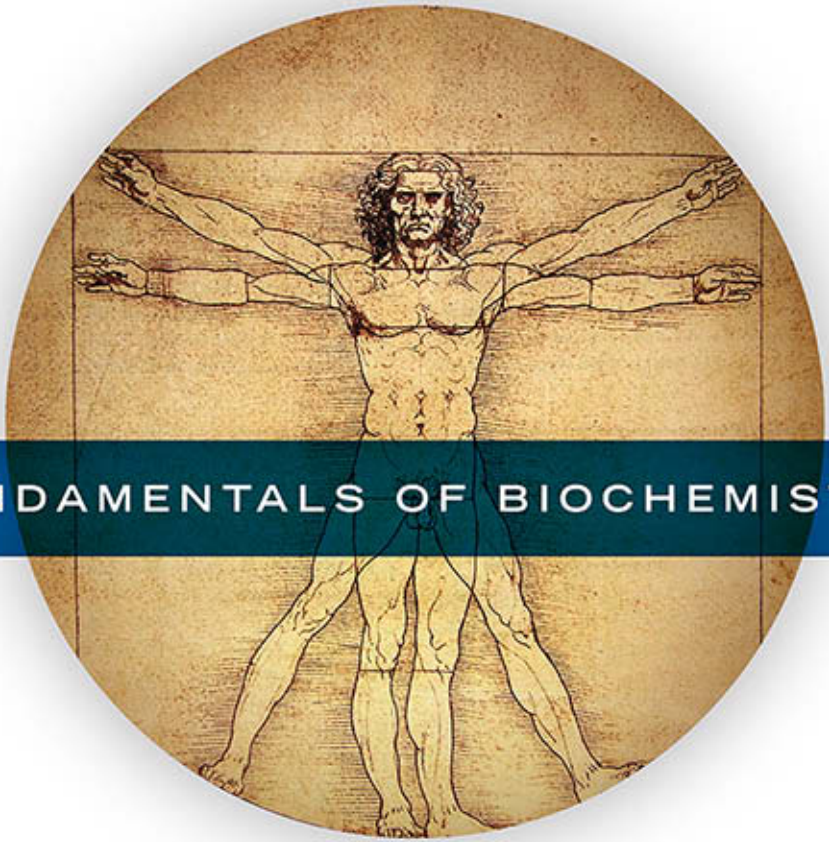
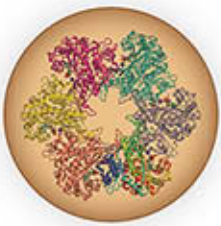
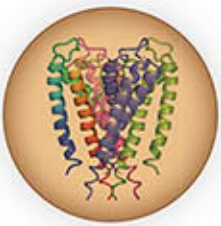


FUNDAMENTALS OF BIOCHEMISTRY

LIFE AT THE MOLECULAR LEVEL

5TH EDITION

DONALD VOET • JUDITH G. VOET • CHARLOTTE W. PRATT

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One- and Three-Letter Symbols for the Amino Acids[a]

A	Ala	Alanine
B	Asx	Asparagine or aspartic acid
C	Cys	Cysteine
D	Asp	Aspartic acid
E	Glu	Glutamic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine
Z	Glx	Glutamine or glutamic acid

[a]The one-letter symbol for an undetermined or nonstandard amino acid is X.

Thermodynamic Constants and Conversion Factors

***Joule* (J)**

$1\ J = 1\ kg \cdot m^2 \cdot s^{-2}$ $\quad 1\ J = 1\ C \cdot V$ (coulomb volt)

$1\ J = 1\ N \cdot m$ (newton meter)

***Calorie* (cal)**

1 cal heats 1 g of H_2O from 14.5 to 15.5°C

$1\ cal = 4.184\ J$

***Large calorie* (Cal)**

$1\ Cal = 1\ kcal$ $\quad 1\ Cal = 4184\ J$

Avogadro's number (N)

$N = 6.0221 \times 10^{23}$ molecules$\cdot$mol^{-1}

***Coulomb* (C)**

$1\ C = 6.241 \times 10^{18}$ electron charges

***Faraday* ($\mathscr{F}$)**

$1\ \mathscr{F} = N$ electron charges

$1\ \mathscr{F} = 96{,}485\ C \cdot mol^{-1} = 96{,}485\ J \cdot V^{-1} \cdot mol^{-1}$

***Kelvin temperature scale* (K)**

$0\ K$ = absolute zero $\quad 273.15\ K = 0°C$

Boltzmann constant (k_B)

$k_B = 1.3807 \times 10^{-23}\ J \cdot K^{-1}$

Gas constant (R)

$R = Nk_B$ $\quad R = 1.9872\ cal \cdot K^{-1} \cdot mol^{-1}$

$R = 8.3145\ J \cdot K^{-1} \cdot mol^{-1}$ $\quad R = 0.08206\ L \cdot atm \cdot K^{-1} \cdot mol^{-1}$

The Standard Genetic Code

First Position (5′ end)	*Second Position*				*Third Position (3′ end)*
	U	C	A	G	
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met[a]	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

[a]AUG forms part of the initiation signal as well as coding for internal Met residues.

FIFTH EDITION

Fundamentals of Biochemistry

LIFE AT THE MOLECULAR LEVEL

Donald Voet
University of Pennsylvania

Judith G Voet
Swarthmore College

Charlotte W. Pratt
Seattle Pacific University

WILEY

In memory of Alexander Rich (1924-2015), a trailblazing molecular biologist and a mentor to numerous eminent scientists

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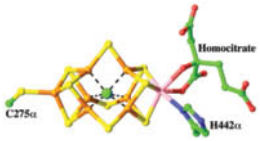
Donald Voet received his B.S. in Chemistry from the California Institute of Technology in 1960, a Ph.D. in Chemistry from Harvard University in 1966 under the direction of William Lipscomb, and then did his postdoctoral research in the Biology Department at MIT with Alexander Rich. Upon completion of his postdoc in 1969, Don became a faculty member in the Chemistry Department at the University of Pennsylvania, where he taught a variety of biochemistry courses as well as general chemistry and X-ray crystallography. Don's research has focused on the X-ray crystallography of molecules of biological interest. He has been a visiting scholar at Oxford University, U.K., the University of California at San Diego, and the Weizmann Institute of Science in Israel. Don is the coauthor of four previous editions of *Fundamentals of Biochemistry* (first published in 1999) as well as four editions of *Biochemistry*, a more advanced textbook (first published in 1990). Together with Judith G. Voet, Don was Co-Editor-in-Chief of the journal *Biochemistry and Molecular Biology Education* from 2000 to 2014. He has been a member of the Education Committee of the International Union of Biochemistry and Molecular Biology (IUBMB) and continues to be an invited speaker at numerous national and international venues. He, together with Judith G. Voet, received the 2012 award for Exemplary Contributions to Education from the American Society for Biochemistry and Molecular Biology (ASBMB). His hobbies include backpacking, scuba diving, skiing, travel, photography, and writing biochemistry textbooks.

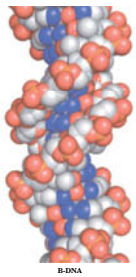
Judith ("Judy") Voet was educated in the New York City public schools, received her B.S. in Chemistry from Antioch College, and her Ph.D. in Biochemistry from Brandeis University under the direction of Robert H. Abeles. She did postdoctoral research at the University of Pennsylvania, Haverford College, and the Fox Chase Cancer Center. Judy's main area of research involves enzyme reaction mechanisms and inhibition. She taught biochemistry at the University of Delaware before moving to Swarthmore College, where she taught biochemistry, introductory chemistry, and instrumental methods for 26 years, reaching the position of James H. Hammons Professor of Chemistry and Biochemistry and twice serving as department chair before going on "permanent sabbatical leave." Judy has been a visiting scholar at Oxford University, U.K., University of California, San Diego, University of Pennsylvania, and the Weizmann Institute of Science, Israel. She is a coauthor of four previous editions of *Fundamentals of Biochemistry* and four editions of the more advanced text, *Biochemistry*. Judy was Co-Editor-in-Chief of the journal *Biochemistry and Molecular Biology Education* from 2000 to 2014. She has been a National Councilor for the American Chemical Society (ACS) Biochemistry Division, a member of the Education and Professional Development Committee of the American Society for Biochemistry and Molecular Biology (ASBMB), and a member of the Education Committee of the International Union of Biochemistry and Molecular Biology (IUBMB). She, together with Donald Voet, received the 2012 award for Exemplary Contributions to Education from the ASBMB. Her hobbies include hiking, backpacking, scuba diving, tap dancing, and playing the Gyil (an African xylophone).

Charlotte Pratt received her B.S. in Biology from the University of Notre Dame and her Ph.D. in Biochemistry from Duke University under the direction of Salvatore Pizzo. Although she originally intended to be a marine biologist, she discovered that biochemistry offered the most compelling answers to many questions about biological structure–function relationships and the molecular basis for human health and disease. She conducted postdoctoral research in the Center for Thrombosis and Hemostasis at the University of North Carolina at Chapel Hill. She has taught at the University of Washington and currently teaches and supervises undergraduate researchers at Seattle Pacific University. Developing new teaching materials for the classroom and student laboratory is a long-term interest. In addition to working as an editor of several biochemistry textbooks, she has co-authored *Essential Biochemistry* and previous editions of *Fundamentals of Biochemistry*. When not teaching or writing, she enjoys hiking and gardening.

BRIEF CONTENTS

CONTENTS





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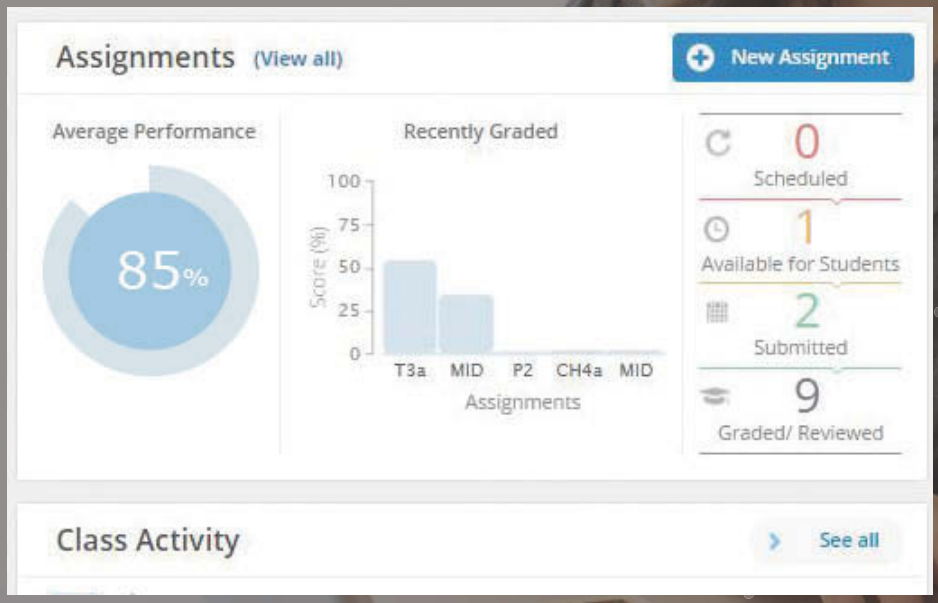

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Visualize molecular processes

Guided Explorations: A set of self-contained presentations, many with narration, employ extensive animated computer graphics to enhance student understanding of key topics.

Animated Figures: A set of figures from the text, illustrating various concepts, techniques, and processes, are presented as brief animations to facilitate learning.

Animated Process Diagrams: The many Process Diagrams in the text have each been broken down into discrete steps that students can navigate at their desired pace.

These resources are intended to enrich the learning process for students, especially those who rely heavily on visual information. Whereas some resources, particularly the Animated Figures and Animated Process Diagrams, are brief and could easily be incorporated into an instructor's classroom lecture, all the resources are ideal for student self-study, allowing students to proceed at their own pace or back up and review as needed. All the media resources are keyed to specific figures or sections of the text, so students can explore molecular structures and processes as they work through a chapter.

Solve problems using real data, using the same analytical tools the experts use

Sample Calculation Videos: *Students come to biochemistry with different levels of math skills. These embedded videos, created by Charlotte Pratt, walk students through the Sample Calculations provided for key equations throughout the text.*

Brief Bioinformatics Exercises: *A series of 74 short, assessable, and content-specific bioinformatics projects (at least two per chapter) by Rakesh Mogul, Cal Poly Pomona. They introduce students to the rich variety of biochemical information and software tools available over the Internet and show them how to mine this information, thereby illuminating the connections between theory and applied biochemistry and stimulating student interest and proficiency in the subject.*

Extended Bioinformatics Projects: *A set of 12 newly updated exercises by Paul Craig, Rochester Institute of Technology, covering the contents and uses of databases related to nucleic acids, protein sequences, protein structures, enzyme inhibition, and other topics. The exercises use real data sets, pose specific questions, and prompt students to obtain information from online databases and to access the software tools for analyzing such data.*

Case Studies: *A set of 33 case studies by Kathleen Cornely, Providence College, using problem-based learning to promote understanding of biochemical concepts. Each case presents data from the literature and asks questions that require students to apply principles to novel situations, often involving topics from multiple chapters in the textbook.*

In WileyPLUS Learning Space instructors can…

Assign a robust variety of practice and assessment questions

Test Bank: *Over 1400 questions in a variety of question types (multiple choice, matching, fill in the blank, and short answer) by Marilee Benore, University of Michigan-Dearborn and Robert Kane, Baylor University, and revised by Amy Stockert, Ohio Northern University and Peter van der Geer, San Diego State University. Each question is keyed to the relevant section in the text and is rated by difficulty level. (Tests can be created and administered online or with test-generator software.)*

Exercises: *Over 1000 conceptually based questions by Rachel Milner and Adrienne Wright, University of Alberta, which can be sorted by chapter and/or topic and can be assigned as graded homework or additional practice.*

Practice Questions: *Quizzes, by Steven Vik, Southern Methodist University, to accompany each chapter, consisting of multiple-choice, true/false, and fill-in-the-blank questions, with instant feedback to help students master concepts.*

Prelecture Questions: *Multiple-choice questions that can be assigned prior to lecture to help students prepare for class.*

Discussion Questions: *Embedded within the WileyPLUS Learning Space etext, these thought-provoking questions serve as a point of departure for student discussion and engagement with the content.*

Access instructors' resources

PowerPoint Slides *contain all images and tables in the text, optimized for viewing onscreen.*

Interactive Protein PowerPoints *contain text images of a wide variety of proteins. Each slide includes a molecular structure and PDB code from the text that links students and instructors to the specific protein in the Protein Data Bank website (http://www.rcsb.org/pdb/home/home.do) The website provides a host of information about the 3D structures of large biological molecules, including proteins and nucleic acids.*

Classroom Response Questions ("Clicker Questions"), *by Rachel Milner and Adrienne Wright, University of Alberta, are interactive questions designed for classroom response systems to facilitate classroom participation and discussion. These questions can also be used by instructors as prelecture questions that help gauge students' knowledge of overall concepts, while addressing common misconceptions.*

PREFACE

Biochemistry is no longer a specialty subject but is part of the core of knowledge for modern biologists and chemists. In addition, familiarity with biochemical principles has become an increasingly valuable component of medical education. In revising this textbook, we asked, "*Can we provide students with a solid foundation in biochemistry, along with the problem-solving skills to use what they know?* We concluded that it is more important than ever to meet the expectations of a standard biochemistry curriculum, to connect biological chemistry to its chemical roots, and to explore the ways that biochemistry can explain human health and disease. We also wanted to provide students with opportunities to develop the practical skills that they will need to meet the scientific and clinical challenges of the future. This revised version of *Fundamentals of Biochemistry* continues to focus on basic principles while taking advantage of new tools for fostering student understanding. Because we believe that students learn through constant questioning, this edition features expanded problem sets, additional questions within the text, and extensive online resources for assessment. As in previous editions, we have strived to provide our students with a textbook that is complete, clearly written, and relevant.

New for the Fifth Edition

The fifth edition of *Fundamentals of Biochemistry* includes significant changes and updates to the contents. In recognition of the tremendous advances in biochemistry, we have added new information about prion diseases, trans fats, membrane transporters, signal transduction pathways, mitochondrial respiratory complexes, photosynthesis, nitrogen fixation, nucleotide synthesis, chromatin structure, and the machinery of DNA replication, transcription, and protein synthesis. New experimental approaches for studying complex systems are introduced, including next generation DNA sequencing techniques, cryo-electron microscopy, metabolomics, genome editing with the CRISPR–Cas9 system, and the role of noncoding RNAs in gene regulation. Notes on a variety of human diseases and pharmacological effectors have been expanded to reflect recent research findings.

Pedagogy

As in the previous four editions of *Fundamentals of Biochemistry,* we have given significant thought to the pedagogy within the text and have concentrated on fine-tuning and adding new elements to promote student learning. Pedagogical enhancements in this fifth edition include the following:

- **Gateway Concepts.** Short statements placed in the margin to summarize some of the general concepts that underpin modern biochemistry, such as Evolution, Macromolecular Structure/Function, Matter/Energy Transformation, and Homeostasis. These reminders help students develop a richer understanding as they place new information in the context of what they have encountered in other coursework.

> **GATEWAY CONCEPT Free Energy Change**
>
> You can think of the free energy change (ΔG) for a reaction in terms of an urge or a force pushing the reactants toward equilibrium. The larger the free energy change, the farther the reaction is from equilibrium and the stronger is the tendency for the reaction to proceed. At equilibrium, of course, the reactants undergo no net change and $\Delta G = 0$.

> **GATEWAY CONCEPT The Steady State**
>
> Although many reactions are near equilibrium, an entire metabolic pathway—and the cell's metabolism as a whole—never reaches equilibrium. This is because materials and energy are constantly entering and leaving the system, which is in a steady state. Metabolic pathways proceed, as if trying to reach equilibrium (Le Châtelier's principle), but they cannot get there because new reactants keep arriving and products do not accumulate.

- **Sample Calculation Videos within WileyPLUS Learning Space.** Students come to biochemistry with different levels of math skills. These embedded videos, created by Charlotte Pratt, walk students through the Sample Calculations provided for key equations throughout the text.
- **Animated Process Diagrams in WileyPLUS Learning Space.** The many Process Diagrams in the text have each been broken down into discrete steps that students can navigate at their desired pace.
- **Brief Bioinformatics Exercises in WileyPLUS Learning Space.** A series of 74 short, assessable, and content-specific bioinformatics projects (at least two per chapter) by Rakesh Mogul, Cal Poly Pomona. They introduce students to the rich variety of biochemical information available over the Internet and show them how to mine this information, thereby illuminating the connections between theory and applied biochemistry and stimulating student interest and proficiency in the subject.
- **Focus on evolution.** An evolutionary tree icon marks passages in the text that illuminate examples of evolution at the biochemical level.
- **Reorganized and Expanded Problem Sets.** End-of-chapter problems are now divided into two categories so that students and instructors can better assess lower- and higher-order engagement: **Exercises** allow students to check their basic understanding of concepts and apply them in straightforward problem solving. **Challenge Questions** require more advanced skills and/or the ability to make connections between topics. The fifth edition contains nearly 1000 problems, an increase of 26% over the previous edition. Most of the problems are arranged as successive pairs that address the same or related topics. Complete solutions to the odd-numbered problems are included in an appendix for quick feedback. (www.wiley.com/college/voet). Complete solutions to both odd- and even-numbered problems are available in the *Student Companion to Accompany Fundamentals of Biochemistry, Fifth Edition.*

Artwork

Students' ability to understand and interpret biochemical diagrams, illustrations, and processes plays a significant role in their understanding both the big picture and details of biochemistry. In addition to designing new illustrations and redesigning existing figures to enhance clarity, we have continued to address the needs of visual learners by usingseveral unique features to help students use the visuals in concert with the text:

- **Figure Questions.** To further underscore the importance of students' ability to interpret various images and data, we have added questions at the ends of figure captions that encourage students to more fully engage the material and test their understanding of the process being illustrated.

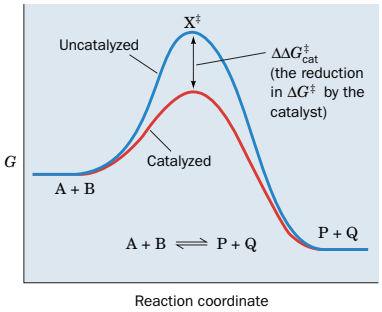

FIG. 11-7 **Effect of a catalyst on the transition state diagram of a reaction.** Here $\Delta\Delta G^{\ddagger}_{cat} = \Delta G^{\ddagger}(\text{uncat}) - \Delta G^{\ddagger}(\text{cat})$.

? **Does the catalyst affect $\Delta G_{reaction}$?**

- **Molecular Graphics.** Numerous figures have been replaced with state-of-the-art molecular graphics. The new figures are more detailed, clearer, and easier to interpret, and in many cases, reflect recent refinements in molecular visualization technology that have led to higher-resolution macromolecular models or have revealed new mechanistic features.

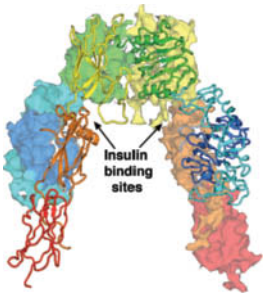

FIG. 13-4 **X-Ray structure of the insulin receptor ectodomain**. One of its αβ protomers is shown in ribbon form with its six domains successively colored in rainbow order with the N-terminal domain blue and the C-terminal domain red. The other protomer is represented by its identically colored surface diagram. The β subunits consist of most of the orange and all of the red domains. The protein is viewed with the plasma membrane below and its twofold axis vertical. In the intact receptor, a single transmembrane helix connects each β subunit to its C-terminal cytoplasmic PTK domain. [Based on an X-ray structure by Michael Weiss, Case Western Reserve University; and Michael Lawrence, Walter and Eliza Hall Institute of Medical Research, Victoria, Australia. PDBid 3LOH.]

- **Media Assets.** WileyPLUS Learning Space plays a key role in students' ability to understand and manipulate structural images. Guided Explorations, Animated Figures, and Animated Process Diagrams employ extensive animations and three-dimensional structures so that students can interact with the materials at their own pace, making them ideal for independent study.

Traditional Pedagogical Strengths

Successful pedagogical elements from prior editions of *Fundamentals of Biochemistry* have been retained. Among these are:

- **Key concepts** at the beginning of each section that prompt students to recognize the important "takeaways" or concepts in each section, providing the scaffolding for understanding by better defining these important points.
- **Checkpoint** questions, a robust set of study questions that appear at the end of every section for students to check their mastery of the section's key concepts. Separate answers are not provided, encouraging students to look back over the chapter to reinforce their understanding, a process that helps develop confidence and student-centered learning.
- **Key sentences** printed in italics to assist with quick visual identification.
- **Overview figures** for many metabolic processes.
- **Detailed enzyme mechanism figures** throughout the text.
- **Process Diagrams.** These visually distinct illustrations highlight important biochemical processes and integrate descriptive text into the figure, appealing to visual learners. By following information in the form of a story, students are more likely to grasp the key principles and less likely to simply memorize random details.

PROCESS DIAGRAM

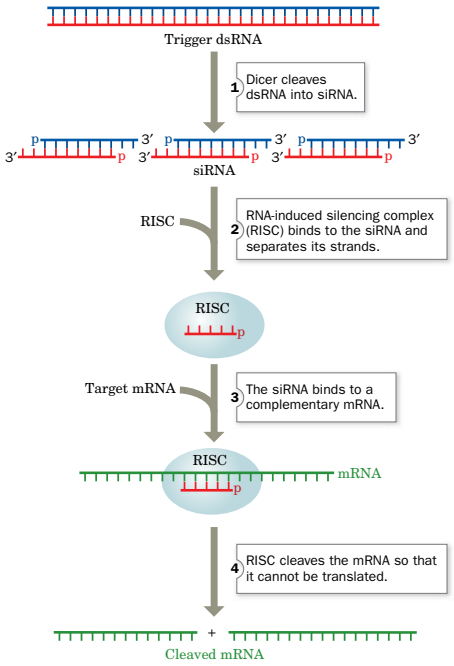

FIG. 28-37 **A mechanism of RNA interference.** ATP is required for Dicer-catalyzed cleavage of RNA and for RISC-associated helicase unwinding of double-stranded RNA. Depending on the species, the mRNA may not be completely degraded. **WPLS See the Animated Process Diagrams.**

? **Explain why RNAi is a mechanism for "silencing" genes.**

- **PDB identification codes** in the figure legend for each molecular structure so that students can easily access the structures online and explore them on their own.
- **Reviews of chemical principles** that underlie biochemical phenomena, including thermodynamics and equilibria, chemical kinetics, and oxidation–reduction reactions.
- **Sample calculations** that demonstrate how students can apply key equations to real data.

SAMPLE CALCULATION 10-1

Show that $\Delta G < 0$ when Ca^{2+} ions move from the endoplasmic reticulum (where $[Ca^{2+}] = 1$ mM) to the cytosol (where $[Ca^{2+}] = 0.1$ μM). Assume $\Delta\Psi = 0$.

The cytosol is *in* and the endoplasmic reticulum is *out*.

$$\Delta G = RT \ln \frac{[Ca^{2+}]_{in}}{[Ca^{2+}]_{out}} = RT \ln \frac{10^{-7}}{10^{-3}}$$

$$= RT(-9.2)$$

Hence, ΔG is negative.

WPLS See Sample Calculation Videos.

- **Boxes to highlight topics** that link students to areas beyond basic biochemistry, such as ocean acidification (Box 2-1), production of complex molecules via polyketide synthesis (Box 20-3), and the intestinal microbiome (Box 22-1).

  Biochemistry in Health and Disease essays highlight the importance of biochemistry in the clinic by focusing on the molecular mechanisms of diseases and their treatment.

  Perspectives in Biochemistry provide enrichment material that would otherwise interrupt the flow of the text. Instead, the material is set aside so that students can appreciate some of the experimental methods and practical applications of biochemistry.

  Pathways of Discovery profile pioneers in various fields, giving students a glimpse of the personalities and scientific challenges that have shaped modern biochemistry.
- **Caduceus symbols** to highlight relevant in-text discussions of medical, health, or drug-related topics. These include common diseases such as diabetes and neurodegenerative diseases as well as lesser known topics that reveal interesting aspects of biochemistry.
- **Expanded chapter summaries** grouped by major section headings, again guiding students to focus on the most important points within each section.
- **More to Explore guides** consisting of a set of questions at the end of each chapter that either extend the material presented in the text or prompt students to reach further and discover topics not covered in the textbook. In addition, WileyPLUS Learning Space offers over 1,000 concept-based questions that can be assigned and automatically graded, providing students with additional valuable practice opportunities.
- Boldfaced **Key terms**.
- **List of key terms** at the end of each chapter, with the **page numbers** where the terms are first defined.
- Comprehensive **glossary containing over 1200 terms**.
- List of **references** for each chapter, selected for their relevance and user-friendliness.

Organization

As in the fourth edition, the text begins with two introductory chapters that discuss the origin of life, evolution, thermodynamics, the properties of water, and acid–base chemistry. Nucleotides and nucleic acids are covered in Chapter 3, since an understanding of the structures and functions of these molecules supports the subsequent study of protein evolution and metabolism.

Four chapters (4 through 7) explore amino acid chemistry, methods for analyzing protein structure and sequence, secondary through quaternary protein structure, protein folding and stability, and structure–function relationships in hemoglobin, muscle proteins, and antibodies. Chapter 8 (Carbohydrates), Chapter 9 (Lipids and Biological Membranes), and Chapter 10 (Membrane Transport) round out the coverage of the basic molecules of life.

The next three chapters examine proteins in action, introducing students first to enzyme mechanisms (Chapter 11), then shepherding them through discussions of enzyme kinetics, the effects of inhibitors, and enzyme regulation (Chapter 12). These themes are continued in Chapter 13, which describes the components of signal transduction pathways.

Metabolism is covered in a series of chapters, beginning with an introductory chapter (Chapter 14) that provides an overview of metabolic pathways, the thermodynamics of "high-energy" compounds, and redox chemistry. Central metabolic pathways are presented in detail (e.g., glycolysis, glycogen metabolism, and the citric acid cycle in Chapters 15–17) so that students can appreciate how individual enzymes catalyze reactions and work in concert to perform complicated biochemical tasks. Chapters 18 (Electron Transport and Oxidative Phosphorylation) and 19 (Photosynthesis) complete a sequence that emphasizes energy-acquiring pathways. Not all pathways are covered in full detail, particularly those related to lipids (Chapter 20), amino acids (Chapter 21), and nucleotides (Chapter 23). Instead, key enzymatic reactions are highlighted for their interesting chemistry or regulatory importance. Chapter 22, on the integration of metabolism, discusses organ specialization and metabolic regulation in mammals.

Six chapters describe the biochemistry of nucleic acids, starting with their metabolism (Chapter 23) and the structure of DNA and its interactions with proteins (Chapter 24). Chapters 25–27 cover the processes of DNA replication, transcription, and translation, highlighting the functions of the RNA and protein molecules that carry out these processes. Chapter 28 deals with a variety of mechanisms for regulating gene expression, including the histone code and the roles of transcription factors and their relevance to cancer and development.

Additional Support

Student Companion to Fundamentals of Biochemistry, 5th Edition

ISBN 978 111 926793 5

This enhanced study resource by Akif Uzman, University of Houston-Downtown, Jerry Johnson, University of Houston-Downtown, William Widger, University of Houston, Joseph Eichberg, University of Houston, Donald Voet, Judith Voet, and Charlotte Pratt, is designed to help students master basic concepts and hone their analytical skills. Each chapter contains a summary, a review of essential concepts, and additional problems. The fifth edition features *Behind the Equations* sections and *Calculation Analogies* that provide connections between key equations in the text and their applications. The authors have also included new categories of questions for the student:

- *Graphical analysis questions,* which focus on quantitative principles and challenge students to apply their knowledge.
- *Play It Forward questions* that draw specifically on knowledge obtained in previous chapters.

The Student Companion contains complete solutions to all of the end of chapter problems in the text.

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The structures that make up this *Paramecium* cell, and the processes that occur within it, can be explained in chemical terms. All cells contain similar types of macromolecules and undergo similar chemical reactions to acquire energy, grow, communicate, and reproduce.

CHAPTER 1

Introduction to the Chemistry of Life

Chapter Contents

Biochemistry is, literally, the study of the chemistry of life. Although it overlaps other disciplines, including cell biology, genetics, immunology, microbiology, pharmacology, and physiology, biochemistry is largely concerned with a limited number of issues:

1. What are the chemical and three-dimensional structures of biological molecules?
2. How do biological molecules interact with one another?
3. How does the cell synthesize and degrade biological molecules?
4. How is energy conserved and used by the cell?
5. What are the mechanisms for organizing biological molecules and coordinating their activities?
6. How is genetic information stored, transmitted, and expressed?

Biochemistry, like other modern sciences, relies on sophisticated instruments to dissect the architecture and operation of systems that are inaccessible to the human senses. In addition to the chemist's tools for separating, quantifying, and otherwise analyzing biological materials, biochemists take advantage of the uniquely biological aspects of their subject by examining the evolutionary histories of organisms, metabolic systems, and individual molecules. In addition to its obvious implications for human health, biochemistry reveals the workings of the natural world, allowing us to understand and appreciate the unique and mysterious condition that we call life. In this introductory chapter, we will review some aspects of chemistry and biology—including the basics of evolution, the different types of cells, and the elementary principles of thermodynamics—to help put biochemistry in context and to introduce some of the themes that recur throughout this book.

1 The Origin of Life

KEY CONCEPTS

- Biological molecules are constructed from a limited number of elements.
- Certain functional groups and linkages characterize different types of biomolecules.
- During chemical evolution, simple compounds condensed to form more complex molecules and polymers.
- Self-replicating molecules were subject to natural selection.

Certain biochemical features are common to all organisms: the way hereditary information is encoded and expressed, for example, and the way biological molecules are built and broken down for energy. The underlying genetic and biochemical unity of modern organisms implies that they are descended from a single ancestor. Although it is impossible to describe exactly how life first arose, paleontological and laboratory studies have provided some insights about the origin of life.

A Biological Molecules Arose from Inanimate Substances

Living matter consists of a relatively small number of elements (Table 1-1). For example, C, H, O, N, P, Ca, and S account for ~97% of the dry weight of the human body (humans and most other organisms are ~70% water). Living organisms may also contain trace amounts of many other elements, including B, F, Al, Si, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Br, Mo, Cd, I, and W, although not every organism makes use of each of these substances.

TABLE 1-1 Most Abundant Elements in the Human Body[a]

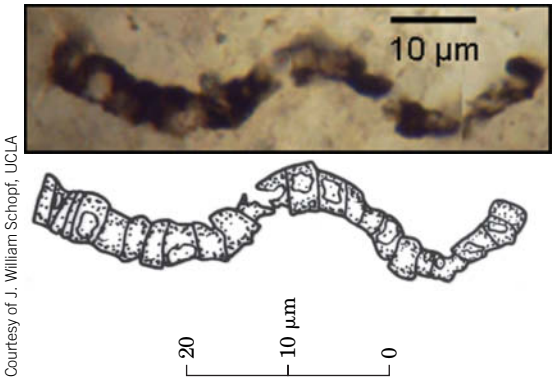
Element	Dry Weight (%)
C	61.7
N	11.0
O	9.3
H	5.7
Ca	5.0
P	3.3
K	1.3
S	1.0
Cl	0.7
Na	0.7
Mg	0.3

[a]Calculated from Frieden, E., *Sci. Am.* **227**(1), 54–55 (1972).

The earliest known fossil evidence of life is ~3.5 billion years old (Fig. 1-1). The preceding **prebiotic era**, which began with the formation of the earth ~4.6 billion years ago, left no direct record, but scientists can experimentally duplicate the sorts of chemical reactions that might have given rise to living organisms during that billion-year period.

The atmosphere of the early earth probably consisted of small, simple compounds such as H_2O, N_2, CO_2, and smaller amounts of CH_4 and NH_3. In the 1920s, Alexander Oparin and J. B. S. Haldane independently suggested that ultraviolet radiation from the sun or lightning discharges caused the molecules of the primordial atmosphere to react to form simple **organic** (carbon-containing) **compounds**. This process was replicated in 1953 by Stanley Miller and Harold Urey, who subjected a mixture of H_2O, CH_4, NH_3, and H_2 to an electric discharge for about a week. The resulting solution contained water-soluble organic compounds, including several amino acids (which are components of proteins) and other biochemically significant compounds.

The assumptions behind the Miller–Urey experiment, principally the composition of the gas used as a starting material, have been challenged by some

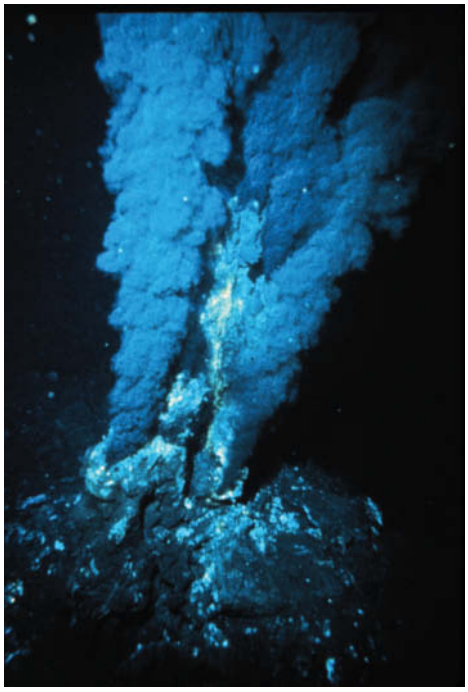


Courtesy of J. William Schopf, UCLA

FIG. 1-1 **Microfossil of filamentous bacterial cells.** This fossil (shown with an interpretive drawing) is from ~3.4-billion-year-old rock from Western Australia.

scientists who have suggested that the first biological molecules were generated in a quite different way: in the dark and under water. Hydrothermal vents in the ocean floor, which emit solutions of metal sulfides at temperatures as high as 400°C (Fig. 1-2), may have provided conditions suitable for the formation of amino acids and other small organic molecules from simple compounds present in seawater.

Whatever their actual origin, the early organic molecules became the precursors of an enormous variety of biological molecules. These can be classified in various ways, depending on their composition and chemical reactivity. A familiarity with organic chemistry is useful for recognizing the **functional groups** (reactive portions) of molecules as well as the **linkages** (bonding arrangements) among them, since these features ultimately determine the biological activity of the molecules. Some of the common functional groups and linkages in biological molecules are shown in Table 1-2.



OAR/National Undersea Research Program (NURP); NOAA

FIG. 1-2 A hydrothermal vent. Such ocean-floor formations are known as "black smokers" because the metal sulfides dissolved in the superheated water they emit precipitate on encountering the much cooler ocean water.

B Complex Self-Replicating Systems Evolved from Simple Molecules

During a period of chemical evolution, the prebiotic era, simple organic molecules condensed to form more complex molecules or combined end-to-end as **polymers** of repeating units. In a **condensation reaction**, the elements of water are lost. The rate of condensation of simple compounds to form a stable polymer must therefore be greater than the rate of **hydrolysis** (splitting by adding the elements of water; Fig. 1-3). In this prebiotic environment, minerals such as clays may have catalyzed polymerization reactions and sequestered the reaction products from water. The size and composition of prebiotic macromolecules would have been limited by the availability of small molecular starting materials, the efficiency with which they could be joined, and their resistance to degradation. The major biological polymers and their individual units **(monomers)** are given in Table 1-3.

Obviously, *combining different monomers and their various functional groups into a single large molecule increases the chemical versatility of that molecule,* allowing it to perform chemical feats beyond the reach of simpler molecules. (This principle of emergent properties can be expressed as "the whole is greater than the sum of its parts.") Separate macromolecules with **complementary arrangements** (reciprocal pairing) of functional groups can associate with each other (Fig. 1-4), giving rise to more complex molecular assemblies with an even greater range of functional possibilities.

Specific pairing between complementary functional groups permits one member of a pair to determine the identity and orientation of the other member. *Such complementarity makes it possible for a macromolecule to* ***replicate****, or copy itself, by directing the assembly of a new molecule from smaller complementary units.* Replication of a simple polymer with intramolecular complementarity is

GATEWAY CONCEPT Functional Groups

Different classes of biological molecules are characterized by different types of functional groups and linkages. A biological molecule may contain multiple functional groups.

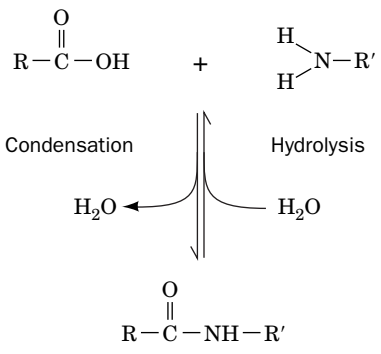


FIG. 1-3 Reaction of a carboxylic acid with an amine. The elements of water are released during condensation. In the reverse process—hydrolysis—water is added to cleave the amide bond. In living systems, condensation reactions are not freely reversible.

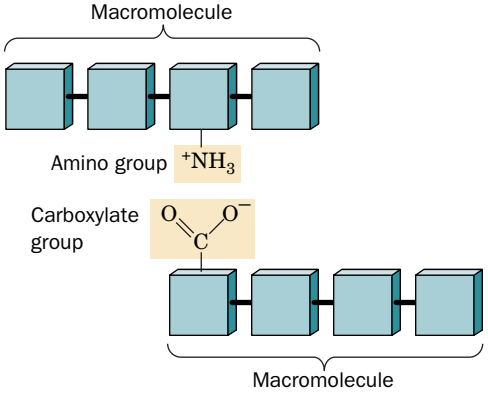
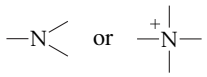
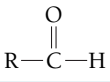
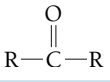
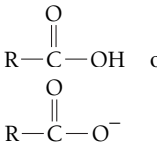
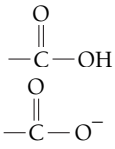
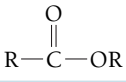
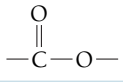
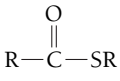
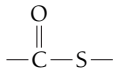
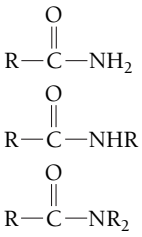
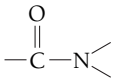
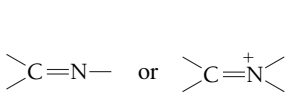
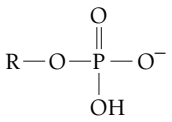
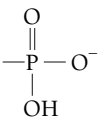
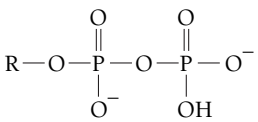
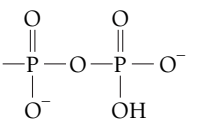
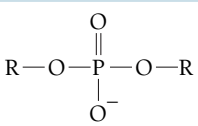
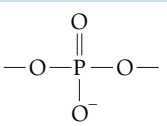


FIG. 1-4 Association of complementary molecules. The positively charged amino group interacts electrostatically with the negatively charged carboxylate group.

TABLE 1-2 Common Functional Groups and Linkages in Biochemistry

Compound Name	Structure[a]	Functional Group or Linkage
Amine[b]	RNH_2 or $R\overset{+}{N}H_3$ R_2NH or $R_2\overset{+}{N}H_2$ R_3N or $R_3\overset{+}{N}H$	 (amino group)
Alcohol	ROH	—OH (hydroxyl group)
Thiol	RSH	—SH (sulfhydryl group)
Ether	ROR	—O— (ether linkage)
Aldehyde		 (carbonyl group)
Ketone		 (carbonyl group)
Carboxylic acid[b]		 (carboxyl group) or (carboxylate group)
Ester		 (ester linkage)  (acyl group)[c]
Thioester		 (thioester linkage)  (acyl group)[c]
Amide		 (amido group)  (acyl group)[c]
Imine (Schiff base)[b]	$R{=}NH$ or $R{=}\overset{+}{N}H_2$ $R{=}NR$ or $R{=}\overset{+}{N}HR$	 (imino group)
Disulfide	R—S—S—R	—S—S— (disulfide linkage)
Phosphate ester[b]		 (phosphoryl group)
Diphosphate ester[b]		 (phosphoanhydride group)
Phosphate diester[b]		 (phosphodiester linkage)

[a]R represents any carbon-containing group. In a molecule with more than one R group, the groups may be the same or different.

[b]Under physiological conditions, these groups are ionized and hence bear a positive or negative charge.

[c]If attached to an atom other than carbon.

? **Cover the Structure column and draw the structure for each compound listed on the left. Do the same for each functional group or linkage.**

TABLE 1-3 Major Biological Polymers and Their Component Monomers

Polymer	Monomer
Protein (polypeptide)	Amino acid
Nucleic acid (polynucleotide)	Nucleotide
Polysaccharide (complex carbohydrate)	Monosaccharide (simple carbohydrate)

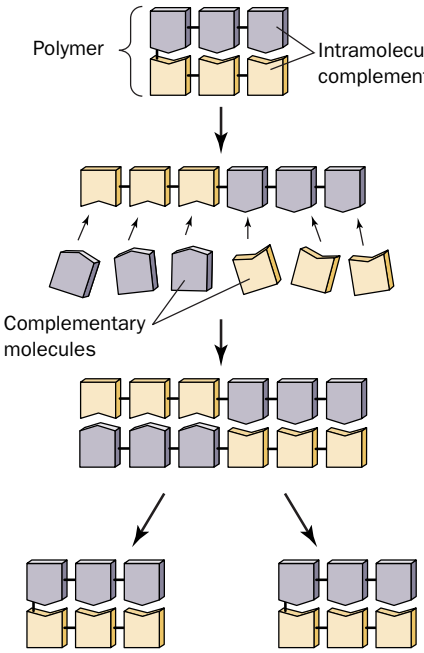


FIG. 1–5 Replication through complementarity. In this simple case, a polymer serves as a template for the assembly of a complementary molecule, which, because of intramolecular complementarity, is an exact copy of the original.

? **Distinguish the covalent bonds from the noncovalent interactions in this polymer.**

illustrated in Fig. 1-5. A similar phenomenon is central to the function of DNA, where the sequence of bases on one strand (e.g., A-C-G-T) absolutely specifies the sequence of bases on the strand to which it is paired (T-G-C-A). When DNA replicates, the two strands separate and direct the synthesis of complementary daughter strands. Complementarity is also the basis for transcribing DNA into RNA and for translating RNA into protein.

A critical moment in chemical evolution was the transition from systems of randomly generated molecules to systems in which molecules were organized and specifically replicated. Once macromolecules gained the ability to self-perpetuate, the primordial environment would have become enriched in molecules that were best able to survive and multiply. The first replicating systems were no doubt somewhat sloppy, with progeny molecules imperfectly complementary to their parents. Over time, **natural selection**, the competitive process by which reproductive preference is given to the better adapted, would have favored molecules that made more accurate copies of themselves.

CHECKPOINT

- Which four elements occur in virtually all biological molecules?
- Summarize the major stages of chemical evolution.
- Practice drawing a simple condensation and hydrolysis reaction.
- Explain why complementarity would have been necessary for the development of self-replicating molecules.

2 Cellular Architecture

KEY CONCEPTS

- Compartmentation of cells promotes efficiency by maintaining high local concentrations of reactants.
- Metabolic pathways evolved to synthesize molecules and generate energy.
- The simplest cells are prokaryotes.
- Eukaryotes are characterized by numerous membrane-bounded organelles, including a nucleus.
- The phylogenetic tree of life includes three domains: bacteria, archaea, and eukarya.
- Evolution occurs as natural selection acts on randomly occurring genetic variations among individuals.

The types of systems described so far would have had to compete with all the other components of the primordial earth for the available resources. A selective advantage would have accrued to a system that was sequestered and protected by boundaries of some sort. How these boundaries first arose, or even what they were made from, is obscure. One theory is that membranous **vesicles** (fluid-filled sacs) first attached to and then enclosed self-replicating systems. These vesicles would have become the first cells.

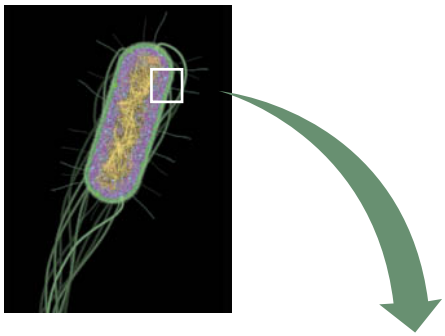
A Cells Carry Out Metabolic Reactions

The advantages of **compartmentation** are several. In addition to receiving some protection from adverse environmental forces, an enclosed system can maintain high local concentrations of components that would otherwise diffuse away. More concentrated substances can react more readily, leading to increased efficiency in polymerization and other types of chemical reactions.

A membrane-bounded compartment that protected its contents would gradually become quite different in composition from its surroundings. Modern cells contain high concentrations of ions, small molecules, and large molecular aggregates that are found only in traces—if at all—outside the cell. For example, a cell of the bacterium ***Escherichia coli* (*E. coli*)** contains millions of molecules, representing some 3000 to 6000 different compounds (**Fig. 1-6**). A typical animal cell may contain 100,000 different types of molecules.

Early cells depended on the environment to supply building materials. As some of the essential components in the prebiotic soup became scarce, natural selection favored organisms that developed **metabolic pathways,** mechanisms for synthesizing the required compounds from simpler but more abundant **precursors**. The first metabolic reactions may have used metal or clay **catalysts** (a catalyst is a substance that promotes a chemical reaction without itself undergoing a net change). In fact, metal ions are still at the heart of many chemical reactions in modern cells. Some catalysts may also have arisen from polymeric molecules that had the appropriate functional groups.

In general, biosynthetic reactions require energy; hence the first cellular reactions also needed an energy source. The eventual depletion of preexisting energy-rich substances in the prebiotic environment would have favored the development of energy-producing metabolic pathways. For example, photosynthesis evolved relatively early to take advantage of a practically inexhaustible energy supply, the sun. However, the accumulation of O_2 generated from H_2O



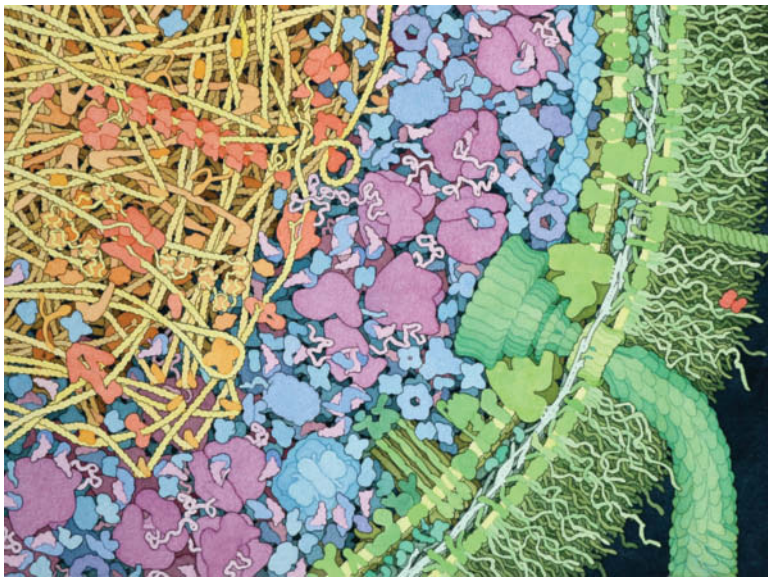


FIG. 1-6 Cross-section through an *E. coli* cell. The cytoplasm is packed with macromolecules. At this magnification (~1,000,000×), individual atoms are too small to resolve. The green structures on the right include the inner and outer membrane components along with a portion of a flagellum. Inside the cell, various proteins are shown in blue, and ribosomes are purple. The gold and orange structures represent DNA and DNA-binding proteins, respectively. In a living cell, the remaining spaces would be crowded with water and small molecules. [From Goodsell, D.S., *The Machinery of Life* (2nd ed.), Springer (2009). Reproduced with permission.]

by photosynthesis (the modern atmosphere is 21% O_2) presented an additional challenge to organisms adapted to life in an oxygen-poor atmosphere. Metabolic refinements eventually permitted organisms not only to avoid oxidative damage but also to use O_2 for oxidative metabolism, a much more efficient form of energy metabolism than anaerobic metabolism. Vestiges of ancient life can be seen in the anaerobic metabolism of certain modern organisms.

Early organisms that developed metabolic strategies to synthesize biological molecules, conserve and utilize energy in a controlled fashion, and replicate within a protective compartment were able to propagate in an ever-widening range of habitats. Adaptation of cells to different external conditions ultimately led to the present diversity of species. Specialization of individual cells also made it possible for groups of differentiated cells to work together in multicellular organisms.

B There Are Two Types of Cells: Prokaryotes and Eukaryotes

All modern organisms are based on the same morphological unit, the cell. There are two major classifications of cells: the **eukaryotes** (Greek: *eu,* good or true + *karyon,* kernel or nut), which have a membrane-enclosed **nucleus** encapsulating their DNA; and the **prokaryotes** (Greek: *pro,* before), which lack a nucleus. *Prokaryotes, comprising the various types of bacteria, have relatively simple structures and are almost all unicellular* (although they may form filaments or colonies of independent cells). *Eukaryotes, which are multicellular as well as unicellular, are vastly more complex than prokaryotes.* (**Viruses** are much simpler entities than cells and are not classified as living because they lack the metabolic apparatus to reproduce outside their host cells.)

Prokaryotes are the most numerous and widespread organisms on the earth. This is because their varied and often highly adaptable metabolisms suit them to an enormous variety of habitats. Prokaryotes range in size from 1 to 10 μm and have one of three basic shapes (**Fig. 1-7**): spheroidal (cocci), rodlike (bacilli), and helically coiled (spirilla). Except for an outer cell membrane, which in most cases is surrounded by a protective cell wall, nearly all prokaryotes lack cellular membranes. However, the prokaryotic **cytoplasm** (cell contents) is by no means a homogeneous soup. Different metabolic functions are carried out in different regions of the cytoplasm (Fig. 1-6). The best characterized prokaryote is *Escherichia coli,* a 2 μm by 1 μm rodlike bacterium that inhabits the mammalian colon.

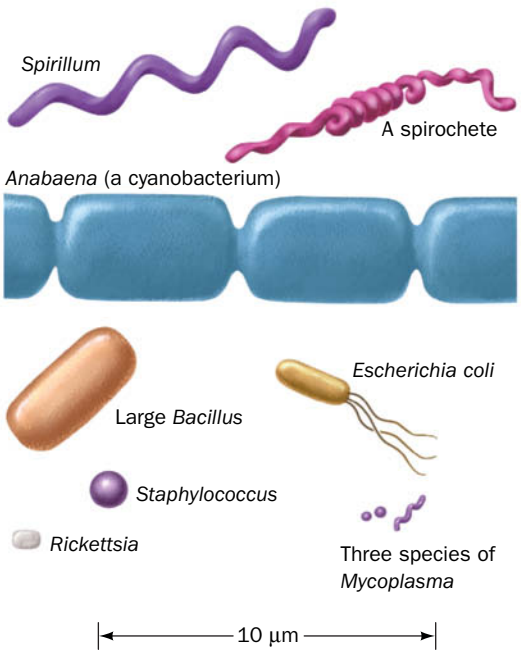


FIG. 1-7 Scale drawings of some prokaryotic cells.

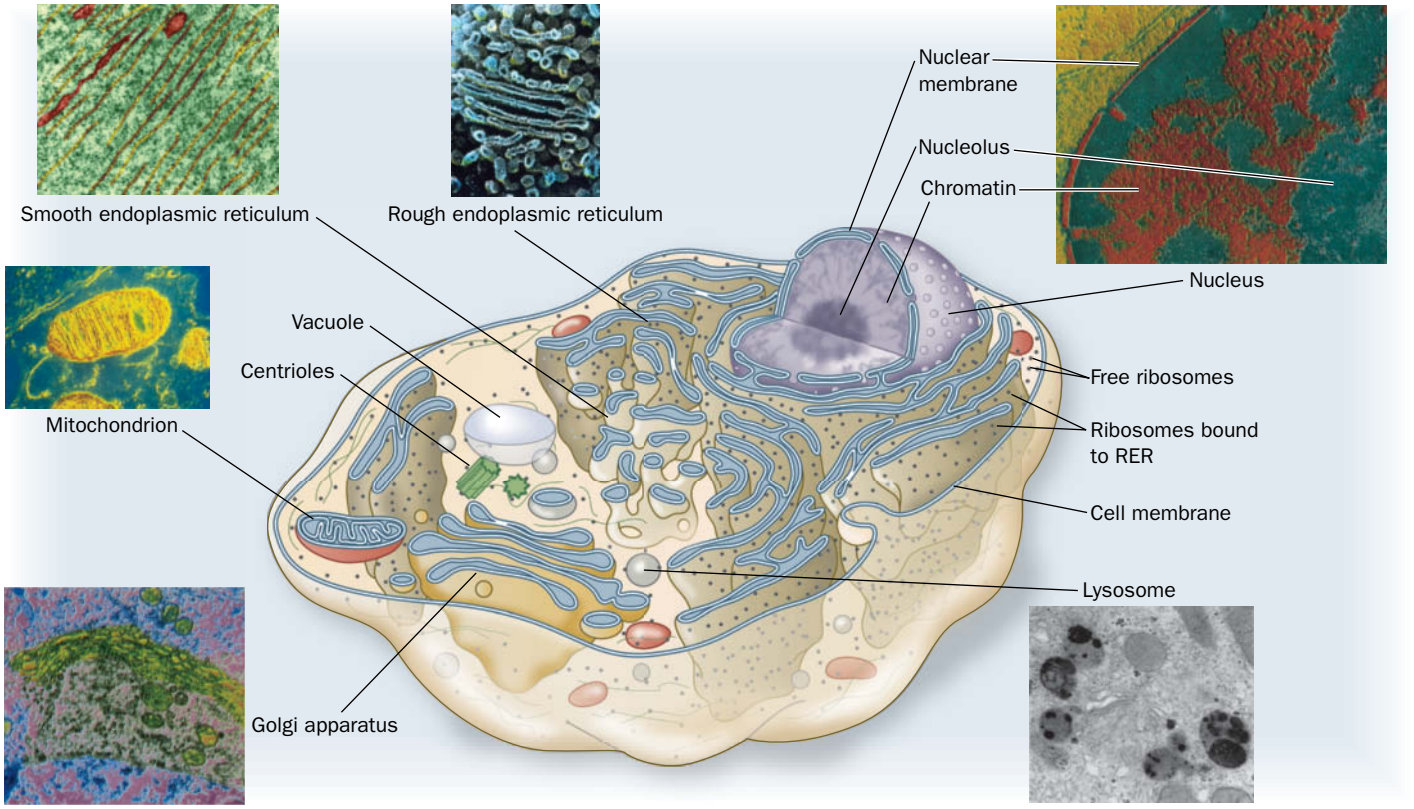


FIG. 1-8 Diagram of a typical animal cell with electron micrographs of its organelles. Membrane-bounded organelles include the nucleus, endoplasmic reticulum, lysosome, peroxisome (not pictured), mitochondrion, vacuole, and Golgi apparatus. The nucleus contains chromatin (a complex of DNA and protein) and the nucleolus (the site of ribosome synthesis). The rough endoplasmic reticulum is studded with ribosomes; the smooth endoplasmic reticulum is not. A pair of centrioles help organize cytoskeletal elements. A typical plant cell differs mainly by the presence of an outer cell wall and chloroplasts in the cytosol. [Smooth endoplasmic reticulum © Dennis Kunkel Microscopy, Inc./Phototake; rough endoplasmic reticulum © Pietro M. Motta & Tomonori Naguro/Photo Researchers, Inc.; nucleus © Tektoff-RM, CNRI/Photo Researchers; mitochondrion © CNRI/Photo Researchers; Golgi apparatus © Secchi-Lecaque/Roussel-UCLAF/CNRI/Photo Researchers; lysosome © Biophoto Associates/Photo Researchers.]

? **With the labels covered, name the parts of this eukaryotic cell.**

Eukaryotic cells are generally 10 to 100 μm in diameter and thus have a thousand to a million times the volume of typical prokaryotes. It is not size, however, but a profusion of membrane-enclosed **organelles** that best characterizes eukaryotic cells (**Fig. 1-8**). In addition to a nucleus, eukaryotes have an **endoplasmic reticulum**, the site of synthesis of many cellular components, some of which are subsequently modified in the **Golgi apparatus**. The bulk of aerobic metabolism takes place in **mitochondria** in almost all eukaryotes, and photosynthetic cells contain **chloroplasts**, which convert the energy of the sun's rays to chemical energy. Other organelles, such as **lysosomes** and **peroxisomes**, perform specialized functions. **Vacuoles**, which are more prominent in plant than in animal cells, usually function as storage depots. The **cytosol** (the cytoplasm minus its membrane-bounded organelles) is organized by the **cytoskeleton**, an extensive array of filaments that also gives the cell its shape and the ability to move.

The various organelles that compartmentalize eukaryotic cells represent a level of complexity that is largely lacking in prokaryotic cells. Nevertheless, prokaryotes are more efficient than eukaryotes in many respects. Prokaryotes have exploited the advantages of simplicity and miniaturization. Their rapid growth rates permit them to occupy ecological niches in which there may be drastic fluctuations of the available nutrients. In contrast, the complexity of eukaryotes, which renders them larger and more slowly growing than prokaryotes, gives them the competitive advantage in stable environments with limited resources. It is therefore erroneous to consider prokaryotes as evolutionarily primitive compared to eukaryotes. Both types of organisms are well adapted to their respective lifestyles.

C Molecular Data Reveal Three Evolutionary Domains of Organisms

The practice of lumping all prokaryotes in a single category based on what they lack—a nucleus—obscures their metabolic diversity and evolutionary history. Conversely, the remarkable morphological diversity of eukaryotic organisms (consider the anatomical differences among, say, an amoeba, an oak tree, and a human being) masks their fundamental similarity at the cellular level. Traditional taxonomic schemes (**taxonomy** is the science of biological classification), which are based on gross morphology, have proved inadequate to describe the actual relationships between organisms as revealed by their evolutionary history (**phylogeny**).

Biological classification schemes based on reproductive or developmental strategies more accurately reflect evolutionary history than those based solely on adult morphology. However, *phylogenetic relationships are best deduced by comparing polymeric molecules—RNA, DNA, or protein—from different organisms.* For example, analysis of RNA led Carl Woese to group all organisms into three domains (**Fig. 1-9**). The **archaea** (also known as **archaebacteria**) are a group of prokaryotes that are as distantly related to other prokaryotes (the **bacteria**, sometimes called **eubacteria**) as both groups are to eukaryotes (**eukarya**). The archaea include some unusual organisms: the **methanogens** (which produce CH_4), the **halobacteria** (which thrive in concentrated brine solutions), and certain **thermophiles** (which inhabit hot springs). The pattern of branches in Woese's diagram indicates the divergence of different types of organisms (each branch point represents a common ancestor). The three-domain scheme also shows that animals, plants, and fungi constitute only a small portion of all life-forms. Such phylogenetic trees supplement the fossil record, which provides a patchy record of life prior to about 600 million years before the present (multicellular organisms arose about 700–900 million years ago).

It is unlikely that eukaryotes are descended from a single prokaryote, because the differences among eubacteria, archaea, and eukaryotes are so profound. Instead, eukaryotes probably evolved from the association of archaebacterial and eubacterial cells. The eukaryotic genetic material includes features that suggest an archaebacterial origin. In addition, the mitochondria and chloroplasts of modern eukaryotic cells resemble eubacteria in size and shape, and both types of organelles contain their own genetic material and protein synthetic machinery. Evidently, as Lynn Margulis proposed, mitochondria and chloroplasts evolved from free-living eubacteria that formed **symbiotic** (mutually beneficial) relationships with a primordial eukaryotic cell (Box 1-1). In fact, certain eukaryotes that lack mitochondria or chloroplasts permanently harbor symbiotic bacteria.

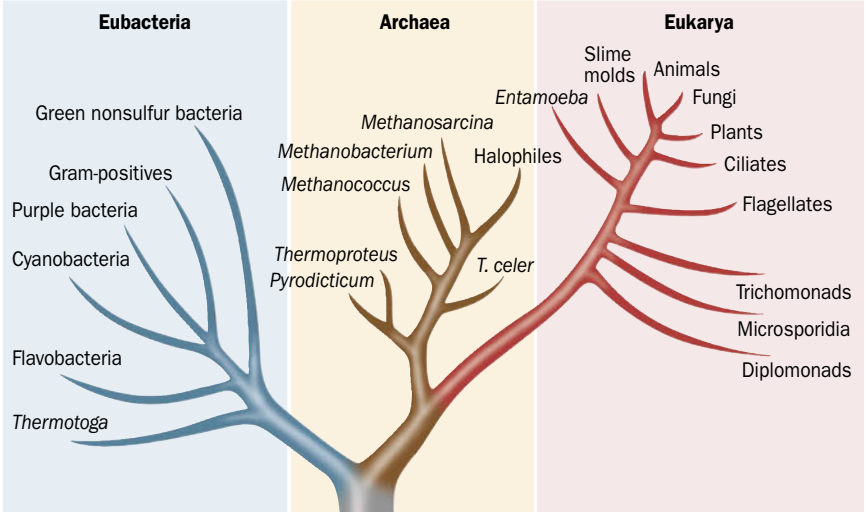


FIG. 1-9 Phylogenetic tree showing the three domains of organisms. The branches indicate the pattern of divergence from a common ancestor. The archaea are prokaryotes, like eubacteria, but share many features with eukaryotes. [After Wheelis, M.L., Kandler, O., and Woese, C.R., *Proc. Natl. Acad. Sci.* **89,** 2931 (1992).]