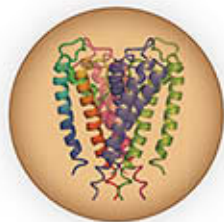
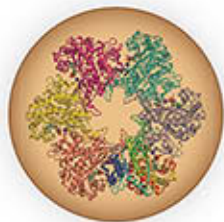
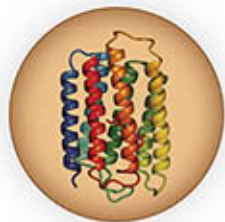


FUNDAMENTALS OF BIOCHEMISTRY

LIFE AT THE MOLECULAR LEVEL

5TH EDITION



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

WILEY

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

^aThe one-letter symbol for an undetermined or nonstandard amino acid is X.

Thermodynamic Constants and Conversion Factors

Joule (J)

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

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

Calorie (cal)

$$1 \text{ cal heats } 1 \text{ g of H}_2\text{O from } 14.5 \text{ to } 15.5^\circ\text{C}$$

$$1 \text{ cal} = 4.184 \text{ J}$$

Large calorie (Cal)

$$1 \text{ Cal} = 1 \text{ kcal} \quad 1 \text{ Cal} = 4184 \text{ J}$$

Avogadro's number (N)

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

Coulomb (C)

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

Faraday (F)

$$1 \mathcal{F} = N \text{ electron charges}$$

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

Kelvin temperature scale (K)

$$0 \text{ K} = \text{absolute zero} \quad 273.15 \text{ K} = 0^\circ\text{C}$$

Boltzmann constant (k_B)

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

Gas constant (R)

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

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

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

^aAUG 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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BRIEF CONTENTS

PART I INTRODUCTION

- 1 Introduction to the Chemistry of Life 1
- 2 Water 23

PART II BIOMOLECULES

- 3 Nucleotides, Nucleic Acids, and Genetic Information 42
- 4 Amino Acids 80
- 5 Proteins: Primary Structure 97
- 6 Proteins: Three-Dimensional Structure 131
- 7 Protein Function: Myoglobin and Hemoglobin, Muscle Contraction, and Antibodies 180
- 8 Carbohydrates 221
- 9 Lipids and Biological Membranes 245
- 10 Membrane Transport 293

PART III ENZYMES

- 11 Enzymatic Catalysis 322
- 12 Enzyme Kinetics, Inhibition, and Control 361
- 13 Biochemical Signaling 402

PART IV METABOLISM

- 14 Introduction to Metabolism 442
- 15 Glucose Catabolism 478
- 16 Glycogen Metabolism and Gluconeogenesis 523
- 17 Citric Acid Cycle 558
- 18 Electron Transport and Oxidative Phosphorylation 588
- 19 Photosynthesis: **Can be found at www.wiley.com/college/voet and in WileyPLUS Learning Space**
- 20 Lipid Metabolism 664
- 21 Amino Acid Metabolism 718
- 22 Mammalian Fuel Metabolism: Integration and Regulation 773

PART V GENE EXPRESSION AND REPLICATION

- 23 Nucleotide Metabolism 802
- 24 Nucleic Acid Structure 831
- 25 DNA Replication, Repair, and Recombination 879
- 26 Transcription and RNA Processing 938
- 27 Protein Synthesis 982
- 28 Regulation of Gene Expression 1033

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Glossary G-1

Index I-1

CONTENTS

Preface xv

Acknowledgments xix

PART I INTRODUCTION

1 Introduction to the Chemistry of Life 1

1 The Origin of Life 2

- A. Biological Molecules Arose from Inanimate Substances 2
- B. Complex Self-Replicating Systems Evolved from Simple Molecules 3

2 Cellular Architecture 5

- A. Cells Carry Out Metabolic Reactions 6
- B. There Are Two Types of Cells: Prokaryotes and Eukaryotes 7
- C. Molecular Data Reveal Three Evolutionary Domains of Organisms 9
- D. Organisms Continue to Evolve 10

3 Thermodynamics 11

- A. The First Law of Thermodynamics States That Energy Is Conserved 11
- B. The Second Law of Thermodynamics States That Entropy Tends to Increase 13
- C. The Free Energy Change Determines the Spontaneity of a Process 14
- D. Free Energy Changes Can Be Calculated from Reactant and Product Concentrations 16
- E. Life Achieves Homeostasis While Obeying the Laws of Thermodynamics 18

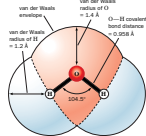
BOX 1-1 Pathways of Discovery **Lynn Margulis and the Theory of Endosymbiosis** 10

BOX 1-2 Perspectives in Biochemistry **Biochemical Conventions** 12

2 Water 23

1 Physical Properties of Water 24

- A. Water Is a Polar Molecule 24
- B. Hydrophilic Substances Dissolve in Water 27
- C. The Hydrophobic Effect Causes Nonpolar Substances to Aggregate in Water 27
- D. Water Moves by Osmosis and Solutes Move by Diffusion 29



2 Chemical Properties of Water 31

- A. Water Ionizes to Form H⁺ and OH⁻ 32
- B. Acids and Bases Alter the pH 33
- C. Buffers Resist Changes in pH 36

BOX 2-1 Perspectives in Biochemistry **The Consequences of Ocean Acidification** 34

BOX 2-2 Biochemistry in Health and Disease **The Blood Buffering System** 38

PART II BIOMOLECULES

3 Nucleotides, Nucleic Acids, and Genetic Information 42

1 Nucleotides 43

2 Introduction to Nucleic Acid Structure 46

- A. Nucleic Acids Are Polymers of Nucleotides 46

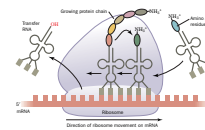
- B. DNA Forms a Double Helix 47
- C. RNA Is a Single-Stranded Nucleic Acid 50

3 Overview of Nucleic Acid Function 50

- A. DNA Carries Genetic Information 51
- B. Genes Direct Protein Synthesis 51

4 Nucleic Acid Sequencing 53

- A. Restriction Endonucleases Cleave DNA at Specific Sequences 54
- B. Electrophoresis Separates Nucleic Acids According to Size 56
- C. Traditional DNA Sequencing Uses the Chain-Terminator Method 57
- D. Next-Generation Sequencing Technologies Are Massively Parallel 59
- E. Entire Genomes Have Been Sequenced 62
- F. Evolution Results from Sequence Mutations 63



5 Manipulating DNA 66

- A. Cloned DNA Is an Amplified Copy 66
- B. DNA Libraries Are Collections of Cloned DNA 70
- C. DNA Is Amplified by the Polymerase Chain Reaction 71
- D. Recombinant DNA Technology Has Numerous Practical Applications 72

BOX 3-1 Pathways to Discovery **Francis Collins and the Gene for Cystic Fibrosis** 61

BOX 3-2 Perspectives in Biochemistry **DNA Fingerprinting** 73

BOX 3-3 Perspectives in Biochemistry **Ethical Aspects of Recombinant DNA Technology** 75

4 Amino Acids 80

1 Amino Acid Structure 81

- A. Amino Acids Are Dipolar Ions 84
- B. Peptide Bonds Link Amino Acids 84
- C. Amino Acid Side Chains Are Nonpolar, Polar, or Charged 84
- D. The pK Values of Ionizable Groups Depend on Nearby Groups 86
- E. Amino Acid Names Are Abbreviated 87

2 Stereochemistry 88

3 Amino Acid Derivatives 91

- A. Protein Side Chains May Be Modified 92
- B. Some Amino Acids Are Biologically Active 92

BOX 4-1 Pathways to Discovery **William C. Rose and the Discovery of Threonine** 81

BOX 4-2 Perspectives in Biochemistry **The RS System** 90

BOX 4-3 Perspectives in Biochemistry **Green Fluorescent Protein** 93

5 Proteins: Primary Structure 97

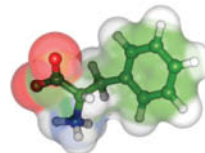
1 Polypeptide Diversity 98

2 Protein Purification and Analysis 99

- A. Purifying a Protein Requires a Strategy 100
- B. Salting Out Separates Proteins by Their Solubility 102
- C. Chromatography Involves Interaction with Mobile and Stationary Phases 103
- D. Electrophoresis Separates Molecules According to Charge and Size 106
- E. Ultracentrifugation Separates Macromolecules by Mass 108

3 Protein Sequencing 110

- A. The First Step Is to Separate Subunits 110
- B. The Polypeptide Chains Are Cleaved 114



- C. Edman Degradation Removes a Peptide's N-Terminal Amino Acid Residue 114
- D. Peptides Can Be Sequenced by Mass Spectrometry 117
- E. Reconstructed Protein Sequences Are Stored in Databases 118

4 Protein Evolution 119

- A. Protein Sequences Reveal Evolutionary Relationships 120
- B. Proteins Evolve by the Duplication of Genes or Gene Segments 122

BOX 5-1 Pathways of Discovery Frederick Sanger and Protein Sequencing 112

6 Proteins: Three-Dimensional Structure 131

1 Secondary Structure 132

- A. The Planar Peptide Group Limits Polypeptide Conformations 132
- B. The Most Common Regular Secondary Structures Are the α Helix and the β Sheet 135
- C. Fibrous Proteins Have Repeating Secondary Structures 140
- D. Most Proteins Include Nonrepetitive Structure 144

2 Tertiary Structure 145

- A. Protein Structures Are Determined by X-Ray Crystallography, Nuclear Magnetic Resonance, and Cryo-Electron Microscopy 145
- B. Side Chain Location Varies with Polarity 149
- C. Tertiary Structures Contain Combinations of Secondary Structure 150
- D. Structure Is Conserved More Than Sequence 154
- E. Structural Bioinformatics Provides Tools for Storing, Visualizing, and Comparing Protein Structural Information 155



3 Quaternary Structure and Symmetry 158

4 Protein Stability 160

- A. Proteins Are Stabilized by Several Forces 160
- B. Proteins Can Undergo Denaturation and Renaturation 162
- C. Proteins Are Dynamic 164

5 Protein Folding 165

- A. Proteins Follow Folding Pathways 165
- B. Molecular Chaperones Assist Protein Folding 168
- C. Many Diseases Are Caused by Protein Misfolding 173

BOX 6-1 Pathways of Discovery Linus Pauling and Structural Biochemistry 136

BOX 6-2 Biochemistry in Health and Disease Collagen Diseases 143

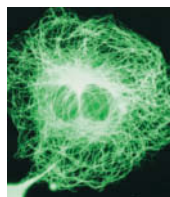
BOX 6-3 Perspectives in Biochemistry Thermostable Proteins 162

BOX 6-4 Perspectives in Biochemistry Protein Structure Prediction and Protein Design 167

7 Protein Function: Myoglobin and Hemoglobin, Muscle Contraction, and Antibodies 180

1 Oxygen Binding to Myoglobin and Hemoglobin 181

- A. Myoglobin Is a Monomeric Oxygen-Binding Protein 181
- B. Hemoglobin Is a Tetramer with Two Conformations 185
- C. Oxygen Binds Cooperatively to Hemoglobin 187
- D. Hemoglobin's Two Conformations Exhibit Different Affinities for Oxygen 190
- E. Mutations May Alter Hemoglobin's Structure and Function 197



2 Muscle Contraction 200

- A. Muscle Consists of Interdigitated Thick and Thin Filaments 201
- B. Muscle Contraction Occurs when Myosin Heads Walk Up Thin Filaments 208
- C. Actin Forms Microfilaments in Nonmuscle Cells 210

3 Antibodies 212

- A. Antibodies Have Constant and Variable Regions 212
- B. Antibodies Recognize a Huge Variety of Antigens 214

BOX 7-1 Perspectives in Biochemistry Other Oxygen-Transport Proteins 185

BOX 7-2 Pathways of Discovery Max Perutz and the Structure and Function of Hemoglobin 186

BOX 7-3 Biochemistry in Health and Disease High-Altitude Adaptation 195

BOX 7-4 Pathways of Discovery Hugh Huxley and the Sliding Filament Model 203

BOX 7-5 Perspectives in Biochemistry Monoclonal Antibodies 216

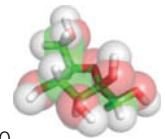
8 Carbohydrates 221

1 Monosaccharides 222

- A. Monosaccharides Are Aldoses or Ketoses 222
- B. Monosaccharides Vary in Configuration and Conformation 223
- C. Sugars Can Be Modified and Covalently Linked 225

2 Polysaccharides 228

- A. Lactose and Sucrose Are Disaccharides 228
- B. Cellulose and Chitin Are Structural Polysaccharides 230
- C. Starch and Glycogen Are Storage Polysaccharides 231
- D. Glycosaminoglycans Form Highly Hydrated Gels 232



3 Glycoproteins 234

- A. Proteoglycans Contain Glycosaminoglycans 235
- B. Bacterial Cell Walls Are Made of Peptidoglycan 235
- C. Many Eukaryotic Proteins Are Glycosylated 238
- D. Oligosaccharides May Determine Glycoprotein Structure, Function, and Recognition 240

BOX 8-1 Biochemistry in Health and Disease Lactose Intolerance 228

BOX 8-2 Perspectives in Biochemistry Artificial Sweeteners 229

BOX 8-3 Biochemistry in Health and Disease Peptidoglycan-Specific Antibiotics 238

9 Lipids and Biological Membranes 245

1 Lipid Classification 246

- A. The Properties of Fatty Acids Depend on Their Hydrocarbon Chains 246
- B. Triacylglycerols Contain Three Esterified Fatty Acids 248
- C. Glycerophospholipids Are Amphiphilic 249
- D. Sphingolipids Are Amino Alcohol Derivatives 252
- E. Steroids Contain Four Fused Rings 254
- F. Other Lipids Perform a Variety of Metabolic Roles 256

2 Lipid Bilayers 259

- A. Bilayer Formation Is Driven by the Hydrophobic Effect 259
- B. Lipid Bilayers Have Fluidlike Properties 260

3 Membrane Proteins 262

- A. Integral Membrane Proteins Interact with Hydrophobic Lipids 262
- B. Lipid-Linked Proteins Are Anchored to the Bilayer 267
- C. Peripheral Proteins Associate Loosely with Membranes 268

4 Membrane Structure and Assembly 269

- A. The Fluid Mosaic Model Accounts for Lateral Diffusion 269
- B. The Membrane Skeleton Helps Define Cell Shape 271
- C. Membrane Lipids Are Distributed Asymmetrically 274
- D. The Secretory Pathway Generates Secreted and Transmembrane Proteins 276
- E. Intracellular Vesicles Transport Proteins 280
- F. Proteins Mediate Vesicle Fusion 284

BOX 9-1 Biochemistry in Health and Disease Lung Surfactant 251

BOX 9-2 Pathways of Discovery Richard Henderson and the Structure of Bacteriorhodopsin 265

BOX 9-3 Biochemistry in Health and Disease Tetanus and Botulinum Toxins Specifically Cleave SNAREs 286

10 Membrane Transport 293

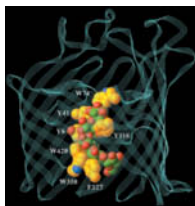
1 Thermodynamics of Transport 294

2 Passive-Mediated Transport 295

- A. Ionophores Carry Ions across Membranes 295
- B. Porins Contain β Barrels 297
- C. Ion Channels Are Highly Selective 297
- D. Aquaporins Mediate the Transmembrane Movement of Water 304
- E. Transport Proteins Alternate between Two Conformations 305

3 Active Transport 309

- A. The $(\text{Na}^+-\text{K}^+)\text{-ATPase}$ Transports Ions in Opposite Directions 310
- B. The $\text{Ca}^{2+}\text{-ATPase}$ Pumps Ca^{2+} Out of the Cytosol 312
- C. ABC Transporters Are Responsible for Drug Resistance 314
- D. Active Transport May Be Driven by Ion Gradients 315



BOX 10-1 Perspectives in Biochemistry Gap Junctions 306

BOX 10-2 Perspectives in Biochemistry Differentiating Mediated and Nonmediated Transport 308

BOX 10-3 Biochemistry in Health and Disease The Action of Cardiac Glycosides 312

PART III ENZYMES

11 Enzymatic Catalysis 322

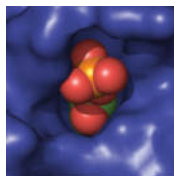
1 General Properties of Enzymes 323

- A. Enzymes Are Classified by the Type of Reaction They Catalyze 324
- B. Enzymes Act on Specific Substrates 324
- C. Some Enzymes Require Cofactors 326

2 Activation Energy and the Reaction Coordinate 327

3 Catalytic Mechanisms 330

- A. Acid–Base Catalysis Occurs by Proton Transfer 330
- B. Covalent Catalysis Usually Requires a Nucleophile 334
- C. Metal Ion Cofactors Act as Catalysts 335
- D. Catalysis Can Occur through Proximity and Orientation Effects 336
- E. Enzymes Catalyze Reactions by Preferentially Binding the Transition State 338



4 Lysozyme 339

- A. Lysozyme's Catalytic Site Was Identified through Model Building 340
- B. The Lysozyme Reaction Proceeds via a Covalent Intermediate 342

5 Serine Proteases 345

- A. Active Site Residues Were Identified by Chemical Labeling 345
- B. X-Ray Structures Provide Information about Catalysis, Substrate Specificity, and Evolution 346
- C. Serine Proteases Use Several Catalytic Mechanisms 350
- D. Zymogens Are Inactive Enzyme Precursors 355

BOX 11-1 Perspectives in Biochemistry Drawing Reaction Mechanisms 331

BOX 11-2 Perspectives in Biochemistry Effects of pH on Enzyme Activity 332

BOX 11-3 Biochemistry in Health and Disease Nerve Poisons 346

BOX 11-4 Biochemistry in Health and Disease The Blood Coagulation Cascade 356

12 Enzyme Kinetics, Inhibition, and Control 361

1 Reaction Kinetics 362

- A. Chemical Kinetics Is Described by Rate Equations 362
- B. Enzyme Kinetics Often Follows the Michaelis–Menten Equation 364
- C. Kinetic Data Can Provide Values of V_{max} and K_M 369
- D. Bisubstrate Reactions Follow One of Several Rate Equations 372

2 Enzyme Inhibition 374

- A. Competitive Inhibition Involves Inhibitor Binding at an Enzyme's Substrate Binding Site 374

- B. Uncompetitive Inhibition Involves Inhibitor Binding to the Enzyme–Substrate Complex 380
- C. Mixed Inhibition Involves Inhibitor Binding to Both the Free Enzyme and the Enzyme–Substrate Complex 381

3 Control of Enzyme Activity 382

- A. Allosteric Control Involves Binding at a Site Other than the Active Site 383
- B. Control by Covalent Modification Usually Involves Protein Phosphorylation 387

4 Drug Design 391

- A. Drug Discovery Employs a Variety of Techniques 392
- B. A Drug's Bioavailability Depends on How It Is Absorbed and Transported in the Body 393
- C. Clinical Trials Test for Efficacy and Safety 393
- D. Cytochromes P450 Are Often Implicated in Adverse Drug Reactions 395

BOX 12-1 Pathways of Discovery J.B.S. Haldane and Enzyme Action 366

BOX 12-2 Perspectives in Biochemistry Kinetics and Transition State Theory 369

BOX 12-3 Biochemistry in Health and Disease HIV Enzyme Inhibitors 376

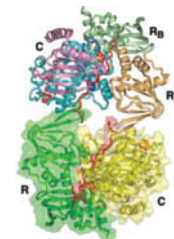
13 Biochemical Signaling 402

1 Hormones 403

- A. Pancreatic Islet Hormones Control Fuel Metabolism 404
- B. Epinephrine and Norepinephrine Prepare the Body for Action 405
- C. Steroid Hormones Regulate a Wide Variety of Metabolic and Sexual Processes 406
- D. Growth Hormone Binds to Receptors in Muscle, Bone, and Cartilage 407

2 Receptor Tyrosine Kinases 408

- A. Receptor Tyrosine Kinases Transmit Signals across the Cell Membrane 409
- B. Kinase Cascades Relay Signals to the Nucleus 412
- C. Some Receptors Are Associated with Nonreceptor Tyrosine Kinases 417
- D. Protein Phosphatases Are Signaling Proteins in Their Own Right 420



3 Heterotrimeric G Proteins 423

- A. G-Protein–Coupled Receptors Contain Seven Transmembrane Helices 424
- B. Heterotrimeric G Proteins Dissociate on Activation 426
- C. Adenylate Cyclase Synthesizes cAMP to Activate Protein Kinase A 427
- D. Phosphodiesterases Limit Second Messenger Activity 432

4 The Phosphoinositide Pathway 432

- A. Ligand Binding Results in the Cytoplasmic Release of the Second Messengers IP_3 and Ca^{2+} 433
- B. Calmodulin Is a Ca^{2+} -Activated Switch 434
- C. DAG Is a Lipid-Soluble Second Messenger That Activates Protein Kinase C 436
- D. Epilog: Complex Systems Have Emergent Properties 437

BOX 13-1 Pathways of Discovery Rosalyn Yalow and the Radioimmunoassay (RIA) 404

BOX 13-2 Perspectives in Biochemistry Receptor–Ligand Binding Can Be Quantitated 410

BOX 13-3 Biochemistry in Health and Disease Oncogenes and Cancer 416

BOX 13-4 Biochemistry in Health and Disease Drugs and Toxins That Affect Cell Signaling 431

PART IV METABOLISM

14 Introduction to Metabolism 442

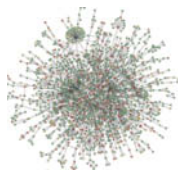
1 Overview of Metabolism 443

- A. Nutrition Involves Food Intake and Use 443

- B. Vitamins and Minerals Assist Metabolic Reactions 444
- C. Metabolic Pathways Consist of Series of Enzymatic Reactions 445
- D. Thermodynamics Dictates the Direction and Regulatory Capacity of Metabolic Pathways 449
- E. Metabolic Flux Must Be Controlled 450

2 “High-Energy” Compounds 452

- A. ATP Has a High Phosphoryl Group-Transfer Potential 454
- B. Coupled Reactions Drive Endergonic Processes 455
- C. Some Other Phosphorylated Compounds Have High Phosphoryl Group-Transfer Potentials 457
- D. Thioesters Are Energy-Rich Compounds 460



3 Oxidation–Reduction Reactions 462

- A. NAD⁺ and FAD Are Electron Carriers 462
- B. The Nernst Equation Describes Oxidation–Reduction Reactions 463
- C. Spontaneity Can Be Determined by Measuring Reduction Potential Differences 465

4 Experimental Approaches to the Study of Metabolism 468

- A. Labeled Metabolites Can Be Traced 468
- B. Studying Metabolic Pathways Often Involves Perturbing the System 470
- C. Systems Biology Has Entered the Study of Metabolism 471

BOX 14-1 Perspectives in Biochemistry Oxidation States of Carbon 447

BOX 14-2 Pathways of Discovery Fritz Lipmann and “High-Energy” Compounds 453

BOX 14-3 Perspectives in Biochemistry ATP and ΔG 455

15 Glucose Catabolism 478

1 Overview of Glycolysis 479

2 The Reactions of Glycolysis 481

- A. Hexokinase Uses the First ATP 482
- B. Phosphoglucose Isomerase Converts Glucose-6-Phosphate to Fructose-6-Phosphate 482
- C. Phosphofruktokinase Uses the Second ATP 484
- D. Aldolase Converts a 6-Carbon Compound to Two 3-Carbon Compounds 484
- E. Triose Phosphate Isomerase Interconverts Dihydroxyacetone Phosphate and Glyceraldehyde-3-Phosphate 485
- F. Glyceraldehyde-3-Phosphate Dehydrogenase Forms the First “High-Energy” Intermediate 489
- G. Phosphoglycerate Kinase Generates the First ATP 491
- H. Phosphoglycerate Mutase Interconverts 3-Phosphoglycerate and 2-Phosphoglycerate 492
- I. Enolase Forms the Second “High-Energy” Intermediate 493
- J. Pyruvate Kinase Generates the Second ATP 494



3 Fermentation: The Anaerobic Fate of Pyruvate 497

- A. Homolactic Fermentation Converts Pyruvate to Lactate 498
- B. Alcoholic Fermentation Converts Pyruvate to Ethanol and CO₂ 498
- C. Fermentation Is Energetically Favorable 501

4 Regulation of Glycolysis 502

- A. Phosphofruktokinase Is the Major Flux-Controlling Enzyme of Glycolysis in Muscle 503
- B. Substrate Cycling Fine-Tunes Flux Control 506

5 Metabolism of Hexoses Other than Glucose 508

- A. Fructose Is Converted to Fructose-6-Phosphate or Glyceraldehyde-3-Phosphate 508
- B. Galactose Is Converted to Glucose-6-Phosphate 510
- C. Mannose Is Converted to Fructose-6-Phosphate 512

6 The Pentose Phosphate Pathway 512

- A. Oxidative Reactions Produce NADPH in Stage 1 514
- B. Isomerization and Epimerization of Ribulose-5-Phosphate Occur in Stage 2 515

- C. Stage 3 Involves Carbon–Carbon Bond Cleavage and Formation 515
- D. The Pentose Phosphate Pathway Must Be Regulated 518

BOX 15-1 Pathways of Discovery Otto Warburg and Studies of Metabolism 479

BOX 15-2 Perspectives in Biochemistry Synthesis of 2,3-Bisphosphoglycerate in Erythrocytes and Its Effect on the Oxygen Carrying Capacity of the Blood 494

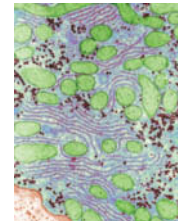
BOX 15-3 Perspectives in Biochemistry Glycolytic ATP Production in Muscle 502

BOX 15-4 Biochemistry in Health and Disease Glucose-6-Phosphate Dehydrogenase Deficiency 518

16 Glycogen Metabolism and Gluconeogenesis 523

1 Glycogen Breakdown 524

- A. Glycogen Phosphorylase Degrades Glycogen to Glucose-1-Phosphate 525
- B. Glycogen Debranching Enzyme Acts as a Glucosyltransferase 528
- C. Phosphoglucomutase Interconverts Glucose-1-Phosphate and Glucose-6-Phosphate 529



2 Glycogen Synthesis 532

- A. UDP–Glucose Pyrophosphorylase Activates Glucosyl Units 532
- B. Glycogen Synthase Extends Glycogen Chains 533
- C. Glycogen Branching Enzyme Transfers Seven-Residue Glycogen Segments 535

3 Control of Glycogen Metabolism 536

- A. Glycogen Phosphorylase and Glycogen Synthase Are under Allosteric Control 536
- B. Glycogen Phosphorylase and Glycogen Synthase Undergo Control by Covalent Modification 536
- C. Glycogen Metabolism Is Subject to Hormonal Control 542

4 Gluconeogenesis 544

- A. Pyruvate Is Converted to Phosphoenolpyruvate in Two Steps 545
- B. Hydrolytic Reactions Bypass Irreversible Glycolytic Reactions 549
- C. Gluconeogenesis and Glycolysis Are Independently Regulated 549

5 Other Carbohydrate Biosynthetic Pathways 551

BOX 16-1 Pathways of Discovery Carl and Gerty Cori and Glucose Metabolism 526

BOX 16-2 Biochemistry in Health and Disease Glycogen Storage Diseases 530

BOX 16-3 Perspectives in Biochemistry Optimizing Glycogen Structure 537

BOX 16-4 Perspectives in Biochemistry Lactose Synthesis 552

17 Citric Acid Cycle 558

1 Overview of the Citric Acid Cycle 559

2 Synthesis of Acetyl-Coenzyme A 562

- A. Pyruvate Dehydrogenase Is a Multienzyme Complex 562
- B. The Pyruvate Dehydrogenase Complex Catalyzes Five Reactions 564

3 Enzymes of the Citric Acid Cycle 568

- A. Citrate Synthase Joins an Acetyl Group to Oxaloacetate 568
- B. Aconitase Interconverts Citrate and Isocitrate 570
- C. NAD⁺-Dependent Isocitrate Dehydrogenase Releases CO₂ 571
- D. α -Ketoglutarate Dehydrogenase Resembles Pyruvate Dehydrogenase 572
- E. Succinyl-CoA Synthetase Produces GTP 572
- F. Succinate Dehydrogenase Generates FADH₂ 574
- G. Fumarase Produces Malate 574
- H. Malate Dehydrogenase Regenerates Oxaloacetate 574

4 Regulation of the Citric Acid Cycle 575

- A. Pyruvate Dehydrogenase Is Regulated by Product Inhibition and Covalent Modification 576

- B. Three Enzymes Control the Rate of the Citric Acid Cycle 577
- 5 Reactions Related to the Citric Acid Cycle** 579
- A. Other Pathways Use Citric Acid Cycle Intermediates 580
 - B. Some Reactions Replenish Citric Acid Cycle Intermediates 581
 - C. The Glyoxylate Cycle Shares Some Steps with the Citric Acid Cycle 582

BOX 17-1 Pathways of Discovery Hans Krebs and the Citric Acid Cycle 561

BOX 17-2 Biochemistry in Health and Disease Arsenic Poisoning 568

BOX 17-3 Perspectives in Biochemistry Evolution of the Citric Acid Cycle 582

18 Electron Transport and Oxidative Phosphorylation 588

1 The Mitochondrion 589

- A. Mitochondria Contain a Highly Folded Inner Membrane 590
- B. Ions and Metabolites Enter Mitochondria via Transporters 591

2 Electron Transport 593

- A. Electron Transport Is an Exergonic Process 593
- B. Electron Carriers Operate in Sequence 594
- C. Complex I Accepts Electrons from NADH 597
- D. Complex II Contributes Electrons to Coenzyme Q 601
- E. Complex III Translocates Protons via the Q Cycle 602
- F. Complex IV Reduces Oxygen to Water 607

3 Oxidative Phosphorylation 609

- A. The Chemiosmotic Theory Links Electron Transport to ATP Synthesis 610
- B. ATP Synthase Is Driven by the Flow of Protons 613
- C. The P/O Ratio Relates the Amount of ATP Synthesized to the Amount of Oxygen Reduced 618
- D. Oxidative Phosphorylation Can Be Uncoupled from Electron Transport 619

4 Control of Oxidative Metabolism 620

- A. The Rate of Oxidative Phosphorylation Depends on the ATP and NADH Concentrations 622
- B. Aerobic Metabolism Has Some Disadvantages 623

BOX 18-1 Perspectives in Biochemistry Cytochromes Are Electron-Transport Heme Proteins 602

BOX 18-2 Pathways of Discovery Peter Mitchell and the Chemiosmotic Theory 611

BOX 18-3 Perspectives in Biochemistry Bacterial Electron Transport and Oxidative Phosphorylation 612

BOX 18-4 Perspectives in Biochemistry Uncoupling in Brown Adipose Tissue Generates Heat 621

BOX 18-5 Biochemistry in Health and Disease Oxygen Deprivation in Heart Attack and Stroke 625

19 Photosynthesis 630

1 Chloroplasts 631

- A. The Light Reactions Take Place in the Thylakoid Membrane 631
- B. Pigment Molecules Absorb Light 632

2 The Light Reactions 635

- A. Light Energy Is Transformed to Chemical Energy 635
- B. Electron Transport in Photosynthetic Bacteria Follows a Circular Path 637
- C. Two-Center Electron Transport Is a Linear Pathway That Produces O₂ and NADPH 639
- D. The Proton Gradient Drives ATP Synthesis by Photophosphorylation 650

3 The Dark Reactions 651

- A. The Calvin Cycle Fixes CO₂ 651
- B. Calvin Cycle Products Are Converted to Starch, Sucrose, and Cellulose 655

- C. The Calvin Cycle Is Controlled Indirectly by Light 656

- D. Photorespiration Competes with Photosynthesis 658

BOX 19-1 Perspectives in Biochemistry Segregation of PSI and PSII 649

CHAPTER 19 can be found at www.wiley.com/college/voet and in WileyPLUS Learning Space **WPLS**

20 Lipid Metabolism 664

1 Lipid Digestion, Absorption, and Transport 664

- A. Triacylglycerols Are Digested before They Are Absorbed 665
- B. Lipids Are Transported as Lipoproteins 667

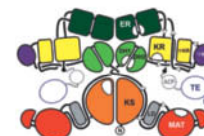
2 Fatty Acid Oxidation 671

- A. Fatty Acids Are Activated by Their Attachment to Coenzyme A 672
- B. Carnitine Carries Acyl Groups across the Mitochondrial Membrane 672
- C. β Oxidation Degrades Fatty Acids to Acetyl-CoA 674
- D. Oxidation of Unsaturated Fatty Acids Requires Additional Enzymes 676
- E. Oxidation of Odd-Chain Fatty Acids Yields Propionyl-CoA 678
- F. Peroxisomal β Oxidation Differs from Mitochondrial β Oxidation 684

3 Ketone Bodies 685

4 Fatty Acid Biosynthesis 686

- A. Mitochondrial Acetyl-CoA Must Be Transported into the Cytosol 687
- B. Acetyl-CoA Carboxylase Produces Malonyl-CoA 688
- C. Fatty Acid Synthase Catalyzes Seven Reactions 689
- D. Fatty Acids May Be Elongated and Desaturated 695
- E. Fatty Acids Are Esterified to Form Triacylglycerols 696



5 Regulation of Fatty Acid Metabolism 697

6 Synthesis of Other Lipids 700

- A. Glycerophospholipids Are Built from Intermediates of Triacylglycerol Synthesis 700
- B. Sphingolipids Are Built from Palmitoyl-CoA and Serine 703
- C. C₂₀ Fatty Acids Are the Precursors of Prostaglandins 704

7 Cholesterol Metabolism 706

- A. Cholesterol Is Synthesized from Acetyl-CoA 707
- B. HMG-CoA Reductase Controls the Rate of Cholesterol Synthesis 710
- C. Abnormal Cholesterol Transport Leads to Atherosclerosis 713

BOX 20-1 Biochemistry in Health and Disease Vitamin B₁₂ Deficiency 680

BOX 20-2 Pathways of Discovery Dorothy Crowfoot Hodgkin and the Structure of Vitamin B₁₂ 680

BOX 20-3 Perspectives in Biochemistry Polyketide Synthesis 694

BOX 20-4 Biochemistry in Health and Disease Sphingolipid Degradation and Lipid Storage Diseases 706

21 Amino Acid Metabolism 718

1 Protein Degradation 719

- A. Lysosomes Degrade Many Proteins 719
- B. Ubiquitin Marks Proteins for Degradation 720
- C. The Proteasome Unfolds and Hydrolyzes Ubiquitinated Polypeptides 721

2 Amino Acid Deamination 724

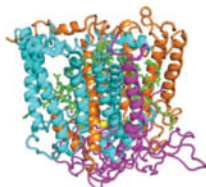
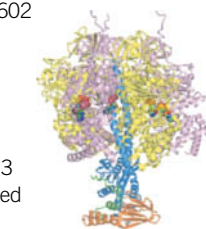
- A. Transaminases Use PLP to Transfer Amino Groups 725
- B. Glutamate Can Be Oxidatively Deaminated 728

3 The Urea Cycle 728

- A. Five Enzymes Carry Out the Urea Cycle 729
- B. The Urea Cycle Is Regulated by Substrate Availability 732

4 Breakdown of Amino Acids 733

- A. Alanine, Cysteine, Glycine, Serine, and Threonine Are Degraded to Pyruvate 734
- B. Asparagine and Aspartate Are Degraded to Oxaloacetate 736



- C. Arginine, Glutamate, Glutamine, Histidine, and Proline Are Degraded to α -Ketoglutarate 737
- D. Methionine, Threonine, Isoleucine, and Valine Are Degraded to Succinyl-CoA 738
- E. Leucine and Lysine Are Degraded Only to Acetyl-CoA and/or Acetoacetate 743
- F. Tryptophan Is Degraded to Alanine and Acetoacetate 744
- G. Phenylalanine and Tyrosine Are Degraded to Fumarate and Acetoacetate 745

5 Amino Acid Biosynthesis 746

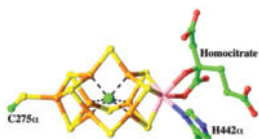
- A. Nonessential Amino Acids Are Synthesized from Common Metabolites 748
- B. Plants and Microorganisms Synthesize the Essential Amino Acids 752

6 Other Products of Amino Acid Metabolism 758

- A. Heme Is Synthesized from Glycine and Succinyl-CoA 758
- B. Amino Acids Are Precursors of Physiologically Active Amines 762
- C. Nitric Oxide Is Derived from Arginine 763

7 Nitrogen Fixation 764

- A. Nitrogenase Reduces N_2 to NH_3 764
- B. Fixed Nitrogen Is Assimilated into Biological Molecules 768



BOX 21-1 Biochemistry in Health and Disease Homocysteine, a Marker of Disease 740

BOX 21-2 Biochemistry in Health and Disease Phenylketonuria and Alcaptonuria Result from Defects in Phenylalanine Degradation 746

BOX 21-3 Biochemistry in Health and Disease The Porphyrins 760

22 Mammalian Fuel Metabolism: Integration and Regulation 773

1 Organ Specialization 774

- A. The Brain Requires a Steady Supply of Glucose 775
- B. Muscle Utilizes Glucose, Fatty Acids, and Ketone Bodies 776
- C. Adipose Tissue Stores and Releases Fatty Acids and Hormones 778
- D. Liver Is the Body's Central Metabolic Clearinghouse 778
- E. Kidney Filters Wastes and Maintains Blood pH 780
- F. Blood Transports Metabolites in Interorgan Metabolic Pathways 780

2 Hormonal Control of Fuel Metabolism 781

- A. Insulin Release Is Triggered by Glucose 782
- B. Glucagon and Catecholamines Counter the Effects of Insulin 783

3 Metabolic Homeostasis: The Regulation of Energy Metabolism, Appetite, and Body Weight 786

- A. AMP-Dependent Protein Kinase Is the Cell's Fuel Gauge 786
- B. Adipocytes and Other Tissues Help Regulate Fuel Metabolism and Appetite 788
- C. Energy Expenditure Can Be Controlled by Adaptive Thermogenesis 789

4 Disturbances in Fuel Metabolism 790

- A. Starvation Leads to Metabolic Adjustments 790
- B. Diabetes Mellitus Is Characterized by High Blood Glucose Levels 792
- C. Obesity Is Usually Caused by Excessive Food Intake 795
- D. Cancer Metabolism 796

BOX 22-1 Biochemistry in Health and Disease The Intestinal Microbiome 777

BOX 22-2 Pathways of Discovery Frederick Banting and Charles Best and the Discovery of Insulin 794

PART V GENE EXPRESSION AND REPLICATION

23 Nucleotide Metabolism 802

1 Synthesis of Purine Ribonucleotides 802

- A. Purine Synthesis Yields Inosine Monophosphate 803

- B. IMP Is Converted to Adenine and Guanine Ribonucleotides 806
- C. Purine Nucleotide Biosynthesis Is Regulated at Several Steps 807
- D. Purines Can Be Salvaged 808

2 Synthesis of Pyrimidine Ribonucleotides 809

- A. UMP Is Synthesized in Six Steps 809
- B. UMP Is Converted to UTP and CTP 811
- C. Pyrimidine Nucleotide Biosynthesis Is Regulated at ATCase or Carbamoyl Phosphate Synthetase II 811

3 Formation of Deoxyribonucleotides 812

- A. Ribonucleotide Reductase Converts Ribonucleotides to Deoxyribonucleotides 812
- B. dUMP Is Methylated to Form Thymine 817

4 Nucleotide Degradation 820

- A. Purine Catabolism Yields Uric Acid 822
- B. Some Animals Degrade Uric Acid 825
- C. Pyrimidines Are Broken Down to Malonyl-CoA and Methylmalonyl-CoA 827

BOX 23-1 Biochemistry in Health and Disease Inhibition of Thymidylate Synthesis in Cancer Therapy 821

BOX 23-2 Pathways of Discovery Gertrude Elion and Purine Derivatives 826

24 Nucleic Acid Structure 831

1 The DNA Helix 832

- A. DNA Can Adopt Different Conformations 832
- B. DNA Has Limited Flexibility 838
- C. DNA Can Be Supercoiled 840
- D. Topoisomerases Alter DNA Supercoiling 842

2 Forces Stabilizing Nucleic Acid Structures 848

- A. Nucleic Acids Are Stabilized by Base Pairing, Stacking, and Ionic Interactions 849
- B. DNA Can Undergo Denaturation and Renaturation 850
- C. RNA Structures Are Highly Variable 852

3 Fractionation of Nucleic Acids 856

- A. Nucleic Acids Can Be Purified by Chromatography 856
- B. Electrophoresis Separates Nucleic Acids by Size 857

4 DNA-Protein Interactions 859

- A. Restriction Endonucleases Distort DNA on Binding 860
- B. Prokaryotic Repressors Often Include a DNA-Binding Helix 861
- C. Eukaryotic Transcription Factors May Include Zinc Fingers or Leucine Zippers 864

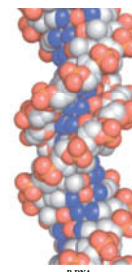
5 Eukaryotic Chromosome Structure 868

- A. DNA Coils around Histones to Form Nucleosomes 868
- B. Chromatin Forms Higher-Order Structures 870

BOX 24-1 Pathways of Discovery Rosalind Franklin and the Structure of DNA 833

BOX 24-2 Biochemistry in Health and Disease Inhibitors of Topoisomerases as Antibiotics and Anticancer Chemotherapeutic Agents 848

BOX 24-3 Perspectives in Biochemistry The RNA World 854



25 DNA Replication, Repair, and Recombination 879

1 Overview of DNA Replication 880

2 Prokaryotic DNA Replication 882

- A. DNA Polymerases Add the Correctly Paired Nucleotides 883
- B. Replication Initiation Requires Helicase and Primase 889

- C. The Leading and Lagging Strands Are Synthesized Simultaneously 891
- D. Replication Terminates at Specific Sites 895
- E. DNA Is Replicated with High Fidelity 897

3 Eukaryotic DNA Replication 898

- A. Eukaryotes Use Several DNA Polymerases 898
- B. Eukaryotic DNA Is Replicated from Multiple Origins 900
- C. Telomerase Extends Chromosome Ends 902

4 DNA Damage 904

- A. Environmental and Chemical Agents Generate Mutations 905
- B. Many Mutagens Are Carcinogens 907

5 DNA Repair 909

- A. Some Damage Can Be Directly Reversed 909
- B. Base Excision Repair Requires a Glycosylase 910
- C. Nucleotide Excision Repair Removes a Segment of a DNA Strand 912
- D. Mismatch Repair Corrects Replication Errors 913
- E. Some DNA Repair Mechanisms Introduce Errors 914

6 Recombination 916

- A. Homologous Recombination Involves Several Protein Complexes 916
- B. DNA Can Be Repaired by Recombination 922
- C. CRISPR–Cas9, a System for Editing and Regulating Genomes 925
- D. Transposition Rearranges Segments of DNA 929

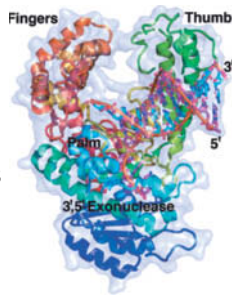
BOX 25-1 Pathways of Discovery **Arthur Kornberg and DNA Polymerase I** 883

BOX 25-2 Perspectives in Biochemistry **Reverse Transcriptase** 900

BOX 25-3 Biochemistry in Health and Disease **Telomerase, Aging, and Cancer** 905

BOX 25-4 Perspectives in Biochemistry **DNA Methylation** 908

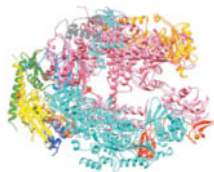
BOX 25-5 Perspectives in Biochemistry **Why Doesn't DNA Contain Uracil?** 911



26 Transcription and RNA Processing 938

1 Prokaryotic RNA Transcription 939

- A. RNA Polymerase Resembles Other Polymerases 939
- B. Transcription Is Initiated at a Promoter 942
- C. The RNA Chain Grows from the 5' to 3' End 943
- D. Transcription Terminates at Specific Sites 946



2 Transcription in Eukaryotes 948

- A. Eukaryotes Have Several RNA Polymerases 949
- B. Each Polymerase Recognizes a Different Type of Promoter 954
- C. Transcription Factors Are Required to Initiate Transcription 956

3 Posttranscriptional Processing 961

- A. Messenger RNAs Undergo 5' Capping and Addition of a 3' Tail 962
- B. Splicing Removes Introns from Eukaryotic Genes 963
- C. Ribosomal RNA Precursors May Be Cleaved, Modified, and Spliced 973
- D. Transfer RNAs Are Processed by Nucleotide Removal, Addition, and Modification 977

BOX 26-1 Perspectives in Biochemistry **Collisions between DNA Polymerase and RNA Polymerase** 945

BOX 26-2 Biochemistry in Health and Disease **Inhibitors of Transcription** 950

BOX 26-3 Pathways of Discovery **Richard Roberts and Phillip Sharp and the Discovery of Introns** 964

27 Protein Synthesis 982

1 The Genetic Code 983

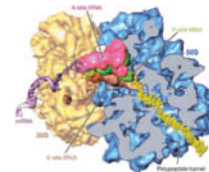
- A. Codons Are Triplets That Are Read Sequentially 983
- B. The Genetic Code Was Systematically Deciphered 984
- C. The Genetic Code Is Degenerate and Nonrandom 986

2 Transfer RNA and Its Aminoacylation 988

- A. All tRNAs Have Similar Structures 988
- B. Aminoacyl-tRNA Synthetases Attach Amino Acids to tRNAs 990
- C. Most tRNAs Recognize More than One Codon 994

3 Ribosomes 996

- A. The Prokaryotic Ribosome Consists of Two Subunits 997
- B. The Eukaryotic Ribosome Contains a Buried Prokaryotic Ribosome 1002



4 Translation 1004

- A. Chain Initiation Requires an Initiator tRNA and Initiation Factors 1006
- B. The Ribosome Decodes the mRNA, Catalyzes Peptide Bond Formation, Then Moves to the Next Codon 1011
- C. Release Factors Terminate Translation 1023

5 Posttranslational Processing 1024

- A. Ribosome-Associated Chaperones Help Proteins Fold 1025
- B. Newly Synthesized Proteins May Be Covalently Modified 1026

BOX 27-1 Perspectives in Biochemistry **Evolution of the Genetic Code** 986

BOX 27-2 Perspectives in Biochemistry **Expanding the Genetic Code** 996

BOX 27-3 Biochemistry in Health and Disease **The Effects of Antibiotics on Protein Synthesis** 1020

28 Regulation of Gene Expression 1033

1 Genome Organization 1034

- A. Gene Number Varies among Organisms 1034
- B. Some Genes Occur in Clusters 1037
- C. Eukaryotic Genomes Contain Repetitive DNA Sequences 1039

2 Regulation of Prokaryotic Gene Expression 1043

- A. The *lac* Operon Is Controlled by a Repressor 1043
- B. Catabolite-Repressed Operons Can Be Activated 1046
- C. Attenuation Regulates Transcription Termination 1048
- D. Riboswitches Are Metabolite-Sensing RNAs 1050

3 Regulation of Eukaryotic Gene Expression 1052

- A. Chromatin Structure Influences Gene Expression 1052
- B. Eukaryotes Contain Multiple Transcriptional Activators 1063
- C. Posttranscriptional Control Mechanisms 1069
- D. Antibody Diversity Results from Somatic Recombination and Hypermutation 1076

4 The Cell Cycle, Cancer, Apoptosis, and Development 1080

- A. Progress through the Cell Cycle Is Tightly Regulated 1080
- B. Tumor Suppressors Prevent Cancer 1082
- C. Apoptosis Is an Orderly Process 1085
- D. Development Has a Molecular Basis 1089



BOX 28-1 Biochemistry in Health and Disease **Trinucleotide Repeat Diseases** 1040

BOX 28-2 Perspectives in Biochemistry **X Chromosome Inactivation** 1053

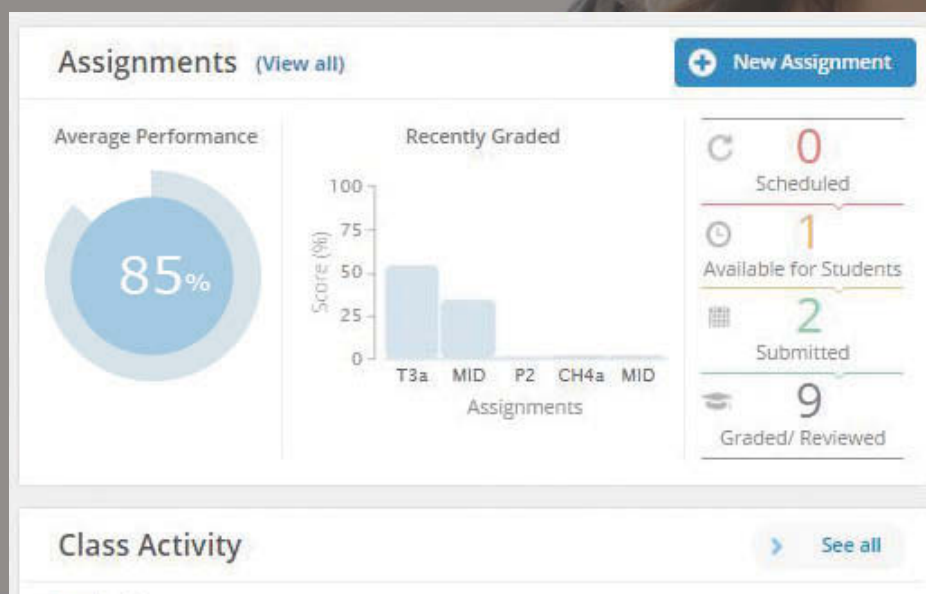
BOX 28-3 Perspectives in Biochemistry **Nonsense-Mediated Decay** 1070

Glossary G-1 **Index** I-1

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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 using several 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.

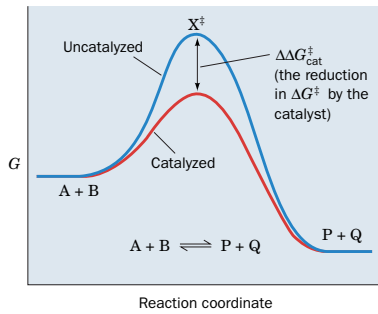


FIG. 11-7 Effect of a catalyst on the transition state diagram of a reaction. Here $\Delta\Delta G_{\text{cat}}^{\ddagger} = \Delta G^{\ddagger}(\text{uncat}) - \Delta G^{\ddagger}(\text{cat})$.

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

- 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.

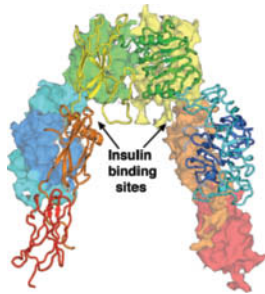


FIG. 13-4 X-Ray structure of the insulin receptor ectodomain. One of its $\alpha\beta$ protomers is shown in ribbon form with its six domains successively colored in rainbow order with the N-terminal domain blue and the C-terminal domain red. The other protomer is represented by its identically colored 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.

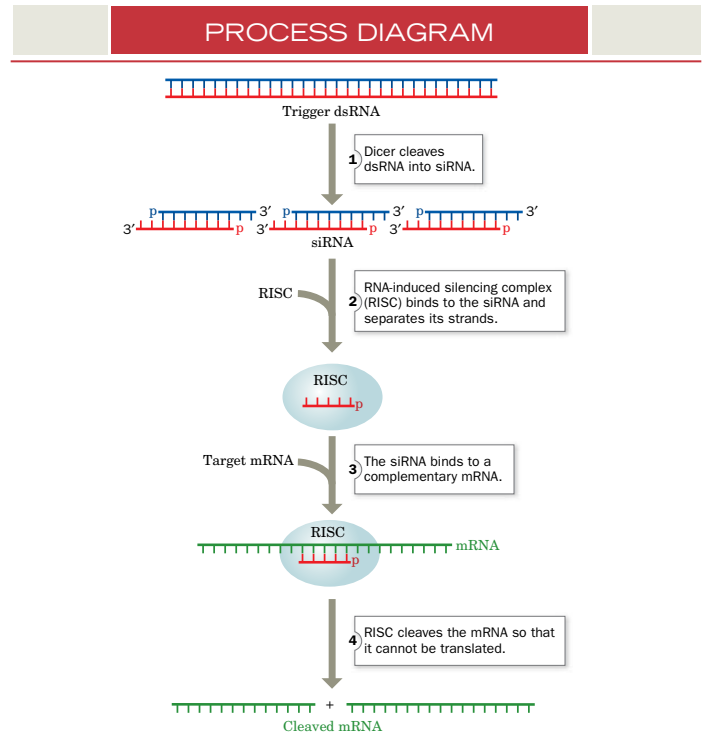


FIG. 28-37 A mechanism of RNA interference. ATP is required for Dicer-catalyzed cleavage of RNA and for RISC-associated helicase unwinding of double-stranded RNA. Depending on the species, the mRNA may not be completely degraded. **WPLS** See the Animated Process Diagrams.

? 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 $[\text{Ca}^{2+}] = 1 \text{ mM}$) to the cytosol (where $[\text{Ca}^{2+}] = 0.1 \mu\text{M}$). Assume $\Delta\psi = 0$.

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

$$\begin{aligned}\Delta G &= RT \ln \frac{[\text{Ca}^{2+}]_{\text{in}}}{[\text{Ca}^{2+}]_{\text{out}}} = RT \ln \frac{10^{-7}}{10^{-3}} \\ &= RT(-9.2)\end{aligned}$$

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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Geraldine Osnato, Senior Product Designer and Sean Hickey, Product Designer developed the *WileyPLUS* Learning Space course.

The atomic coordinates of many of the proteins and nucleic acids that we have drawn for use in this textbook were obtained from the Protein Data Bank (PDB) maintained by the Research Collaboratory for Structural Bioinformatics (RCSB). We created the drawings using the molecular graphics programs PyMOL by Warren DeLano; RIBBONS by Mike Carson; and GRASP by Anthony Nicholls, Kim Sharp, and Barry Honig.

The Internet resources and student printed resources were prepared by the following individuals. Brief Bioinformatics Exercises: Rakesh Mogul, Cal Poly Pomona, Pomona, California; Extended Bioinformatics Projects: Paul Craig, Rochester Institute of Technology, Rochester, New York; Exercises and Classroom Response Questions: Rachel Milner and Adrienne Wright, University of Alberta, Edmonton, Alberta, Canada; Practice Questions: Steven Vik, Southern Methodist University, Dallas, Texas; Case Studies: Kathleen Cornely, Providence College, Providence, Rhode Island; Student Companion: Akif Uzman, University of Houston-Downtown, Houston, Texas, Jerry Johnson, University of Houston-Downtown, Houston, Texas, William Widger, University of Houston, Houston, Texas, Joseph Eichberg, University of Houston, Houston, Texas, Donald Voet, Judith Voet, and Charlotte Pratt; Test Bank: Amy Stockert, Ohio Northern University, Ada, Ohio, Peter van der Geer, San Diego State University, San Diego, California, Marilee Benore, University of Michigan-Dearborn, Dearborn, Michigan, and Robert Kane, Baylor University, Waco, Texas.

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CHAPTER 1

Introduction to the Chemistry of Life

Chapter Contents

1 The Origin of Life

- A Biological Molecules Arose from Inanimate Substances
- B Complex Self-Replicating Systems Evolved from Simple Molecules

2 Cellular Architecture

- A Cells Carry Out Metabolic Reactions
- B There Are Two Types of Cells: Prokaryotes and Eukaryotes
- C Molecular Data Reveal Three Evolutionary Domains of Organisms
- D Organisms Continue to Evolve

3 Thermodynamics

- A The First Law of Thermodynamics States That Energy Is Conserved
- B The Second Law of Thermodynamics States That Entropy Tends to Increase
- C The Free Energy Change Determines the Spontaneity of a Process
- D Free Energy Changes Can Be Calculated from Reactant and Product Concentrations
- E Life Achieves Homeostasis While Obeying the Laws of Thermodynamics

M. I. Walker/Science Source Images



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.

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.

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.

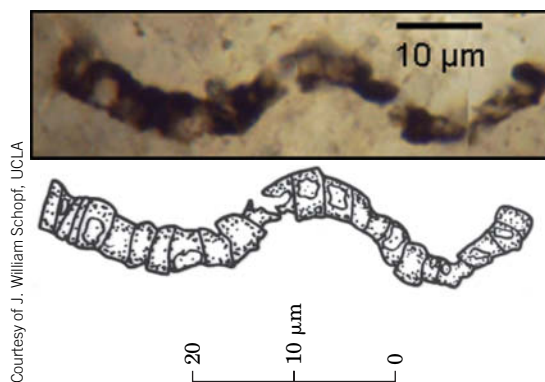
The atmosphere of the early earth probably consisted of small, simple compounds such as H₂O, N₂, CO₂, and smaller amounts of CH₄ and NH₃. In the 1920s, Alexander Oparin and J. B. S. Haldane independently suggested that ultraviolet radiation from the sun or lightning discharges caused the molecules of 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 H₂O, CH₄, NH₃, and H₂ 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

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

^aCalculated from Frieden, E., *Sci. Am.* **227**(1), 54–55 (1972).



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.

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

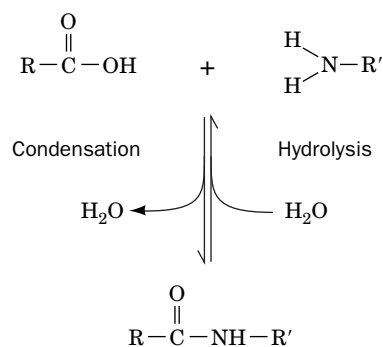
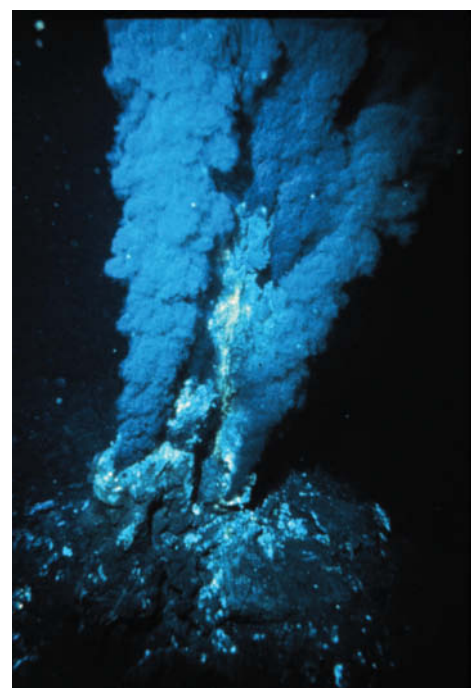


FIG. 1-3 Reaction of a carboxylic acid with an amine. The elements of water are released during condensation. In the reverse process—hydrolysis—water is added to cleave the amide bond. In living systems, condensation reactions are not freely reversible.



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.

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.

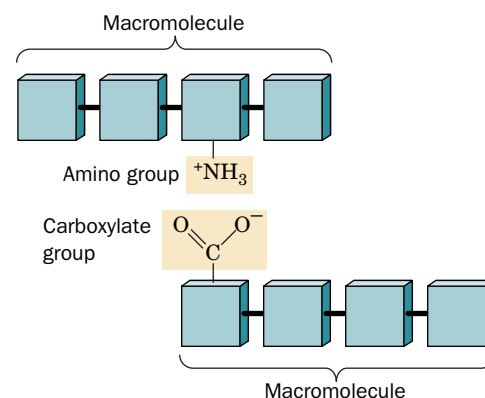


FIG. 1-4 Association of complementary molecules. The positively charged amino group interacts electrostatically with the negatively charged carboxylate group.

TABLE 1-2 Common Functional Groups and Linkages in Biochemistry

Compound Name	Structure ^a	Functional Group or Linkage
Amine ^b	RNH_2 or $\text{R}\overset{+}{\text{N}}\text{H}_3$ R_2NH or $\text{R}_2\overset{+}{\text{N}}\text{H}_2$ R_3N or $\text{R}_3\overset{+}{\text{N}}\text{H}$	$-\text{N}<$ or $-\overset{+}{\text{N}}-$ (amino group)
Alcohol	ROH	$-\text{OH}$ (hydroxyl group)
Thiol	RSH	$-\text{SH}$ (sulfhydryl group)
Ether	ROR	$-\text{O}-$ (ether linkage)
Aldehyde	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	$-\overset{\text{O}}{\parallel}{\text{C}}-$ (carbonyl group)
Ketone	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$	$-\overset{\text{O}}{\parallel}{\text{C}}-$ (carbonyl group)
Carboxylic acid ^b	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$ or $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^-$	$-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$ (carboxyl group) or $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^-$ (carboxylate group)
Ester	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}$	$-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$ (ester linkage) $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$ (acyl group) ^c
Thioester	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SR}$	$-\overset{\text{O}}{\parallel}{\text{C}}-\text{S}-$ (thioester linkage) $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$ (acyl group) ^c
Amide	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}_2$ $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}$ $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}_2$	$-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}<$ (amido group) $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$ (acyl group) ^c
Imine (Schiff base) ^b	$\text{R}=\text{NH}$ or $\text{R}=\overset{+}{\text{N}}\text{H}_2$ $\text{R}=\text{NR}$ or $\text{R}=\overset{+}{\text{N}}\text{HR}$	$>\text{C}=\text{N}-$ or $>\text{C}=\overset{+}{\text{N}}<$ (imino group)
Disulfide	$\text{R}-\text{S}-\text{S}-\text{R}$	$-\text{S}-\text{S}-$ (disulfide linkage)
Phosphate ester ^b	$\text{R}-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OH})-\text{O}^-$	$-\overset{\text{O}}{\parallel}{\text{P}}(\text{OH})-\text{O}^-$ (phosphoryl group)
Diphosphate ester ^b	$\text{R}-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{O}^-)-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OH})-\text{O}^-$	$-\overset{\text{O}}{\parallel}{\text{P}}(\text{O}^-)-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{OH})-\text{O}^-$ (phosphoanhydride group)
Phosphate diester ^b	$\text{R}-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{O}^-)-\text{O}-\text{R}$	$-\text{O}-\overset{\text{O}}{\parallel}{\text{P}}(\text{O}^-)-\text{O}-$ (phosphodiester linkage)

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

^bUnder physiological conditions, these groups are ionized and hence bear a positive or negative charge.

^cIf 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)

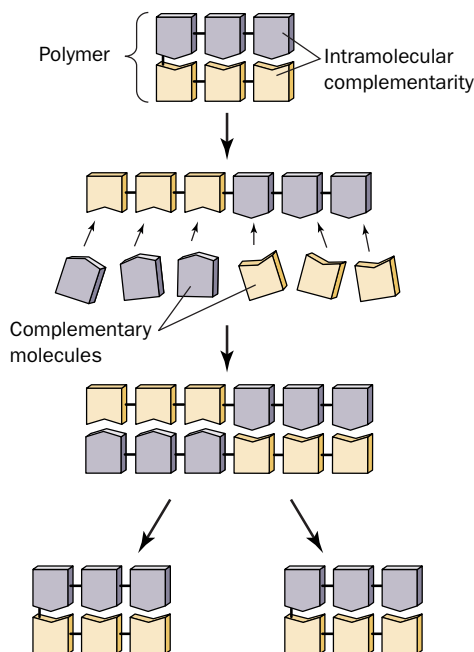


FIG. 1-5 Replication through complementarity. In this simple case, a polymer serves as a template for the assembly of a complementary molecule, which, because of intramolecular complementarity, is an exact copy of the original.

? 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

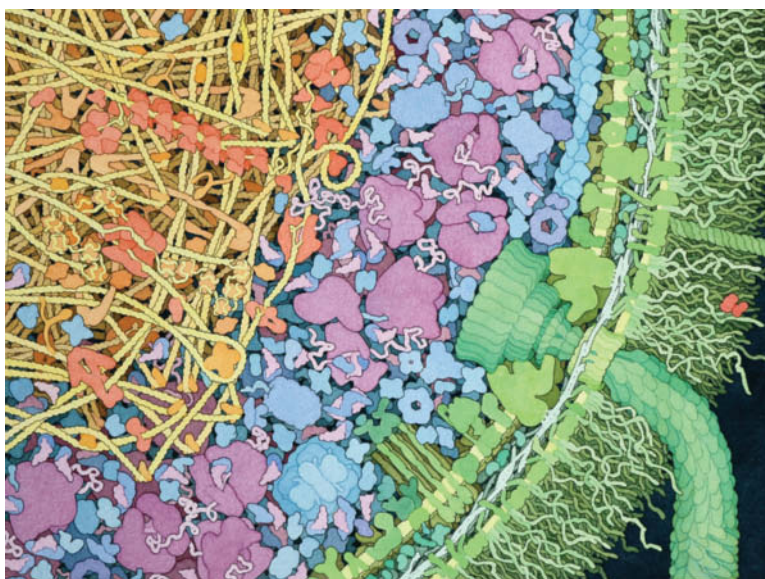
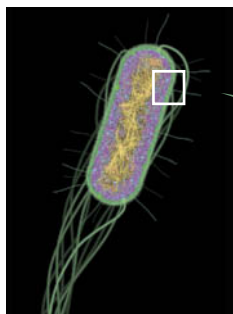


FIG. 1-6 Cross-section through an *E. coli* cell.

The cytoplasm is packed with macromolecules. At this magnification ($\sim 1,000,000\times$), 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% O₂) 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 O₂ 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.

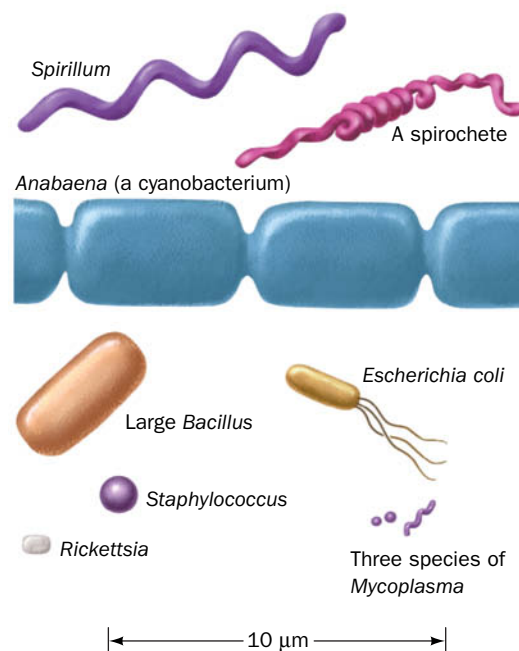


FIG. 1-7 Scale drawings of some prokaryotic cells.

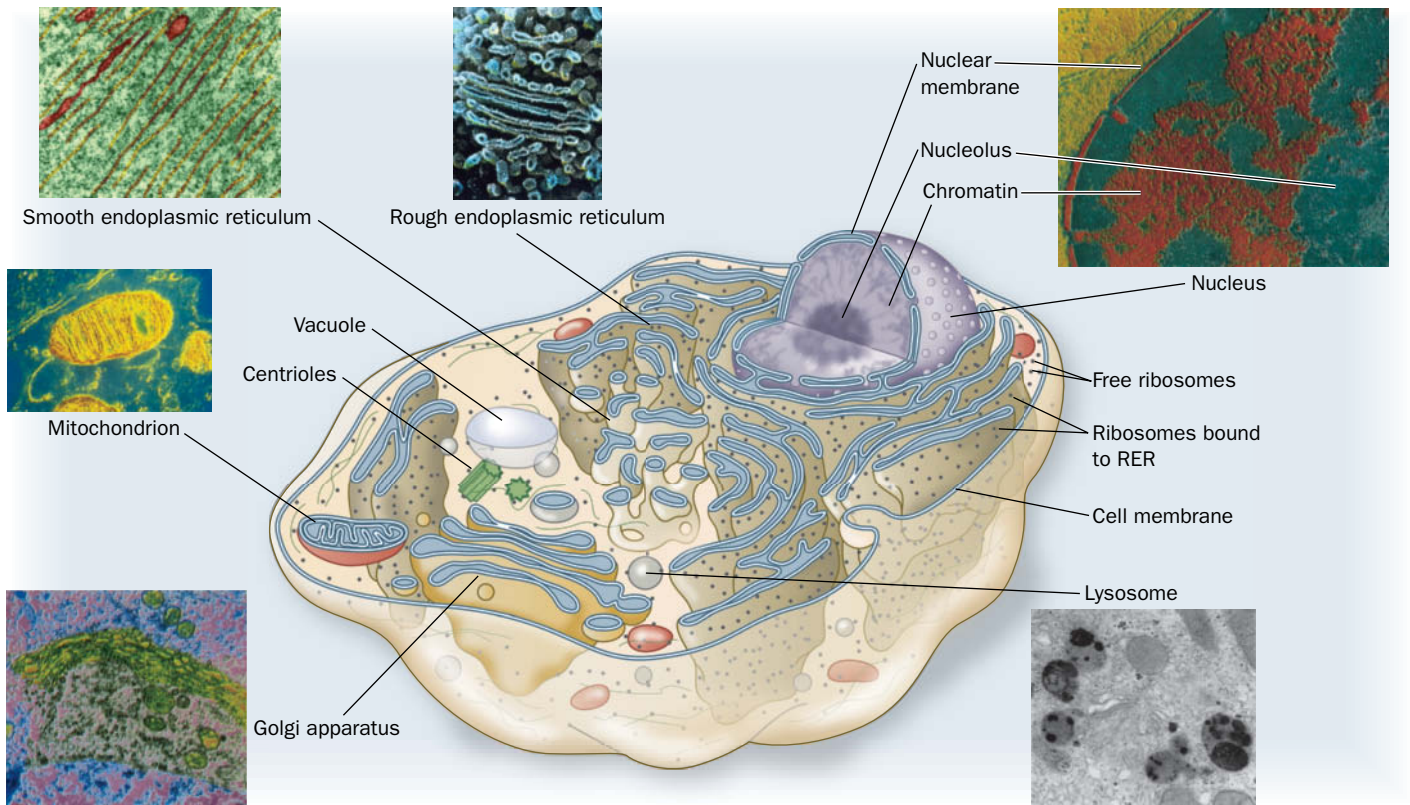


FIG. 1-8 Diagram of a typical animal cell with electron micrographs of its organelles. Membrane-bounded organelles include the nucleus, endoplasmic reticulum, lysosome, peroxisome (not pictured), mitochondrion, vacuole, and Golgi apparatus. The nucleus contains chromatin (a complex of DNA and protein) 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.

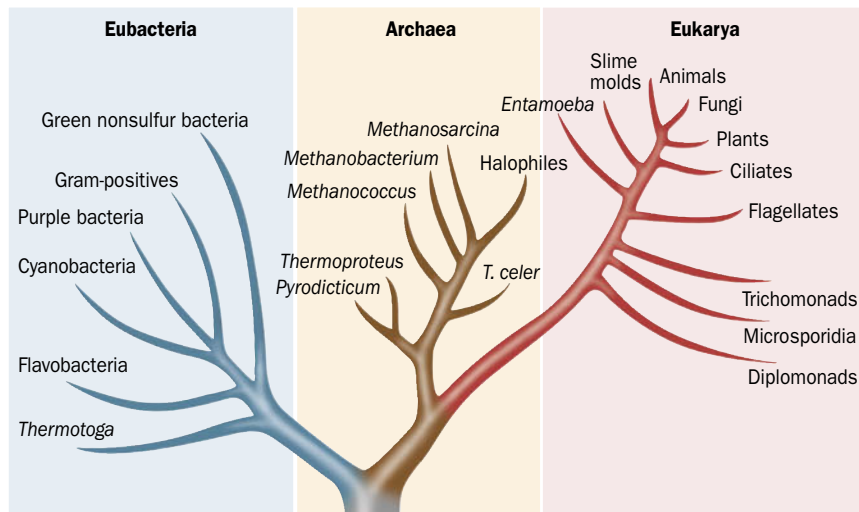


FIG. 1-9 Phylogenetic tree showing the three domains of organisms. The branches indicate the pattern of divergence from a common ancestor. The archaea are prokaryotes, like eubacteria, but share many features with eukaryotes. [After Wheelis, M.L., Kandler, O., and Woese, C.R., *Proc. Natl. Acad. Sci.*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