top of the figure), genetic information is read out and put to use through a two-step process: First, in *transcription*, segments of the DNA sequence are used to guide the synthesis of molecules of RNA. Then, in *translation*, RNA molecules are used to guide the synthesis of proteins, which are polymers made of amino acid subunits (discussed shortly).

All Cells Use Proteins as Catalysts

Like DNA and RNA molecules, **protein** molecules are long unbranched polymer chains, formed by stringing together monomeric building blocks (subunits) drawn from a standard repertoire that is the same for all living cells. Like DNA and RNA, proteins carry information in the form of a linear sequence of subunits in the same way as a human message written in an alphabetic script. There are many different protein molecules in each cell, and—if we ignore water molecules—they form the major portion of the cell's mass.

The subunits of proteins are the **amino acids**, which are quite different from the nucleotides of DNA and RNA, and there are 20 types instead of 4. Each amino acid is built around a core structure that allows it to be covalently linked in a standard way to any other amino acid in the set; attached to this core is a side group of atoms that gives each amino acid a distinctive chemical character. Each protein molecule is a *polypeptide* chain that is created by joining its amino acids in a particular sequence; this sequence determines how the polypeptide folds up, giving the protein its unique three-dimensional structure. Through several billion years of evolution, these sequences have been selected to give each protein a useful function.

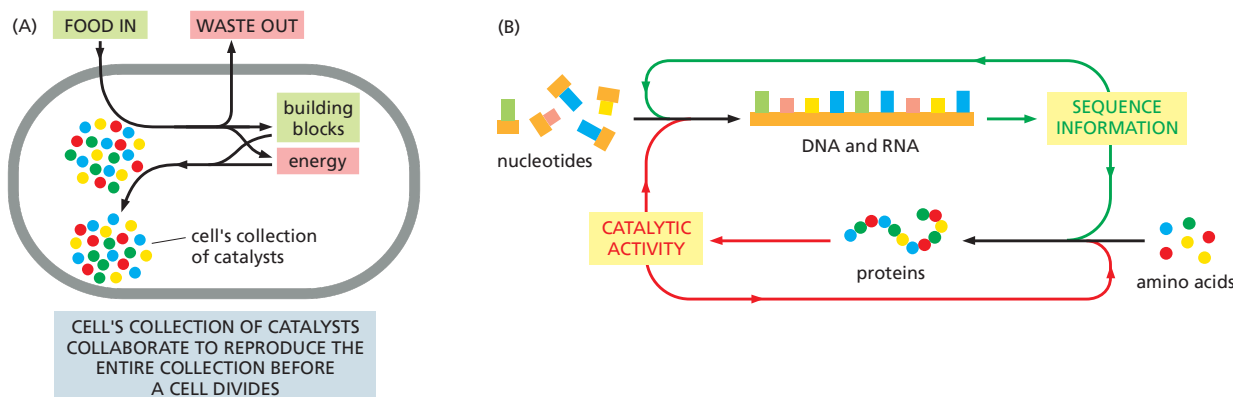
By folding into a precise structure that binds with high specificity to other molecules, each protein performs a specific function according to its genetically specified sequence of amino acids. Proteins form and maintain diverse cell and extracellular structures, generate movements, sense signals, and so on. Many have reactive sites on their surface, allowing them to act as *enzymes* that catalyze reactions that make or break specific covalent bonds. Proteins, above all, are the main molecules that put the cell's genetic information into action. Thus, polynucleotides (DNA and mRNAs) specify the amino acid sequences of proteins. Proteins, in turn, serve as *catalysts* to cause many different chemical reactions to occur, including those that synthesize new DNA and RNA molecules.

In everyday speech, a catalyst refers to “any agent that provokes or speeds significant change or action.” But in chemistry, the term **catalyst** is defined more narrowly, being applied to any molecule that speeds up a specific chemical reaction without itself being changed. From the most fundamental point of view, a living cell is a self-replicating collection of catalysts that takes in food, processes this food to provide both the building blocks and energy needed to make more catalysts, and discards the materials left over as waste (Figure 1-5A). Together, these feedback loops that connect proteins and polynucleotides form the basis for this autocatalytic, self-reproducing behavior of all living organisms (Figure 1-5B).

All Cells Translate RNA into Protein in the Same Way

How the information in DNA specifies the production of proteins was a complete mystery in the 1950s when the double-strand structure of DNA was first revealed as the basis of heredity. But in subsequent years, scientists discovered the elegant

Figure 1-5 Life as an autocatalytic process. (A) The living cell is a self-replicating collection of catalysts. (B) Life can be viewed as an autocatalytic process. DNA and RNA molecules provide the nucleotide sequence information (*green arrows*) that is used both to produce proteins and to copy themselves. Proteins, in turn, provide the catalytic activity (*red arrows*) needed to synthesize DNA, RNA, and proteins themselves. Together, these feedback loops create the self-replicating system that endows cells with the ability to reproduce. Although the great majority of the catalysts in the cell are proteins (known as enzymes), a few RNA molecules (known as ribozymes) also have this property, as we will see in Chapter 6.



mechanisms involved. The translation of genetic information from the 4-letter alphabet of polynucleotides into the 20-letter alphabet of proteins is a complex process. The rules of this translation seem in some respects neat and rational but in other respects strangely arbitrary, given that they are (with minor exceptions) identical in all living things. These arbitrary features, it is thought, reflect frozen accidents in the early history of life. They stem from the chance properties of the earliest organisms that were passed on by heredity and have become so deeply embedded in the constitution of all living cells that they cannot be changed without disastrous consequences.

It turns out that the information in the sequence of a messenger RNA (mRNA) molecule is read out in groups of three nucleotides at a time: each triplet of nucleotides, or *codon*, specifies (codes for, or encodes) a single amino acid in a corresponding protein. Because the number of distinct triplets that can be formed from four nucleotides is 4^3 , there are 64 possible codons, all of which occur in nature. However, there are only 20 naturally occurring amino acids, which means there are necessarily many cases in which several codons correspond to the same amino acid. This *genetic code* is read out by a special class of small RNA molecules, called *transfer RNAs* (tRNAs). Each type of tRNA becomes attached at one end to a specific amino acid and displays at its other end a specific sequence of three nucleotides—an *anticodon*—that enables it to recognize, through base-pairing, a particular codon or subset of codons in mRNA. The intricate chemistry that enables these tRNAs to translate a specific sequence of A, C, G, and U nucleotides in an mRNA molecule into a specific sequence of amino acids in a protein molecule occurs on a *ribosome*, a large multimolecular machine composed of both protein and *ribosomal RNA*. All of these processes will be described in detail in Chapter 6.

Each Protein Is Encoded by a Specific Gene

DNA molecules as a rule are very large, containing the specifications for thousands of proteins and RNA molecules. Special sequences in the DNA serve as punctuation, defining where the information for each RNA and protein begins and ends. And individual segments of the long DNA sequence are transcribed into separate mRNA molecules, coding for different proteins. Each such DNA segment represents one gene. As previously mentioned, some DNA segments—a smaller number—are transcribed into RNA molecules that are not translated into protein but have other functions in the cell; such DNA segments also count as genes. A **gene** therefore is defined as the segment of DNA sequence corresponding either to a single protein (but sometimes to a set of closely related, alternative protein variants) or to a single catalytic, regulatory, or structural RNA molecule.

In all cells, the *expression* of individual genes is regulated: instead of manufacturing its full repertoire of possible proteins and RNAs at full tilt all the time, the cell adjusts the rate of transcription and translation of different genes independently, according to need. As we shall see in Chapter 7, stretches of *regulatory DNA* are interspersed among the segments that code for protein, and these noncoding regions bind to special protein molecules that control the rate of transcription of individual genes. The organization of this regulatory DNA varies widely from one class of organisms to another, but the basic strategy is universal. In this way, the genome of the cell dictates not only the nature of the cell's proteins but also when and where they are to be made.

Life Requires a Continual Input of Free Energy

A living cell is a dynamic chemical system, operating far from chemical equilibrium. For a cell to grow or to make a new cell in its own image, it must take in *free energy* from the environment, as well as raw materials, to drive the necessary synthetic reactions. This consumption of free energy is fundamental to life. When this energy is not available, a cell decays toward chemical equilibrium and soon dies.

As one example, free energy is required for the propagation of genetic information. Picture the molecules in a cell as a swarm of objects endowed with thermal energy, moving around violently at random, buffeted by collisions with one another. To copy genetic information—in the form of a DNA sequence, for example—nucleotide molecules from this wild crowd must be captured, arranged in a specific order defined by a preexisting template, and linked together in a fixed relationship. The bonds that hold the nucleotides in their proper places on the template and join them together must be strong enough to resist the disordering effect of thermal motion, which we describe shortly. The joining process is driven forward by a consumption of free energy, which is needed to ensure that the correct bonds are made, and made robustly. As an analogy, the molecules might be compared with spring-loaded traps, ready to snap into a more stable, lower-energy attached state when they meet their proper partners. As they snap together into the bonded arrangement, their available stored energy—their free energy—like the energy of the spring in the trap, is released and dissipated as heat. In a cell, the chemical processes underlying information transfer are more complex, but the same basic principle applies: free energy must be spent for the creation of order.

To replicate its genetic information faithfully, and indeed to make all its complex molecules according to the correct specifications, the cell therefore requires free energy, which has to be imported somehow from the surroundings. As we will discuss in detail in Chapter 2, the free energy required by animal cells is derived from chemical bonds in food molecules that the animals eat, whereas plants get their free energy from sunlight.

All Cells Function as Biochemical Factories

Because all cells make DNA, RNA, and protein, they all have to contain and manipulate a similar collection of small organic (carbon-containing) molecules, including simple sugars, nucleotides, and amino acids, as well as other substances that are universally required. All cells, for example, require the phosphorylated nucleotide *ATP* (*adenosine triphosphate*), not only as a building block for the synthesis of DNA and RNA but also as a carrier of the free energy that is needed to drive a huge number of chemical reactions in the cell.

Although all cells function as biochemical factories of a broadly similar type, many of the details of their small-molecule transactions differ. Plants, for example, require only the simplest of nutrients because they harness the energy of sunlight to make all their own small organic molecules. Other organisms, such as animals and some bacteria, feed on living (or once living) organisms and must obtain many of their organic molecules ready-made. We return to this point later in the chapter.

All Cells Are Enclosed in a Plasma Membrane Across Which Nutrients and Waste Materials Must Pass

Each living cell is enclosed by a membrane—the **plasma membrane**. This membrane acts as a selective barrier that enables the cell to concentrate nutrients gathered from its environment and retain the products it synthesizes for its own use, while excreting its waste products. Without a plasma membrane, the cell could not maintain its integrity as a coordinated chemical system.

The molecules that form cell membranes have the simple physicochemical property of being *amphiphilic*; that is, they consist of one part that is hydrophilic (water-soluble) and another part that is hydrophobic (water-insoluble). Such molecules placed in water aggregate spontaneously, arranging their hydrophobic portions to be as much in contact with one another as possible to hide them from the water, while keeping their hydrophilic portions exposed. Amphiphilic molecules of appropriate shape, such as the *phospholipid* molecules that compose most of the molecules of the plasma membrane, spontaneously aggregate in water to create a *bilayer* that forms small closed vesicles (Figure 1-6).

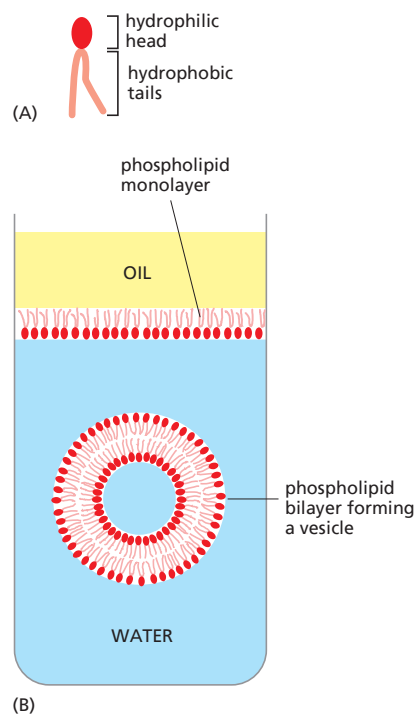


Figure 1-6 Behavior of phospholipid molecules in water. (A) A phospholipid molecule is amphiphilic, having a hydrophilic (water-loving) phosphate head group and a hydrophobic (water-avoiding) hydrocarbon tail. (B) At an interface between oil and water, phospholipids arrange themselves as a single sheet (a monolayer), with their head groups facing the water and their tail groups facing the oil. When immersed in water, however, phospholipids aggregate to form lipid bilayers that fold in on themselves to form sealed aqueous compartments known as vesicles.

Although the chemical details vary, the hydrophobic tails of the predominant lipid molecules in all cells are hydrocarbon polymers ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-$), and their spontaneous assembly into a lipid bilayer is but one of many examples of an important general principle: cells produce molecules whose chemical properties cause them to *self-assemble* into the structures that a cell needs.

The cell boundary cannot be totally impermeable. If a cell is to grow and reproduce, it must be able to import raw materials and export waste across its plasma membrane. All cells therefore have specialized proteins embedded in their plasma membrane that transport specific molecules from one side to the other. Some of these *membrane transport proteins*, like some of the proteins that catalyze the fundamental small-molecule reactions inside the cell, have been so well conserved over the course of evolution that we can recognize the family resemblances between them when even the most distantly related organisms are compared.

The transport proteins in the plasma membrane largely determine which molecules enter the cell, while the catalytic proteins (enzymes) inside the cell determine the reactions that the entering molecules undergo. Thus, by specifying the RNAs and proteins that the cell produces, the genetic information recorded in the DNA sequence dictates the entire chemistry of the cell—in fact, not only its chemistry but also its form and its behavior, for these too are chiefly determined and controlled by the cell's proteins.

Cells Operate at a Microscopic Scale Dominated by Random Thermal Motion

Thus far we have described the cell as a self-replicating, membrane-bound bag of chemicals and macromolecules; but, as the unit of life, the cell is much more than the sum of its parts. Although not obvious from microscopy images, even the simplest cell is highly ordered internally: its individual components must self-assemble and become highly organized for the cell to function. And the cell contents are in perpetual motion. The most obvious movements are catalyzed by *motor proteins*, enzymes that use the energy of ATP hydrolysis for a wide variety of purposes; these include pumping ions across the plasma membrane, translocating large assemblies from one intracellular site to another, and propelling the cell through its environment. In addition, and as previously mentioned, random thermal motions of molecules (including water) are prominent at the scale of cells—whose dimensions can be as small as a micrometer (10^{-6} meters) in diameter. This type of spontaneous movement, called *thermal* or **Brownian motion**, was first observed by Robert Brown in 1827, while looking through a microscope at pollen grains immersed in water. Caused by random molecular collisions, the constant fluctuating movement has important repercussions. Brownian motion drives a process called *diffusion*, and it determines the rates of biochemical reactions as molecules collide with one another within the interior of a cell (described in Chapter 2; see Movie 2.4).

Even though random, the cell can harness Brownian motion for its own advantage. For example, during one step in the crawling migration of animal cells, the plasma membrane at the leading edge extends forward (see Chapter 16). This movement does not involve motor proteins. Instead, a cytoskeletal filament (an actin polymer) polymerizes adjacent to the inner membrane surface. When the membrane fluctuates in the forward direction, actin quickly fills in the gap so that the membrane cannot slip back to its original position. This phenomenon, in which random thermal motions are harnessed in a directed way, creates a *Brownian ratchet* (Figure 1-7).

Because an object at the micrometer scale is constantly buffeted by water molecules, its movement requires overcoming high viscous drag forces. As a result, the directed movement of a complex of molecules inside the cell (by a motor protein, for example) will stop immediately when the motor disengages, leaving the complex to be randomly buffeted by thermal motion. There is no “gliding” inside the cell.

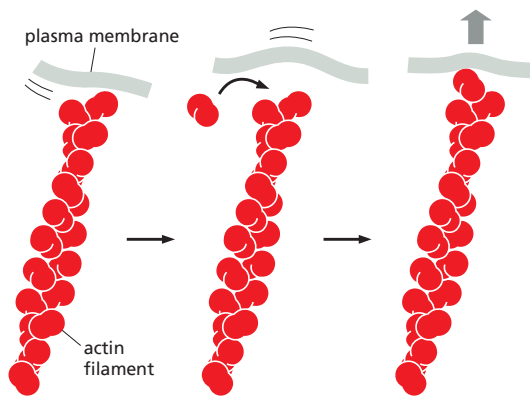


Figure 1–7 How membrane protrusion is driven by a simple Brownian ratchet. A single actin filament is shown abutting the plasma membrane, which is fluctuating back and forth because of random thermal motions. When the membrane happens to move away from the end of the filament, it creates sufficient space for an additional subunit, which quickly adds on. The slightly longer filament acts as a ratchet and prevents the membrane from moving back to its original position. In a migrating animal cell, this Brownian ratchet process drives protrusion of the membrane and contributes to forward movement of the cell, as described in Chapter 16 (see pp. 956–957).

A Living Cell Can Exist with 500 Genes

We have seen how genomes carry the information for all the proteins and RNA molecules of a cell, and how, through catalysis, all the other building blocks of the cell are made. But how complex are real living cells? In particular, what are the minimum requirements of a living cell? One measure of complexity is based on the total number of genes in an organism's genome. A species that has one of the smallest known genomes is the bacterium *Mycoplasma genitalium*, which causes a common, sexually transmitted, human disease (Figure 1–8). This organism lives as a parasite in mammals, where the environment provides it with many of the small molecules it needs ready-made. Nevertheless, it still has to make all the large molecules—DNA, RNAs, and proteins. It has 525 genes, most of which are essential. Its genome of 580,070 nucleotide pairs represents 145,018 bytes of information—about as much as it takes to record the text of one chapter of this book. Cell biology may be complicated, but it is not unimaginably so.

Summary

The individual cell is the minimal self-reproducing unit of life. A cell consists of a self-replicating collection of catalysts, enclosed in a plasma membrane. All cells operate as biochemical factories, driven by the free energy released in a complicated network of chemical reactions. Central to a cell's ability to reproduce is the transmission of its genetic information to its progeny cells when it divides. All cells store their genetic information in double-strand DNA, and the complete sequence of DNA nucleotides for each organism is known as its genome. The cell replicates this information by separating the paired DNA strands and using each as a template for polymerization to make a new DNA strand with a complementary sequence of nucleotide subunits. The same strategy of templated polymerization is used in the transcription of portions of the DNA into molecules of the closely related polynucleotide polymer, RNA. Most of these RNA molecules are mRNAs that in turn guide the synthesis of protein molecules by the process of translation. Proteins are polymers of amino acid subunits and are the catalysts for almost all the cell's chemical reactions. They are also responsible for the selective import and export of molecules across the plasma membrane that surrounds each cell. The specific shape and function of each protein depend on its amino acid sequence, which is specified by the nucleotide sequence of a corresponding segment of the DNA—the gene that codes for that protein. In this way, the DNA of the cell determines the cell's chemistry, which is fundamentally similar in all cells, reflecting their ultimate origin from a common ancestor cell that existed on Earth more than 3.5 billion years ago.

GENOME DIVERSIFICATION AND THE TREE OF LIFE

The success of living organisms based on DNA, RNA, and protein has been spectacular. Through its billions of years of proliferation, life has populated the oceans, covered the land, penetrated deep into Earth's crust, and molded the surface of

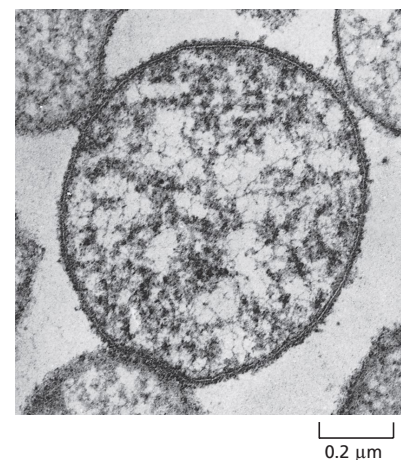


Figure 1–8 The small bacterium *Mycoplasma genitalium*. It is viewed here in cross section in an *electron microscope*, which uses a beam of electrons instead of light to create an image with a resolution that is many times higher than that of an image viewed in a conventional light microscope. Of the 525 genes this bacterium contains, 43 code for transfer RNAs, ribosomal RNAs, and other nonprotein-coding RNAs. Of the 482 protein-coding genes, 154 are involved in replication, transcription, translation, and related processes involving DNA, RNA, and protein; 98 are involved in the membrane and surface structures of the cell; 46 are involved in the transport of nutrients and other molecules across the plasma membrane; and 71 are involved in energy conversion and the synthesis and degradation of small molecules. (Courtesy of Roger Cole, in *Medical Microbiology*, 4th ed. [S. Baron, ed.]. Galveston: University of Texas Medical Branch, 1996.)

our planet. Our oxygen-rich atmosphere, the deposits of coal and oil, the layers of iron ores, the cliffs of chalk and limestone and marble—all these are products, directly or indirectly, of past biological activity on Earth.

Living things are not confined to the familiar temperate realm of land, water, and sunlight inhabited by plants and animals. They are found in the darkest depths of the ocean, in hot volcanic mud, in pools beneath the frozen surface of the Antarctic, and buried kilometers deep in Earth's crust. The creatures that live in these extreme environments are generally unfamiliar, not only because they are inaccessible, but also because they are mostly microscopic and cannot be maintained in a laboratory. Even in more familiar habitats, most organisms are too small for us to see without special equipment: they tend to go unnoticed, unless they cause a disease or rot the timbers of our houses. Yet such *microorganisms* (microbes) are by far the most numerous living organisms on our planet. Only recently, through new methods of molecular analysis including rapid *DNA sequencing*, have we begun to get a picture of life on Earth that is not grossly distorted by our biased perspective as large animals living on dry land.

In this section, we consider—in very broad terms—the diversity of organisms on our planet and the relationships among them. Because the genetic information for every organism is written in the universal language of DNA sequences, and because the DNA sequence of any organism's genome can be readily determined, it is now possible to characterize, catalog, and compare any set of living organisms with reference to these sequences. From such comparisons we can specify the place of each organism in the family tree of living species—the “tree of life.”

The Tree of Life Has Three Major Domains: Eukaryotes, Bacteria, and Archaea

The classification of living things has traditionally depended on comparisons of their outward appearances: we can see that a fish has eyes, jaws, backbone, brain, and so on, just as humans do, and that a worm does not—just as we can see that a rosebush is more similar to an apple tree than to grass. As Darwin showed, we can readily interpret such close family resemblances in terms of an evolution from common ancestors, and we can find the remains of many of these ancestors preserved in the fossil record. In this way, it became possible to draw a family tree of living organisms, showing the various lines of descent, as well as branch points in evolutionary history, where the ancestors of one group of species became different from those of another.

When the disparities between organisms become very great, however, these methods begin to fail. How do we decide whether a fungus is more closely related to a plant or to an animal? When it comes to microscopic organisms such as bacteria, the task becomes harder still: one tiny rod or sphere can look much like another. Moreover, much of our knowledge of the microbial world was traditionally restricted to those species that can be isolated and cultured in the laboratory. But direct DNA sequencing of populations of microbes in their natural habitats—such as soil, ocean water, or even the human mouth—has taught us that the vast majority of microbes cannot be easily cultured in the laboratory. Often, they thrive in the wild as components of complex ecosystems and—when separated from their natural surroundings—cannot survive. Until modern DNA sequencing was developed, these organisms were largely unknown to us, especially those that inhabit extreme environments such as the deep Earth's crust or seawater miles below the ocean surface.

Genome analysis has now provided us with a simple, direct, and powerful way to determine evolutionary relationships. The complete DNA sequence of an organism defines its nature with almost perfect precision and in exhaustive detail. Moreover, this specification is in a digital form—a string of letters—that can be entered into a computer and compared with the corresponding information for any other organism. Because DNA is subject to random changes that accumulate over long periods of time (as we will see shortly), the number of differences

between the DNA sequences of two organisms can provide a direct, objective, and quantitative indication of the evolutionary distance between them.

For constructing a comprehensive tree of life, it is necessary to begin with a segment of DNA that is easily recognized in the genomes of all organisms. We discussed earlier how all cells use the same fundamental mechanism to translate a nucleotide sequence into a protein sequence, and we saw that the ribosome is the “decoding machine” that carries this out. Ribosomes are fundamentally similar in all organisms, and an especially well-conserved component of them is the RNA molecules that make up their core. Although the exact sequence of these *ribosomal RNAs (rRNAs)* differs across organisms, they are similar enough to use them as a ruler to judge how closely two species are related: the more similar the ribosomal RNA sequences, the more recently the two species diverged from a common ancestor and the more related they must be. Once a rough approximation of the tree of life has been obtained in this way, many additional DNA sequences in genomes—those that might not be identifiable in all organisms—can accurately determine relationships among more closely related species.

This approach has revealed that the living world consists of three major divisions, or *domains*: eukaryotes, bacteria, and archaea, as illustrated in [Figure 1–9](#); in the following paragraphs, we briefly introduce each in turn.

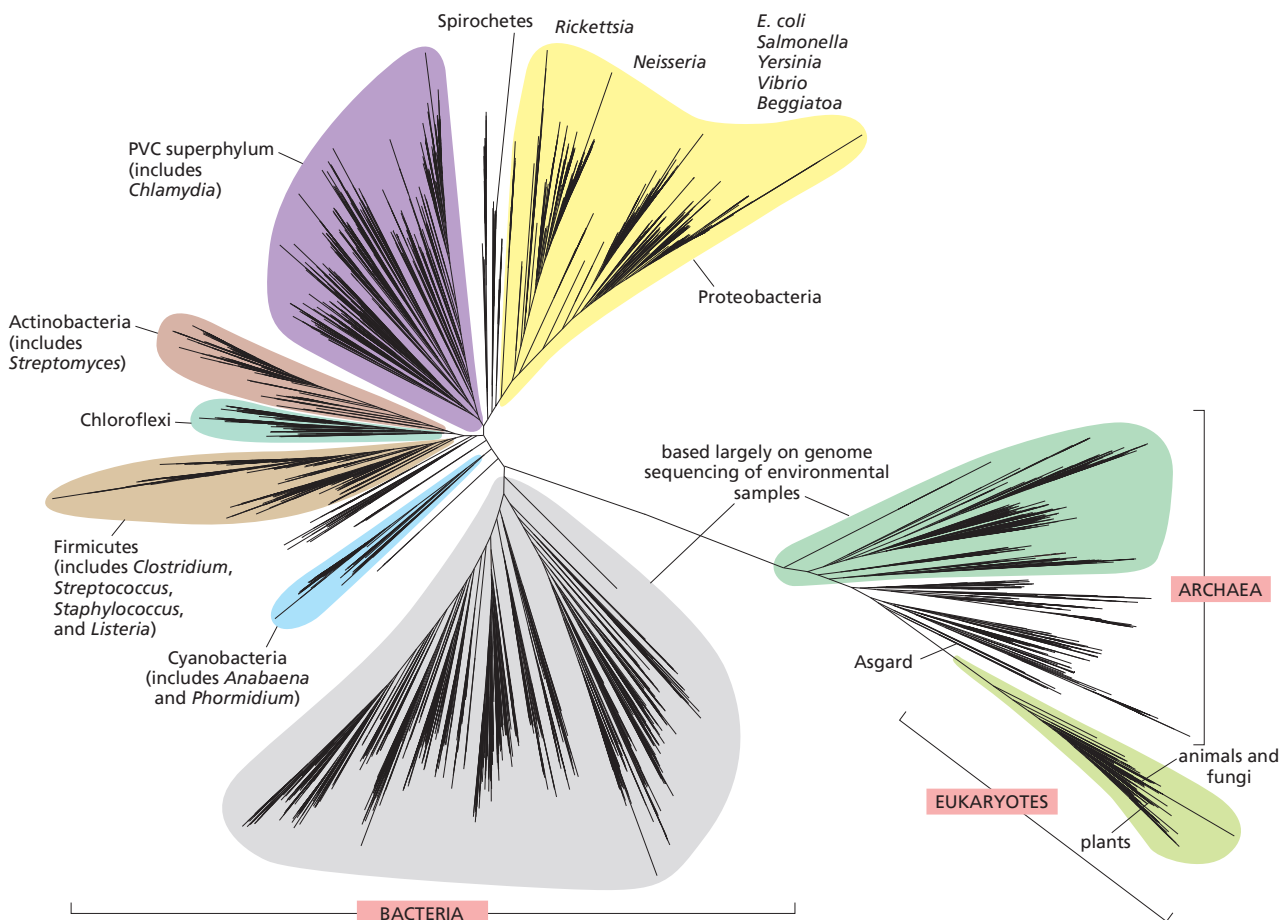


Figure 1–9 A global tree of life, based on genome comparisons, shows the three major divisions (domains) of the living world. The lengths of the branches are proportional to differences among genomes using common genes that can be recognized and compared across many different species. Some of the organisms discussed in this and later chapters are indicated. Of the three domains of life (bacteria, archaea, and eukaryotes), bacteria encompass by far the greatest diversity, commensurate with their ability to colonize nearly every ecological niche on the planet. So many new bacterial species are currently being identified through DNA sequencing of environmental samples that simply naming them has become a challenge. Although eukaryotes (and especially animals) are the main focus of this book, they comprise only a small slice of the global diversity. An expanded eukaryotic tree is shown in Figure 1–35, and an expanded tree of mammals is given in Figure 4–67. (Adapted from C.J. Castelle and J.F. Banfield, *Cell* 172:1181–1197, 2018.)

Eukaryotes Make Up the Domain of Life That Is Most Familiar to Us

The great variety of living creatures that we see around us are eukaryotes. The name is from the Greek, meaning “truly nucleated” (from the words *eu*, “well” or “truly,” and *karyon*, “kernel” or “nucleus”), reflecting the fact that the cells of these organisms have their DNA enclosed in a membrane-bound organelle called the *nucleus*. Visible by simple light microscopy, this feature was used in the early twentieth century to classify living organisms as either **eukaryotes** (those with a nucleus) or **prokaryotes** (those without a nucleus). We now know that prokaryotes comprise two of the three major domains of life, the bacteria and archaea. Eukaryotic cells are typically much larger than those of bacteria and archaea; in addition to a nucleus, they typically contain a variety of membrane-bound organelles that are also lacking in the prokaryotes. The genomes of eukaryotes also tend to run much larger—containing more than 20,000 genes for humans and corals, for example, compared with 4000–6000 genes for the typical bacteria or archaea.

In addition to plants and animals, the eukaryotes include fungi (such as mushrooms or the yeasts used in beer- and bread-making), as well as an astonishing variety of single-celled, microscopic forms of life. Most of this book is focused on the cell biology of eukaryotic organisms (especially animals); in the final sections of this chapter, we shall return to eukaryotes and focus on the variety within this group.

On the Basis of Genome Analysis, Bacteria Are the Most Diverse Group of Organisms on the Planet

When modern trees of life were constructed using genome information, one of the big surprises was how much more evolutionarily diverse the bacterial world is compared with the eukaryotes; we now know that this great diversity reflects the much earlier appearance of bacteria in the evolutionary history of the planet. Bacteria are usually very small (and invisible to the unaided eye), and they generally live as independent individuals or in loosely organized communities, rather than as multicellular organisms. They are typically spherical or rod-shaped and measure a few micrometers (μm) in linear dimension (**Figure 1–10**). They often have a tough protective coat, called a cell wall, beneath which a plasma membrane encloses a single cytoplasmic compartment—the *cytoplasm*—containing DNA, RNA, proteins, and the many small molecules needed for life (**Figure 1–11**). Although difficult to discern in the light microscope, the interior of a bacterium is nevertheless highly organized, a topic we discuss in Chapter 16.

Commensurate with the diversity of their genomes, bacteria live in an enormous variety of ecological niches, and they are astonishingly varied in their

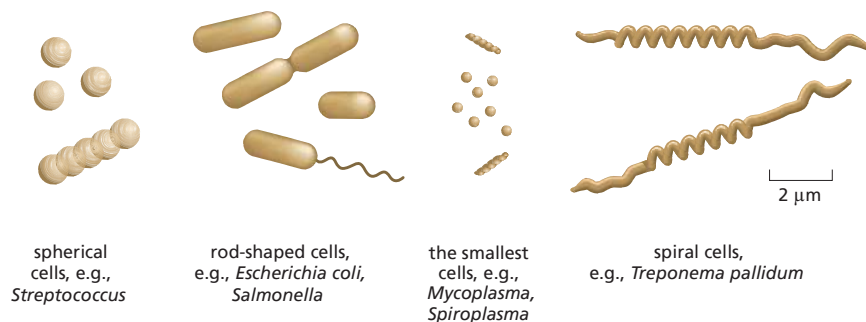


Figure 1–10 Shapes and sizes of some bacteria. Although most are small, as shown, measuring a few micrometers in linear dimension, there are also some giant species. An extreme example is the cigar-shaped bacterium *Epulopiscium fishelsoni*, which lives in the gut of a surgeonfish and can be up to 600 μm long (not shown).

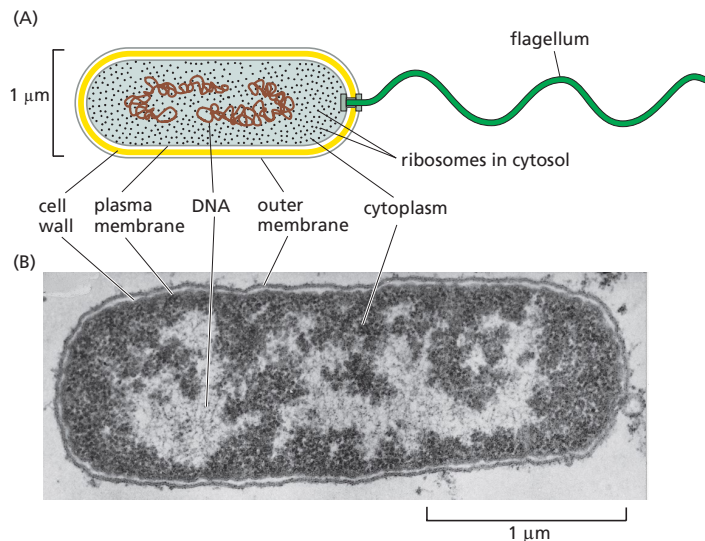


Figure 1-11 Bacterial structure. (A) A drawing of the bacterium *Vibrio cholerae*, showing its simple internal organization. This species can infect the human small intestine to cause cholera; the severe diarrhea that accompanies this disease kills more than 100,000 people a year worldwide. Like many other bacteria, *Vibrio* has a helical appendage at one end—a flagellum—that rotates as a propeller to drive the cell forward. (B) An electron micrograph of a longitudinal section through the widely studied bacterium *Escherichia coli* (*E. coli*). *E. coli* is part of our normal intestinal *microbiota*, the complete collection of microbes in our gut. It has many flagella distributed over its surface, but they are not visible in this section. Both of the bacteria shown here are Gram negative, having both an outer and an inner (plasma) membrane. However, many bacterial species lack the outer membrane; these are classified as Gram positive. (B, courtesy of E. Kellenberger.)

biochemical capabilities. There exist species that can utilize virtually any type of organic molecule as food, ranging from sugars and amino acids to hydrocarbons, including the simplest hydrocarbon, methane gas (CH_4). Other species (Figure 1-12) harvest light energy in a variety of ways; some, like plants, carry out photosynthesis and generate oxygen as a by-product. Still others can feed on a plain diet of inorganic nutrients, getting their carbon from CO_2 , and relying on a host of other chemicals that occur in the environment to fuel their energy needs—including H_2 , Fe^{2+} , H_2S , and elemental sulfur (Figure 1-13).

A wide range of bacteria directly affect human health. The bubonic plague of the Middle Ages (estimated to have killed half the population of Europe) and the current tuberculosis pandemic (more than a million deaths a year) are each due to a specific species of bacteria. And thousands of different bacterial species reside in our gut and on our skin, where they are often beneficial to us. We shall discuss bacteria throughout the book, as it is the study of these relatively simple cells that led to much of our understanding of basic biological processes—including DNA replication, transcription, and translation. We focus again on bacteria in Chapter 24 when we examine the cell biology of infectious disease. Finally, genetic

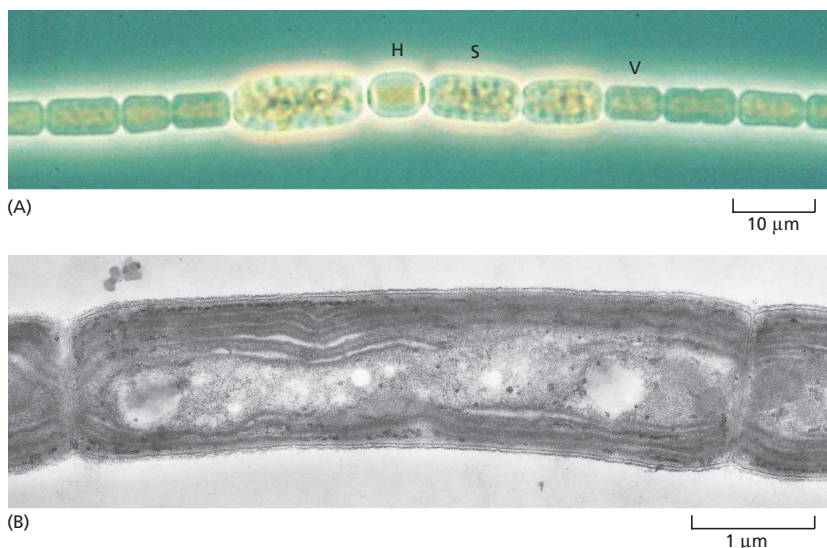


Figure 1-12 Photosynthetic bacteria. (A) A light micrograph of the bacterium *Anabaena cylindrica*. Its cells form long chains, in which most of the cells (labeled V) perform photosynthesis (and thereby capture CO_2 and incorporate C into organic compounds); others (labeled H) become specialized for fixing N from N_2 ; and still others (labeled S) develop into spores, which can resist unfavorable conditions. (B) An electron micrograph of a related photosynthetic bacterium, *Phormidium lamosum*, which shows the intracellular membranes where photosynthesis occurs. As shown in these micrographs, some prokaryotes have intracellular membranes and form colonies that resemble simple multicellular organisms. (A, courtesy of David Adams; B, courtesy of D.P. Hill and C.J. Howe.)

engineering techniques allow bacteria to be put to use as small “factories” to produce human pharmaceuticals, biofuels, and other high-value chemical products, as we discuss in Chapter 8.

Archaea: The Most Mysterious Domain of Life

Of the three domains of life, archaea remains the most poorly understood. Most of its members have been identified only by DNA sequencing of samples from the environment, and relatively few have been cultured and studied up close in the laboratory. Like bacteria, the archaea we know most about are small and lack the internal, membrane-bound organelles that distinguish the eukaryotes. But they differ from bacteria in many ways, including the chemistry of their cell walls, the kinds of lipids that make up their membrane, and the range of biochemical reactions that they can carry out. Another surprising conclusion came from genome comparisons: although archaea resemble bacteria in their outward appearances, their genomes are much more closely related to eukaryotes than to bacteria (see Figure 1–9). It has even been proposed that the tree of life should be considered to have only two principal domains, with the archaea and eukaryotes making up one domain and bacteria constituting the other. The close relationship of archaea and eukaryotes has also changed our views on how the earliest eukaryotic cell evolved, a topic addressed later in this chapter.

At first it was thought that archaea occupied only extreme environments such as volcanoes, salt lakes, acid hot springs, and the stomachs of cattle, but they are now recognized to be present also in more congenial surroundings such as soils, seawater, and our skin. Commensurate with the wide variety of ecological niches in which they have been found, different species of archaea have highly diverse chemistries. They are believed to be the predominant life-form in soil and seawater, and they play major roles in recycling nitrogen and carbon, two of the most important elements for all cells.

Organisms Occupy Most of Our Planet

To understand life on Earth, we need to understand more than its diversity; we also need to know where life is found on our planet and how various living species are distributed. Organisms inhabit nearly all of the planet, and we continue to discover new habitats. Amazingly, some bacteria and archaea even live miles down in Earth’s deep crust and in the deepest and most hostile parts of the oceans.

How are the main groups of organisms distributed among different environments? DNA sequencing and other advanced technologies have been used recently to address this question. The total biomass on Earth is estimated to contain ~550 gigatons (10^{15} grams) of carbon, of which 450 gigatons of carbon (Gt C) is plants, 70 Gt C is bacteria, 7 Gt C is archaea, and 2 Gt C is animals (Figure 1–14). The plants are mainly terrestrial; the bacteria and archaea are mainly in the soil and Earth’s crust. Total terrestrial biomass is 100 times greater than that in the oceans, although most of the animal mass is found in the oceans. The human biomass is 10 times greater than that of all measurable wild animals together, and—while human biomass continues to increase—that of wild animals is falling, largely as a result of human activities.

Although humans and other animals make up a small fraction of Earth’s biomass, their existence depends completely on other forms of life. In the next section, we shall see some of the ways that these different life-forms work together to capture and recycle energy from Earth’s inanimate features.

Cells Can Be Powered by a Wide Variety of Free-Energy Sources

Organisms obtain the free energy needed for life in different ways. Some—such as animals, fungi, and the many different bacteria that live in the human gut—get it by feeding on other living things or the organic chemicals they produce; such organisms are called *organotrophic* (from the Greek word *trophe*, meaning

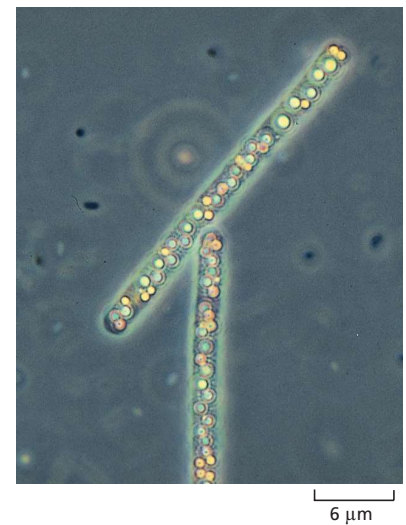


Figure 1–13 The bacterium *Beggiatoa*. It lives in sulfurous environments (for example, see Figure 1–15) and gets its energy by oxidizing H_2S ; it can fix carbon even in the dark. Note the yellow deposits of sulfur inside the cells. (Courtesy of Ralph S. Wolfe.)

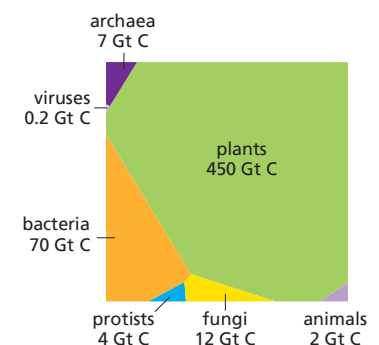


Figure 1–14 The distribution of living biomass on Earth. The total biomass on Earth expressed as gigatons of carbon (Gt C) is estimated to be ~550 Gt C. In the graph shown, the area of each taxon represented is proportional to the taxon’s global biomass, so plants account for about 80% (450/550) of the total biomass, whereas animals account for 0.4% (2/550). These recent estimates are based on various advanced techniques, including DNA sequencing and remote sensing. (Adapted from Y.M. Bar-On et al., *Proc. Natl. Acad. Sci. USA* 115:6506–6511, 2018. With permission from the authors.)

“food”). Others derive their free energy directly from the nonliving world. These primary energy converters fall into two classes: those that harvest the energy of sunlight, and those that capture their energy from energy-rich systems of inorganic chemicals in the environment (chemical systems that are far from chemical equilibrium). Organisms of the former class are called *phototrophic* (feeding on sunlight); those of the latter are called *lithotrophic* (feeding on rock). The organotrophic organisms like ourselves could not exist without these primary energy converters, which are the most plentiful form of life.

The phototrophic organisms include many types of bacteria, as well as algae and plants, on which we—and virtually all the living things that we ordinarily see around us—depend. Phototrophic organisms have changed the whole chemistry of our environment: as a prime example, the oxygen in Earth’s atmosphere is a by-product of their biosynthetic activities.

Lithotrophic organisms are not such an obvious feature of our world, because they are microscopic and mostly live in habitats that humans do not frequent—deep in the ocean, buried in Earth’s crust, or in various other seemingly inhospitable environments. But they are a major part of the living world, and they are especially important in any consideration of the history of life on Earth.

Some lithotrophs get energy from *aerobic* reactions, which use molecular oxygen from the environment; because atmospheric O_2 is ultimately the product of living phototrophic organisms, these aerobic lithotrophs are, in a sense, feeding on the products of past life. There are, however, many other lithotrophs that live *anaerobically*, in places where little or no molecular oxygen is present; these are circumstances similar to those that existed in the early days of life on Earth, before oxygen had accumulated.

The most dramatic of the anaerobic sites are the hot *hydrothermal vents* on the floor of the Pacific and Atlantic Oceans. They are located where the ocean floor is spreading as new portions of Earth’s crust form by a gradual upwelling of material from Earth’s interior (Figure 1–15). Downward-percolating seawater is heated and driven back upward as a submarine geyser, carrying with it a current of chemicals from the hot rocks below. A typical cocktail might include H_2S , H_2 , CO , Mn^{2+} , Fe^{2+} , Ni^{2+} , CH_4 , NH_4^+ , and phosphorus-containing compounds.

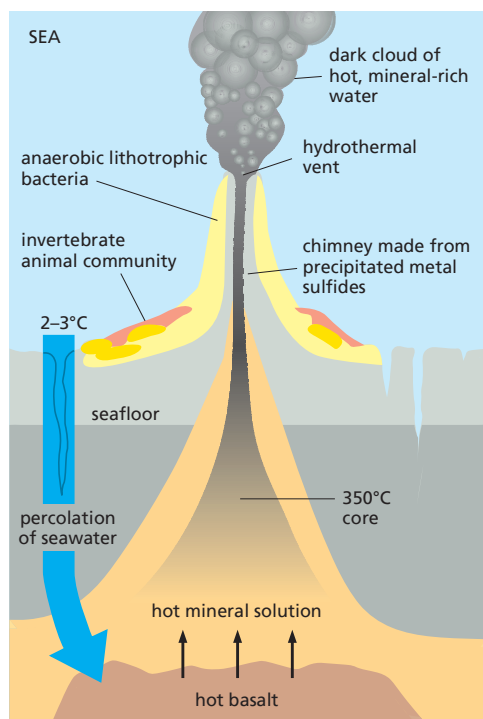


Figure 1–15 The geology of a hot hydrothermal vent in the ocean floor.

As indicated, seawater percolates down toward the hot, molten, volcanic rock upwelling (basalt) from Earth’s interior and is heated and driven back upward, carrying a mixture of minerals leached from the hot rock. A temperature gradient is set up, from more than 350°C near the core of the vent, down to 2–3°C in the surrounding ocean. Minerals precipitate from the water as it cools, forming a chimney. Different classes of organisms, thriving at different temperatures, live in different neighborhoods of the chimney. A typical chimney might be a few meters tall, spewing out hot, mineral-rich water. The locations of lithotrophic bacteria and the invertebrate marine animals that depend on them are also shown (see Figure 1–16).

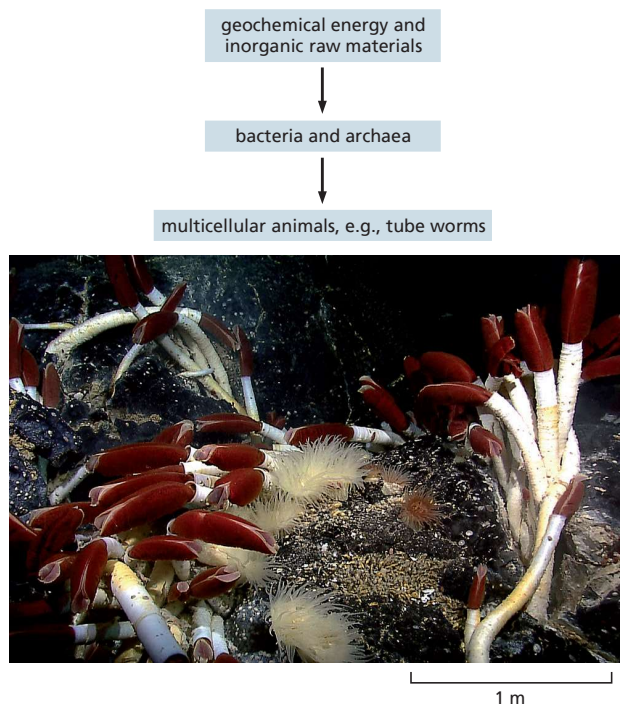


Figure 1–16 Organisms living at a depth of 2500 meters near a vent in the ocean floor. Close to the vent, at temperatures up to about 120°C, various lithotrophic species of bacteria and archaea live, directly fueled by geochemical energy. A little further away, where the temperature is lower, various invertebrate animals live by feeding on these microorganisms. Most remarkable are the giant (2-meter-long) tube worms, *Riftia pachyptila*, which are shown in the photograph. Rather than feed on the lithotrophic microbes, these worms live in symbiosis with them: specialized organs in the worms harbor huge numbers of symbiotic sulfur-oxidizing bacteria, which harness geochemical energy and supply nourishment to their hosts, which have no mouth, gut, or anus. The tube worms are thought to have evolved from more conventional animals and to have become secondarily adapted to life at hydrothermal vents. (Science History Images/Alamy Stock Photo.)

A dense population of microorganisms lives in the neighborhood of the vent, thriving on this austere diet and harvesting free energy from reactions between the available chemicals. Various invertebrate marine animals—clams, mussels, and giant marine worms—in turn, live off the microbes at the vent, forming an entire ecosystem analogous to the world of plants and animals that we belong to, but one powered by geochemical energy instead of light (Figure 1–16).

Some Cells Fix Nitrogen and Carbon Dioxide for Other Cells

To make a living cell requires matter, as well as free energy. DNA, RNA, and protein are composed of just six elements: hydrogen, carbon, nitrogen, oxygen, sulfur, and phosphorus. These are all plentiful in the nonliving environment, in Earth's rocks, water, and atmosphere. But they are not present in chemical forms that allow easy incorporation into biological molecules. Atmospheric N_2 and CO_2 , in particular, are extremely unreactive. A large amount of free energy is required to drive the reactions that use these inorganic molecules to make the organic compounds needed for further biosynthesis; that is, to *fix* nitrogen and carbon dioxide, so as to make N and C available to living organisms. Many types of cells lack the biochemical machinery to achieve this fixation; they instead rely on other classes of cells to do the job for them. We animals depend on plants, directly or indirectly, for our supplies of carbon- and nitrogen-containing organic compounds. Plants in turn, although they can fix carbon dioxide from the atmosphere, lack the ability to fix atmospheric nitrogen; they depend in part on nitrogen-fixing bacteria to supply their need for nitrogen-containing organic compounds. Plants of the pea family, for example, harbor symbiotic nitrogen-fixing bacteria in nodules in their roots.

Because living cells can differ widely in some of the most basic aspects of their biochemistry, cells with complementary needs and capabilities have frequently developed close associations. Some of these *symbiotic* associations, as we will see later, have evolved to the point where the partners have lost their separate identities altogether: they have joined forces to form a single composite cell—an *endosymbiotic* association, as opposed to an *ectosymbiotic* one between separate organisms.

Genomes Diversify Over Evolutionary Time, Producing New Types of Organisms

Having discussed our current views on the diversity of life-forms, how they are distributed across Earth, and how they depend on one another, we now turn to the question of how this great diversity was generated. All life depends on the storage of genetic information in the form of each organism's DNA genome, so our focus is on how genomes change over evolutionary time.

In storing and copying genetic information, random accidents and errors occur, altering the nucleotide sequence; that is, creating **mutations**. Therefore, when a cell divides, the genomes of its two daughters are often not quite identical to each other or to that of the parent cell. On rare occasions, the error may represent a change for the better; more probably, it will cause no significant difference in the cell's prospects. But in some cases, the error will cause serious damage; for example, by disrupting the coding sequence for a key protein or RNA molecule. Changes due to mistakes of the first type will tend to be perpetuated, because the altered cell has an increased likelihood of surviving and reproducing itself. Changes due to mistakes of the second type—*neutral* changes—may be perpetuated or not: in the competition for limited resources, it is a matter of chance whether the altered cell or its cousins will succeed. But changes that cause serious damage lead nowhere: the cell that suffers them dies, leaving no progeny. Through endless repetition of this cycle of error and trial—of *mutation* and *natural selection*—organisms evolve: their genetic specifications change, sometimes giving organisms new ways to exploit the environment more effectively, to survive in competition with others, and to reproduce successfully.

Some parts of the genome will change more readily than others in the course of evolution. A segment of DNA that does not code for protein or RNA and has no significant regulatory role is free to change at a rate limited only by the frequency of random errors. In contrast, a gene that codes for a highly optimized, essential protein or RNA molecule cannot alter so easily: when mistakes occur, the faulty cells are almost always disabled and eliminated. Genes of this latter sort are therefore *highly conserved*. Through 3.5 billion years or more of evolutionary history, many DNA sequences have changed beyond all recognition, but the most highly conserved genes remain perfectly recognizable in all living species.

These latter genes are the ones we must examine if we wish to trace family relationships between the most distantly related organisms in the tree of life. We discussed an example of one such gene—that for ribosomal RNA—when we introduced the classification of the living world into the three domains of eukaryotes, bacteria, and archaea. Because the production of proteins is fundamental to all living cells, this component of the ribosome has been highly conserved since early in the history of life on Earth (Figure 1-17).

The ribosomal RNA genes are exceptional in being so well conserved, whereas most parts of genomes have diversified much more dramatically over evolutionary time. A complete DNA sequence for an organism—its genome sequence—reveals all the genes that an organism possesses, as well as those it lacks. When we

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GTTCGGGGGGAGTATGGTTGCAAGCTGAAACTTAAAGGAATTGACGGAAGGGCACCACAGGAGTGGAGCCTGCGGCTTAATTTGACTCAACACGGGAAACCTCACCC human
|||||
GCCGCTGGGGAGTACGGTCCGAAGACTGAAACTTAAAGGAATTGCGGGGGAGCACTACAACGGGTGGAGCCTCGGTTAATTGGATTCAACGCCGGGCATCTTACCA Methanococcus
|||||
ACCGCTGGGGAGTACGGCCCAAGTTAAACTCAAATGAATTGACGGGGGCCCGC•ACAAGCGTGGAGCATGTGGTTAATTCGATGCAACGGGAAGAACCTTACCT E. coli
|||||
GTTCGGGGGGAGTATGGTTGCAAGCTGAAACTTAAAGGAATTGACGGAAGGGCACCACAGGAGTGGAGCCTGCGGCTTAATTTGACTCAACACGGGAAACCTCACCC human

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Figure 1-17 Genetic information conserved since the days of the last universal common ancestor of all living things.

A part of the gene that codes for the smaller of the two main ribosomal RNA (rRNA) molecules in the ribosome is shown. (The complete molecule is about 1500–1900 nucleotides long, depending on the species.) Corresponding segments of nucleotide sequences from an archaeon (*Methanococcus jannaschii*), a bacterium (*Escherichia coli*), and a eukaryote (*Homo sapiens*) are aligned. The *red vertical lines* indicate sites where the nucleotides are identical between the species; the human sequence is repeated at the bottom of the alignment so that all three two-way comparisons can be seen. The *black dot* halfway along the *E. coli* sequence denotes a site where a nucleotide has been either deleted from the bacterial lineage in the course of evolution or inserted in the other two lineages. Note that the sequences from these three organisms, representative of the three domains of the living world, still retain unmistakable similarities.

compare the three domains of the living world, we can begin to see which genes are common to all of them—and must therefore have been present in the last universal common ancestral cell that was the founder of all present-day living things. We can also identify those genes that are peculiar to a single branch in the tree of life. To explain such findings, we need to consider how new genes arise and, more generally, how genomes evolve.

New Genes Are Generated from Preexisting Genes

The raw material of evolution is the DNA sequence that already exists: there is no natural mechanism for making long stretches of new, random, DNA sequence. In this sense, no gene is ever entirely new. Innovation can, however, occur in several ways (Figure 1–18):

1. *Intragenic mutation*: an existing gene can be randomly modified by changes in its DNA sequence, through various types of errors that occur in the process of DNA replication and DNA repair.
2. *Gene duplication*: an existing gene can be accidentally duplicated, creating a pair of initially identical genes within a single cell; these two genes may then diverge in the course of evolution.
3. *DNA segment shuffling*: two or more existing genes can break and rejoin to make a hybrid gene consisting of DNA segments that originally belonged to separate genes.
4. *Horizontal (intercellular) DNA transfer*: a piece of DNA can be transferred from the genome of one cell to that of another—including between species. This process contrasts with the usual *vertical transfer* of genetic information from parent to progeny.

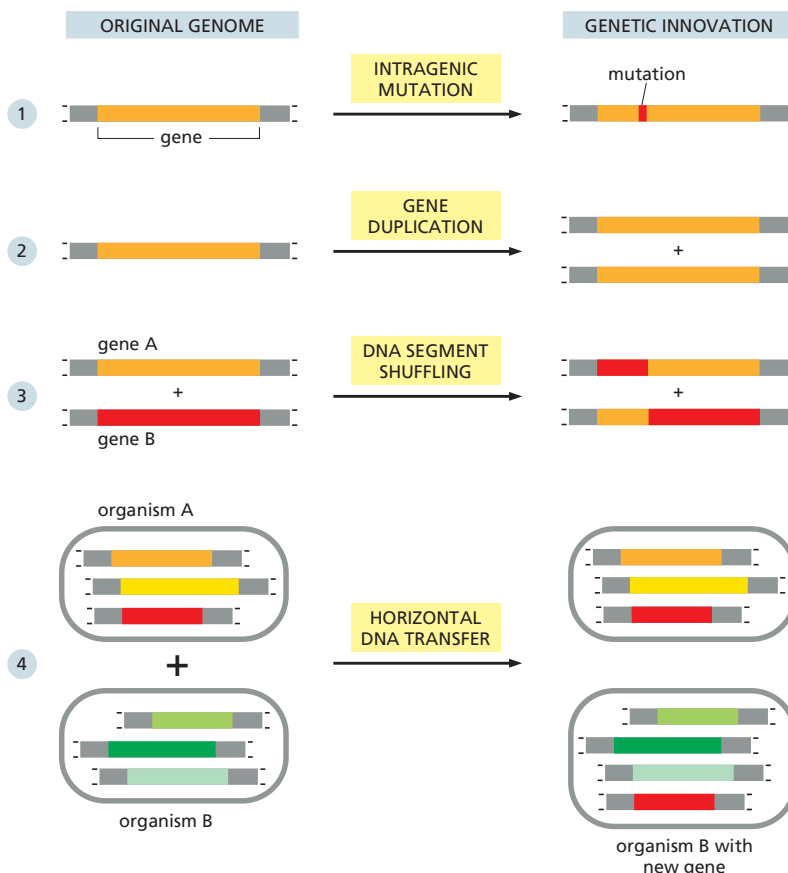


Figure 1–18 Four modes of genetic innovation and their effects on the DNA sequence of an organism. A special form of horizontal transfer occurs when cells of two different species enter into a permanent symbiotic association; genes from one of the cells may subsequently be transferred to the genome of the other, as we will see later when we discuss the likely evolutionary origins of mitochondria and chloroplasts.

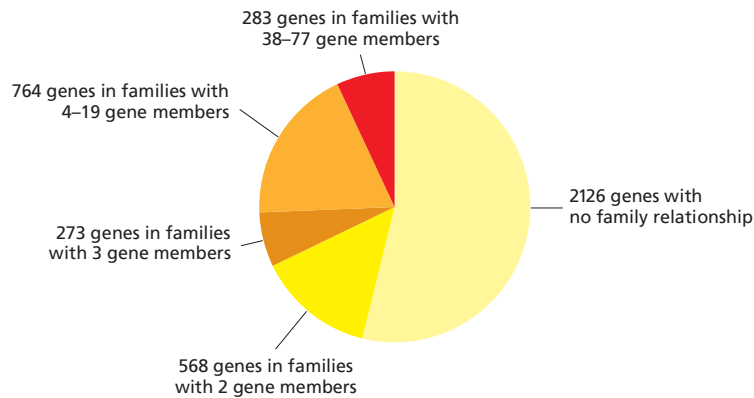


Figure 1–19 Families of evolutionarily related genes in the genome of *Bacillus subtilis*. The largest gene family in this bacterium consists of 77 genes coding for varieties of a class of membrane transport proteins called ABC transporters, which are found in all three domains of the living world. (Adapted from F. Kunst et al., *Nature* 390:249–256, 1997.)

Each of these types of change leaves a characteristic trace in the DNA sequence of the organism, and there is clear evidence that all four processes have occurred frequently during evolution. In Chapters 4 and 5, we discuss the mechanisms underlying these changes, but for the present we focus on the consequences.

Gene Duplications Give Rise to Families of Related Genes Within a Single Genome

A cell duplicates its entire genome each time it divides into two daughter cells. However, accidents occasionally result in the inappropriate duplication of just part of the genome, with retention of both the original and duplicate segments in a single cell. Once a gene has been duplicated in this way (see mode 2 in Figure 1–18), the two gene copies can acquire mutations and become specialized to perform different functions within the same cell and its descendants. Repeated rounds of this process of gene duplication and divergence, over many millions of years, have enabled one gene to give rise to a family of related genes within a single genome. Analysis of the DNA sequence of prokaryotic genomes reveals many examples of such **gene families**: in the bacterium *Bacillus subtilis*, for example, 47% of the genes have one or more obvious relatives (Figure 1–19).

The above evolutionary process must be distinguished from the genetic divergence that occurs when one species of organism splits into two separate lines of descent at a branch point in the family tree—when the human line separated from that of chimpanzees, for example. In the latter case, the genes gradually become different in the course of evolution, but they are likely to continue to have corresponding functions in the two sister species. Genes that are related by descent in this way—that is, genes in two separate species that derive from the same ancestral gene in the last common ancestor of those two species—are called **orthologs**. Related genes that have resulted from a gene duplication event within a single genome—and are likely to have diverged in their function—are called **paralogs**. Genes that are related by descent in either way are called **homologs**, a general term used to cover both types of relationship (Figure 1–20).

The Function of a Gene Can Often Be Deduced from Its Nucleotide Sequence

Family relationships among genes are important not just for their evolutionary interest, but also because they simplify the task of deciphering gene functions. Once the nucleotide sequence of a newly discovered gene has been determined, a scientist can tap a few keys on a computer to search large databases of known gene sequences for gene relatives. In many cases, the function of one or more of these homologs will have been already determined experimentally—generally in one of the model organisms described later in this chapter. Because gene sequence determines gene function, one can frequently make a good guess at the new gene's function, as it is likely to be similar to that of the already

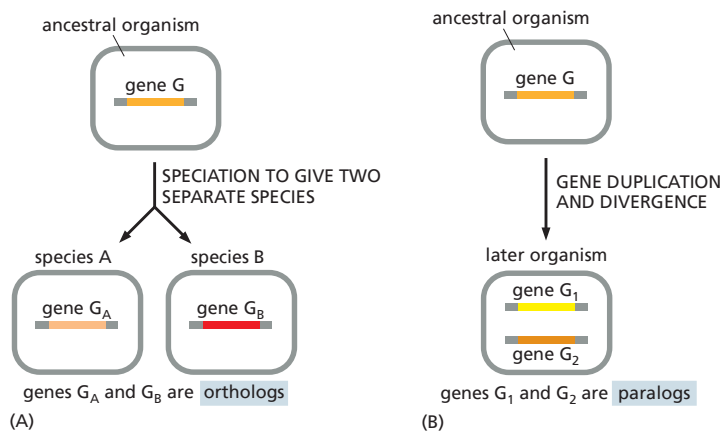


Figure 1–20 Two types of gene homology based on different evolutionary pathways. (A) Orthologs. (B) Paralogous. Genes related by either mechanism are called homologs.

known homologs. In this way, it is possible to decipher a great deal about the biology of an organism simply by analyzing the DNA sequence of its genome.

More Than 200 Gene Families Are Common to All Three Domains of Life

Given the complete genome sequences of representative organisms from all three domains of life—eukaryotes, bacteria, and archaea—we can search systematically for homologies that span this enormous evolutionary divide. In this way, we can begin to take stock of the common inheritance of all living things. There are considerable difficulties in this enterprise. For example, individual species have often lost some of the ancestral genes, and other genes have almost certainly been acquired by horizontal transfer from another species and therefore are not truly ancestral. In fact, genome comparisons strongly suggest that both lineage-specific gene loss and horizontal gene transfer, in some cases between evolutionarily distant species, have been major factors in evolution, at least among bacteria and archaea. As an additional difficulty, in the course of 2 or 3 billion years, some genes that were initially shared will have changed beyond recognition through mutation.

Because of all these vagaries of the evolutionary process, it is difficult, if not impossible, to determine the ancestral gene set that diversified into the present-day variety of life. A crude approximation can be obtained by tallying the gene families that have representatives in multiple—but not necessarily all—species from the three major domains of life. One such analysis revealed 264 ancient conserved families, each of which could be assigned a function on the basis of the best-characterized family member. As shown in [Table 1-1](#), the largest number of shared gene families were involved in translation and in amino acid metabolism and transport. However, it must be emphasized that this set of highly conserved gene families represents only a very rough sketch of the common inheritance of all modern life.

Summary

For most of human history, the living world around us was classified by what we could see. Genome sequencing has radically changed our view of life on the planet, and we now realize that living things fall into three broad domains: bacteria, archaea, and eukaryotes. The organisms in the first two domains are largely invisible to our naked eye, and many of them cannot yet be grown in a laboratory—being known only by their DNA sequences. But they make up the vast majority of life's evolutionary diversity, including species that can obtain all their energy and nutrients from inorganic chemical sources—such as the reactive mixtures of minerals released at hydrothermal vents on the ocean floor—the sort of diet that may