

Marcello Forconi, *College of Charleston*
Wilson Francisco, *Arizona State University*
Greta Giles, *Georgia Gwinnett College*
Glenda Gillaspay, *Virginia Tech University*
Margaret Glasner, *Texas A&M University*
James Gober, *University of California, Los Angeles*
Burt Goldberg, *New York University*
Julie Gosse, *University of Maine*
Lesley Greene, *Old Dominion University*
Eric Hegg, *Michigan State University*
Justin Hines, *Lafayette College*
Peter Hinkle, *Cornell University*
Pui Ho, *Colorado State University*
David Hurley, *Gatton College of Pharmacy, ETSU*
Joseph Jez, *Washington University in St. Louis*
Kelly Johanson, *Xavier University of Louisiana*
Douglas Julin, *University of Maryland*
Mark Kearley, *Florida State University*
Dmitry Kolpashchikov, *University of Central Florida*
Min-Hao Kuo, *Michigan State University*
Nicole LaRonde-LeBlanc, *University of Maryland*
Scott Lefler, *Arizona State University*
Andy LiWang, *University of California, Merced*
Thomas Marsh, *University of St. Thomas*
Michele McGuirl, *The University of Montana*
Michael Mendenhall, *University of Kentucky*
David Merkler, *University of South Florida*
Debra Moriarity, *University of Alabama: Huntsville*
Hunter Moseley, *University of Louisville*
Allen Nicholson, *Temple University*
James Ntambi, *University of Wisconsin–Madison*
Neil Osheroﬀ, *Vanderbilt University School of Medicine*
Donald Ourth, *University of Memphis*
Terry Platt, *University of Rochester*
Wendy Pogozelski, *State University of New York, Geneseo*
Joseph Provost, *Minnesota State University, Moorhead*
Gregory Raner, *University of North Carolina, Greensboro*
Lisa Rezende, *University of Arizona*
Douglas Root, *University of North Texas*
Johannes Rudolph, *University of Colorado*

Phillip Ryals, *University of West Florida*
Kevin Siebenlist, *Marquette University*
Kerry Smith, *Clemson University*
Julian Snow, *University of the Sciences*
Alejandra Stenger, *University of Illinois, Urbana–Champaign*
Amy Stockert, *Ohio Northern University*
Jon Stoltzfus, *Michigan State University*
Toni Vidal-Puig, *University of Cambridge*
Chuan Xiao, *University of Texas, El Paso*
Michael Yaffe, *Massachusetts Institute of Technology*
Laura Zapanta, *University of Pittsburgh*

We lack the space here to acknowledge all the other individuals whose special efforts went into this book. We offer instead our sincere thanks—and the finished book that they helped guide to completion. We, of course, assume full responsibility for errors of fact or emphasis.

We want especially to thank our students at the University of Wisconsin–Madison for their numerous comments and suggestions. If something in the book does not work, they are never shy about letting us know it. We are grateful to the students and staff of our research groups, who helped us balance the competing demands on our time; to our colleagues in the Department of Biochemistry at the University of Wisconsin–Madison, who helped us with advice and criticism; and to the many students and teachers who have written to suggest ways of improving the book. We hope our readers will continue to provide input for future editions.

Finally, we express our deepest appreciation to our wives, Brook and Beth, and our families, who showed extraordinary patience with, and support for, our book writing.

David L. Nelson
Michael M. Cox
Madison, Wisconsin
June 2012

Contents in Brief

Preface	vi
1 The Foundations of Biochemistry	1
I STRUCTURE AND CATALYSIS	45
2 Water	47
3 Amino Acids, Peptides, and Proteins	75
4 The Three-Dimensional Structure of Proteins	115
5 Protein Function	157
6 Enzymes	189
7 Carbohydrates and Glycobiology	243
8 Nucleotides and Nucleic Acids	281
9 DNA-Based Information Technologies	313
10 Lipids	357
11 Biological Membranes and Transport	385
12 Biosignaling	433
II BIOENERGETICS AND METABOLISM	501
13 Bioenergetics and Biochemical Reaction Types	505
14 Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway	543
15 Principles of Metabolic Regulation	587
16 The Citric Acid Cycle	633
17 Fatty Acid Catabolism	667
18 Amino Acid Oxidation and the Production of Urea	695
19 Oxidative Phosphorylation and Photophosphorylation	731
20 Carbohydrate Biosynthesis in Plants and Bacteria	799
21 Lipid Biosynthesis	833
22 Biosynthesis of Amino Acids, Nucleotides, and Related Molecules	881
23 Hormonal Regulation and Integration of Mammalian Metabolism	929
III INFORMATION PATHWAYS	977
24 Genes and Chromosomes	979
25 DNA Metabolism	1009
26 RNA Metabolism	1057
27 Protein Metabolism	1103
28 Regulation of Gene Expression	1155
Abbreviated Solutions to Problems	AS-1
Glossary	G-1
Credits	C-1
Index	I-1

Contents

1 The Foundations of Biochemistry	1
1.1 Cellular Foundations	2
Cells Are the Structural and Functional Units of All Living Organisms	3
Cellular Dimensions Are Limited by Diffusion	3
There Are Three Distinct Domains of Life	3
Organisms Differ Widely in Their Sources of Energy and Biosynthetic Precursors	4
Bacterial and Archaeal Cells Share Common Features but Differ in Important Ways	4
Eukaryotic Cells Have a Variety of Membranous Organelles, Which Can Be Isolated for Study	6
The Cytoplasm Is Organized by the Cytoskeleton and Is Highly Dynamic	8
Cells Build Supramolecular Structures	9
In Vitro Studies May Overlook Important Interactions among Molecules	9
1.2 Chemical Foundations	11
Biomolecules Are Compounds of Carbon with a Variety of Functional Groups	12
Cells Contain a Universal Set of Small Molecules	14
BOX 1–1 Molecular Weight, Molecular Mass, and Their Correct Units	14
Macromolecules Are the Major Constituents of Cells	15
Three-Dimensional Structure Is Described by Configuration and Conformation	16
BOX 1–2 Louis Pasteur and Optical Activity: In Vino, Veritas	18
Interactions between Biomolecules Are Stereospecific	19
1.3 Physical Foundations	20
Living Organisms Exist in a Dynamic Steady State, Never at Equilibrium with Their Surroundings	21
Organisms Transform Energy and Matter from Their Surroundings	21
BOX 1–3 Entropy: Things Fall Apart	22
The Flow of Electrons Provides Energy for Organisms	22
Creating and Maintaining Order Requires Work and Energy	22
Energy Coupling Links Reactions in Biology	24
K _{eq} and ΔG° Are Measures of a Reaction's Tendency to Proceed Spontaneously	25
Enzymes Promote Sequences of Chemical Reactions	27
Metabolism Is Regulated to Achieve Balance and Economy	28
1.4 Genetic Foundations	29
Genetic Continuity Is Vested in Single DNA Molecules	30
The Structure of DNA Allows for Its Replication and Repair with Near-Perfect Fidelity	30
The Linear Sequence in DNA Encodes Proteins with Three-Dimensional Structures	30

1.5 Evolutionary Foundations	32
Changes in the Hereditary Instructions Allow Evolution	32
Biomolecules First Arose by Chemical Evolution	33
RNA or Related Precursors May Have Been the First Genes and Catalysts	34
Biological Evolution Began More Than Three and a Half Billion Years Ago	35
The First Cell Probably Used Inorganic Fuels	35
Eukaryotic Cells Evolved from Simpler Precursors in Several Stages	36
Molecular Anatomy Reveals Evolutionary Relationships	37
Functional Genomics Shows the Allocations of Genes to Specific Cellular Processes	38
Genomic Comparisons Have Increasing Importance in Human Biology and Medicine	39
I STRUCTURE AND CATALYSIS	45
2 Water	47
2.1 Weak Interactions in Aqueous Systems	47
Hydrogen Bonding Gives Water Its Unusual Properties	47
Water Forms Hydrogen Bonds with Polar Solutes	49
Water Interacts Electrostatically with Charged Solutes	50
Entropy Increases as Crystalline Substances Dissolve	51
Nonpolar Gases Are Poorly Soluble in Water	51
Nonpolar Compounds Force Energetically Unfavorable Changes in the Structure of Water	51
van der Waals Interactions Are Weak Interatomic Attractions	53
Weak Interactions Are Crucial to Macromolecular Structure and Function	54
Solutes Affect the Colligative Properties of Aqueous Solutions	55
2.2 Ionization of Water, Weak Acids, and Weak Bases	58
Pure Water Is Slightly Ionized	58
The Ionization of Water Is Expressed by an Equilibrium Constant	59
The pH Scale Designates the H^+ and OH^- Concentrations	60
Weak Acids and Bases Have Characteristic Acid Dissociation Constants	61
Titration Curves Reveal the pK_a of Weak Acids	62
2.3 Buffering against pH Changes in Biological Systems	63
Buffers Are Mixtures of Weak Acids and Their Conjugate Bases	64
The Henderson-Hasselbalch Equation Relates pH, pK_a , and Buffer Concentration	64
Weak Acids or Bases Buffer Cells and Tissues against pH Changes	65
Untreated Diabetes Produces Life-Threatening Acidosis	67
BOX 2-1 MEDICINE: On Being One's Own Rabbit (Don't Try This at Home!)	68

2.4 Water as a Reactant	69
2.5 The Fitness of the Aqueous Environment for Living Organisms	69
3 Amino Acids, Peptides, and Proteins	75
3.1 Amino Acids	76
Amino Acids Share Common Structural Features	76
The Amino Acid Residues in Proteins Are L Stereoisomers	78
Amino Acids Can Be Classified by R Group	78
BOX 3-1 METHODS: Absorption of Light by Molecules: The Lambert-Beer Law	80
Uncommon Amino Acids Also Have Important Functions	81
Amino Acids Can Act as Acids and Bases	81
Amino Acids Have Characteristic Titration Curves	82
Titration Curves Predict the Electric Charge of Amino Acids	84
Amino Acids Differ in Their Acid-Base Properties	84
3.2 Peptides and Proteins	85
Peptides Are Chains of Amino Acids	85
Peptides Can Be Distinguished by Their Ionization Behavior	86
Biologically Active Peptides and Polypeptides Occur in a Vast Range of Sizes and Compositions	87
Some Proteins Contain Chemical Groups Other Than Amino Acids	89
3.3 Working with Proteins	89
Proteins Can Be Separated and Purified	89
Proteins Can Be Separated and Characterized by Electrophoresis	92
Unseparated Proteins Can Be Quantified	95
3.4 The Structure of Proteins: Primary Structure	96
The Function of a Protein Depends on Its Amino Acid Sequence	97
The Amino Acid Sequences of Millions of Proteins Have Been Determined	97
Protein Chemistry Is Enriched by Methods Derived from Classical Polypeptide Sequencing	98
Mass Spectrometry Offers an Alternative Method to Determine Amino Acid Sequences	100
Small Peptides and Proteins Can Be Chemically Synthesized	102
Amino Acid Sequences Provide Important Biochemical Information	104
Protein Sequences Can Elucidate the History of Life on Earth	104
BOX 3-2 Consensus Sequences and Sequence Logos	105
4 The Three-Dimensional Structure of Proteins	115
4.1 Overview of Protein Structure	115
A Protein's Conformation Is Stabilized Largely by Weak Interactions	116
The Peptide Bond Is Rigid and Planar	117

4.2 Protein Secondary Structure	119
The α Helix Is a Common Protein Secondary Structure	120
Amino Acid Sequence Affects Stability of the α Helix	121
BOX 4-1 METHODS: Knowing the Right Hand from the Left	121
The β Conformation Organizes Polypeptide Chains into Sheets	123
β Turns Are Common in Proteins	123
Common Secondary Structures Have Characteristic Dihedral Angles	123
Common Secondary Structures Can Be Assessed by Circular Dichroism	124
4.3 Protein Tertiary and Quaternary Structures	125
Fibrous Proteins Are Adapted for a Structural Function	125
BOX 4-2 Permanent Waving Is Biochemical Engineering	127
BOX 4-3 MEDICINE: Why Sailors, Explorers, and College Students Should Eat Their Fresh Fruits and Vegetables	128
Structural Diversity Reflects Functional Diversity in Globular Proteins	130
Myoglobin Provided Early Clues about the Complexity of Globular Protein Structure	131
BOX 4-4 The Protein Data Bank	132
Globular Proteins Have a Variety of Tertiary Structures	133
BOX 4-5 METHODS: Methods for Determining the Three-Dimensional Structure of a Protein	134
Protein Motifs Are the Basis for Protein Structural Classification	138
Protein Quaternary Structures Range from Simple Dimers to Large Complexes	140
Some Proteins or Protein Segments Are Intrinsically Disordered	141
4.4 Protein Denaturation and Folding	143
Loss of Protein Structure Results in Loss of Function	143
Amino Acid Sequence Determines Tertiary Structure	144
Polypeptides Fold Rapidly by a Stepwise Process	144
Some Proteins Undergo Assisted Folding	146
Defects in Protein Folding Provide the Molecular Basis for a Wide Range of Human Genetic Disorders	148
BOX 4-6 MEDICINE: Death by Misfolding: The Prion Diseases	150
5 Protein Function	157
5.1 Reversible Binding of a Protein to a Ligand: Oxygen-Binding Proteins	158
Oxygen Can Bind to a Heme Prosthetic Group	158
Globins Are a Family of Oxygen-Binding Proteins	159
Myoglobin Has a Single Binding Site for Oxygen	159
Protein-Ligand Interactions Can Be Described Quantitatively	159
Protein Structure Affects How Ligands Bind	162
Hemoglobin Transports Oxygen in Blood	163
Hemoglobin Subunits Are Structurally Similar to Myoglobin	163
Hemoglobin Undergoes a Structural Change on Binding Oxygen	163

Hemoglobin Binds Oxygen Cooperatively	165
Cooperative Ligand Binding Can Be Described Quantitatively	167
Two Models Suggest Mechanisms for Cooperative Binding	167
BOX 5-1 MEDICINE: Carbon Monoxide: A Stealthy Killer	168
Hemoglobin Also Transports H^+ and CO_2	169
Oxygen Binding to Hemoglobin Is Regulated by 2,3-Bisphosphoglycerate	171
Sickle-Cell Anemia Is a Molecular Disease of Hemoglobin	172
5.2 Complementary Interactions between Proteins and Ligands: The Immune System and Immunoglobulins	174
The Immune Response Features a Specialized Array of Cells and Proteins	174
Antibodies Have Two Identical Antigen-Binding Sites	175
Antibodies Bind Tightly and Specifically to Antigen	177
The Antibody-Antigen Interaction Is the Basis for a Variety of Important Analytical Procedures	178
5.3 Protein Interactions Modulated by Chemical Energy: Actin, Myosin, and Molecular Motors	179
The Major Proteins of Muscle Are Myosin and Actin	179
Additional Proteins Organize the Thin and Thick Filaments into Ordered Structures	181
Myosin Thick Filaments Slide along Actin Thin Filaments	182
6 Enzymes	189
6.1 An Introduction to Enzymes	189
Most Enzymes Are Proteins	190
Enzymes Are Classified by the Reactions They Catalyze	190
6.2 How Enzymes Work	192
Enzymes Affect Reaction Rates, Not Equilibria	192
Reaction Rates and Equilibria Have Precise Thermodynamic Definitions	194
A Few Principles Explain the Catalytic Power and Specificity of Enzymes	194
Weak Interactions between Enzyme and Substrate Are Optimized in the Transition State	195
Binding Energy Contributes to Reaction Specificity and Catalysis	197
Specific Catalytic Groups Contribute to Catalysis	199
6.3 Enzyme Kinetics as an Approach to Understanding Mechanism	200
Substrate Concentration Affects the Rate of Enzyme-Catalyzed Reactions	200
The Relationship between Substrate Concentration and Reaction Rate Can Be Expressed Quantitatively	202
Kinetic Parameters Are Used to Compare Enzyme Activities	203
BOX 6-1 Transformations of the Michaelis-Menten Equation: The Double-Reciprocal Plot	204

Many Enzymes Catalyze Reactions with Two or More Substrates	206	Steric Factors and Hydrogen Bonding Influence Homopolysaccharide Folding	257
Pre-Steady State Kinetics Can Provide Evidence for Specific Reaction Steps	207	Bacterial and Algal Cell Walls Contain Structural Heteropolysaccharides	259
Enzymes Are Subject to Reversible or Irreversible Inhibition	207	Glycosaminoglycans Are Heteropolysaccharides of the Extracellular Matrix	260
BOX 6-2 Kinetic Tests for Determining Inhibition Mechanisms	209	7.3 Glycoconjugates: Proteoglycans, Glycoproteins, and Glycosphingolipids	263
BOX 6-3 MEDICINE: Curing African Sleeping Sickness with a Biochemical Trojan Horse	211	Proteoglycans Are Glycosaminoglycan-Containing Macromolecules of the Cell Surface and Extracellular Matrix	264
Enzyme Activity Depends on pH	212	Glycoproteins Have Covalently Attached Oligosaccharides	266
6.4 Examples of Enzymatic Reactions	214	Glycolipids and Lipopolysaccharides Are Membrane Components	268
The Chymotrypsin Mechanism Involves Acylation and Deacylation of a Ser Residue	214	7.4 Carbohydrates as Informational Molecules: The Sugar Code	269
An Understanding of Protease Mechanisms Leads to New Treatments for HIV Infections	218	Lectins Are Proteins That Read the Sugar Code and Mediate Many Biological Processes	269
Hexokinase Undergoes Induced Fit on Substrate Binding	219	Lectin-Carbohydrate Interactions Are Highly Specific and Often Multivalent	272
The Enolase Reaction Mechanism Requires Metal Ions	220	7.5 Working with Carbohydrates	274
Lysozyme Uses Two Successive Nucleophilic Displacement Reactions	220	8 Nucleotides and Nucleic Acids	281
An Understanding of Enzyme Mechanism Produces Useful Antibiotics	224	8.1 Some Basics	281
6.5 Regulatory Enzymes	226	Nucleotides and Nucleic Acids Have Characteristic Bases and Pentoses	281
Allosteric Enzymes Undergo Conformational Changes in Response to Modulator Binding	226	Phosphodiester Bonds Link Successive Nucleotides in Nucleic Acids	284
The Kinetic Properties of Allosteric Enzymes Diverge from Michaelis-Menten Behavior	227	The Properties of Nucleotide Bases Affect the Three-Dimensional Structure of Nucleic Acids	286
Some Enzymes Are Regulated by Reversible Covalent Modification	228	8.2 Nucleic Acid Structure	287
Phosphoryl Groups Affect the Structure and Catalytic Activity of Enzymes	229	DNA Is a Double Helix That Stores Genetic Information	288
Multiple Phosphorylations Allow Exquisite Regulatory Control	230	DNA Can Occur in Different Three-Dimensional Forms	290
Some Enzymes and Other Proteins Are Regulated by Proteolytic Cleavage of an Enzyme Precursor	231	Certain DNA Sequences Adopt Unusual Structures	291
A Cascade of Proteolytically Activated Zymogens Leads to Blood Coagulation	232	Messenger RNAs Code for Polypeptide Chains	293
Some Regulatory Enzymes Use Several Regulatory Mechanisms	235	Many RNAs Have More Complex Three-Dimensional Structures	294
7 Carbohydrates and Glycobiology	243	8.3 Nucleic Acid Chemistry	297
7.1 Monosaccharides and Disaccharides	243	Double-Helical DNA and RNA Can Be Denatured	297
The Two Families of Monosaccharides Are Aldoses and Ketoses	244	Nucleic Acids from Different Species Can Form Hybrids	298
Monosaccharides Have Asymmetric Centers	244	Nucleotides and Nucleic Acids Undergo Nonenzymatic Transformations	299
The Common Monosaccharides Have Cyclic Structures	245	Some Bases of DNA Are Methylated	302
Organisms Contain a Variety of Hexose Derivatives	249	The Sequences of Long DNA Strands Can Be Determined	302
BOX 7-1 MEDICINE: Blood Glucose Measurements in the Diagnosis and Treatment of Diabetes	250	The Chemical Synthesis of DNA Has Been Automated	304
Monosaccharides Are Reducing Agents	251	8.4 Other Functions of Nucleotides	306
Disaccharides Contain a Glycosidic Bond	252	Nucleotides Carry Chemical Energy in Cells	306
BOX 7-2 Sugar Is Sweet, and So Are . . . a Few Other Things	254	Adenine Nucleotides Are Components of Many Enzyme Cofactors	306
7.2 Polysaccharides	254	Some Nucleotides Are Regulatory Molecules	308
Some Homopolysaccharides Are Stored Forms of Fuel	255		
Some Homopolysaccharides Serve Structural Roles	256		

9 DNA-Based Information Technologies	313	Some Glycerophospholipids Have Ether-Linked Fatty Acids	364
9.1 Studying Genes and Their Products	314	Chloroplasts Contain Galactolipids and Sulfolipids	365
Genes Can Be Isolated by DNA Cloning	314	Archaea Contain Unique Membrane Lipids	365
Restriction Endonucleases and DNA Ligases Yield Recombinant DNA	314	Sphingolipids Are Derivatives of Sphingosine	366
Cloning Vectors Allow Amplification of Inserted DNA Segments	317	Sphingolipids at Cell Surfaces Are Sites of Biological Recognition	367
Cloned Genes Can Be Expressed to Amplify Protein Production	321	Phospholipids and Sphingolipids Are Degraded in Lysosomes	368
Many Different Systems Are Used to Express Recombinant Proteins	322	Sterols Have Four Fused Carbon Rings	368
Alteration of Cloned Genes Produces Altered Proteins	323	BOX 10-1 MEDICINE: Abnormal Accumulations of Membrane Lipids: Some Inherited Human Diseases	369
Terminal Tags Provide Handles for Affinity Purification	325	10.3 Lipids as Signals, Cofactors, and Pigments	370
Gene Sequences Can Be Amplified with the Polymerase Chain Reaction	327	Phosphatidylinositols and Sphingosine Derivatives Act as Intracellular Signals	370
BOX 9-1 METHODS: A Powerful Tool in Forensic Medicine	329	Eicosanoids Carry Messages to Nearby Cells	371
9.2 Using DNA-Based Methods to Understand Protein Function	331	Steroid Hormones Carry Messages between Tissues	372
DNA Libraries Are Specialized Catalogs of Genetic Information	332	Vascular Plants Produce Thousands of Volatile Signals	372
Sequence or Structural Relationships Provide Information on Protein Function	333	Vitamins A and D Are Hormone Precursors	373
Fusion Proteins and Immunofluorescence Can Localize Proteins in Cells	333	Vitamins E and K and the Lipid Quinones Are Oxidation-Reduction Cofactors	374
Protein-Protein Interactions Can Help Elucidate Protein Function	334	Dolichols Activate Sugar Precursors for Biosynthesis	375
DNA Microarrays Reveal RNA Expression Patterns and Other Information	337	Many Natural Pigments Are Lipidic Conjugated Dienes	376
9.3 Genomics and the Human Story	339	Polyketides Are Natural Products with Potent Biological Activities	376
Genomic Sequencing Is Aided by New Generations of DNA-Sequencing Methods	339	10.4 Working with Lipids	377
BOX 9-2 MEDICINE: Personalized Genomic Medicine	340	Lipid Extraction Requires Organic Solvents	377
The Human Genome Contains Genes and Many Other Types of Sequences	342	Adsorption Chromatography Separates Lipids of Different Polarity	378
Genome Sequencing Informs Us about Our Humanity	345	Gas-Liquid Chromatography Resolves Mixtures of Volatile Lipid Derivatives	378
Genome Comparisons Help Locate Genes Involved in Disease	347	Specific Hydrolysis Aids in Determination of Lipid Structure	378
Genome Sequences Inform Us about Our Past and Provide Opportunities for the Future	349	Mass Spectrometry Reveals Complete Lipid Structure	378
BOX 9-3 Getting to Know the Neanderthals	350	Lipidomics Seeks to Catalog All Lipids and Their Functions	379
10 Lipids	357	11 Biological Membranes and Transport	385
10.1 Storage Lipids	357	11.1 The Composition and Architecture of Membranes	386
Fatty Acids Are Hydrocarbon Derivatives	357	Each Type of Membrane Has Characteristic Lipids and Proteins	386
Triacylglycerols Are Fatty Acid Esters of Glycerol	360	All Biological Membranes Share Some Fundamental Properties	387
Triacylglycerols Provide Stored Energy and Insulation	360	A Lipid Bilayer Is the Basic Structural Element of Membranes	387
Partial Hydrogenation of Cooking Oils Produces Trans Fatty Acids	361	Three Types of Membrane Proteins Differ in Their Association with the Membrane	389
Waxes Serve as Energy Stores and Water Repellents	362	Many Membrane Proteins Span the Lipid Bilayer	390
10.2 Structural Lipids in Membranes	362	Integral Proteins Are Held in the Membrane by Hydrophobic Interactions with Lipids	390
Glycerophospholipids Are Derivatives of Phosphatidic Acid	363	The Topology of an Integral Membrane Protein Can Sometimes Be Predicted from Its Sequence	391
		Covalently Attached Lipids Anchor Some Membrane Proteins	394

11.2 Membrane Dynamics	395
Acyl Groups in the Bilayer Interior Are Ordered to Varying Degrees	395
Transbilayer Movement of Lipids Requires Catalysis	396
Lipids and Proteins Diffuse Laterally in the Bilayer	397
Sphingolipids and Cholesterol Cluster Together in Membrane Rafts	398
Membrane Curvature and Fusion Are Central to Many Biological Processes	399
Integral Proteins of the Plasma Membrane Are Involved in Surface Adhesion, Signaling, and Other Cellular Processes	402
11.3 Solute Transport across Membranes	402
Passive Transport Is Facilitated by Membrane Proteins	403
Transporters and Ion Channels Are Fundamentally Different	404
The Glucose Transporter of Erythrocytes Mediates Passive Transport	405
The Chloride-Bicarbonate Exchanger Catalyzes Electroneutral Cotransport of Anions across the Plasma Membrane	407
BOX 11-1 MEDICINE: Defective Glucose and Water Transport in Two Forms of Diabetes	408
Active Transport Results in Solute Movement against a Concentration or Electrochemical Gradient	409
P-Type ATPases Undergo Phosphorylation during Their Catalytic Cycles	410
V-Type and F-Type ATPases Are Reversible, ATP-Driven Proton Pumps	412
ABC Transporters Use ATP to Drive the Active Transport of a Wide Variety of Substrates	413
Ion Gradients Provide the Energy for Secondary Active Transport	414
BOX 11-2 MEDICINE: A Defective Ion Channel in Cystic Fibrosis	415
Aquaporins Form Hydrophilic Transmembrane Channels for the Passage of Water	418
Ion-Selective Channels Allow Rapid Movement of Ions across Membranes	420
Ion-Channel Function Is Measured Electrically	421
The Structure of a K ⁺ Channel Reveals the Basis for Its Specificity	422
Gated Ion Channels Are Central in Neuronal Function	424
Defective Ion Channels Can Have Severe Physiological Consequences	424
12 Biosignaling	433
12.1 General Features of Signal Transduction	433
BOX 12-1 METHODS: Scatchard Analysis Quantifies the Receptor-Ligand Interaction	435
12.2 G Protein-Coupled Receptors and Second Messengers	437
The β -Adrenergic Receptor System Acts through the Second Messenger cAMP	438

BOX 12-2 MEDICINE: G Proteins: Binary Switches in Health and Disease	441
Several Mechanisms Cause Termination of the β -Adrenergic Response	444
The β -Adrenergic Receptor Is Desensitized by Phosphorylation and by Association with Arrestin	445
Cyclic AMP Acts as a Second Messenger for Many Regulatory Molecules	446
Diacylglycerol, Inositol Trisphosphate, and Ca ²⁺ Have Related Roles as Second Messengers	447
BOX 12-3 METHODS: FRET: Biochemistry Visualized in a Living Cell	448
Calcium Is a Second Messenger That May Be Localized in Space and Time	451
GPCRs Mediate the Actions of a Wide Variety of Signals	452
12.3 Receptor Tyrosine Kinases	453
Stimulation of the Insulin Receptor Initiates a Cascade of Protein Phosphorylation Reactions	453
The Membrane Phospholipid PIP ₃ Functions at a Branch in Insulin Signaling	456
The JAK-STAT Signaling System Also Involves Tyrosine Kinase Activity	457
Cross Talk among Signaling Systems Is Common and Complex	458
12.4 Receptor Guanylyl Cyclases, cGMP, and Protein Kinase G	459
12.5 Multivalent Adaptor Proteins and Membrane Rafts	460
Protein Modules Bind Phosphorylated Tyr, Ser, or Thr Residues in Partner Proteins	460
Membrane Rafts and Caveolae May Segregate Signaling Proteins	463
12.6 Gated Ion Channels	464
Ion Channels Underlie Electrical Signaling in Excitable Cells	464
Voltage-Gated Ion Channels Produce Neuronal Action Potentials	465
The Acetylcholine Receptor Is a Ligand-Gated Ion Channel	467
Neurons Have Receptor Channels That Respond to Different Neurotransmitters	468
Toxins Target Ion Channels	468
12.7 Integrins: Bidirectional Cell Adhesion Receptors	470
12.8 Regulation of Transcription by Nuclear Hormone Receptors	471
12.9 Signaling in Microorganisms and Plants	473
Bacterial Signaling Entails Phosphorylation in a Two-Component System	473
Signaling Systems of Plants Have Some of the Same Components Used by Microbes and Mammals	473
Plants Detect Ethylene through a Two-Component System and a MAPK Cascade	475

Receptorlike Protein Kinases Transduce Signals from Peptides	476
12.10 Sensory Transduction in Vision, Olfaction, and Gustation	477
The Visual System Uses Classic GPCR Mechanisms	477
Excited Rhodopsin Acts through the G Protein Transducin to Reduce the cGMP Concentration	478
The Visual Signal Is Quickly Terminated	480
Cone Cells Specialize in Color Vision	480
BOX 12-4 MEDICINE: Color Blindness: John Dalton's Experiment from the Grave	481
Vertebrate Olfaction and Gustation Use Mechanisms Similar to the Visual System	481
GPCRs of the Sensory Systems Share Several Features with GPCRs of Hormone Signaling Systems	482
12.11 Regulation of the Cell Cycle by Protein Kinases	484
The Cell Cycle Has Four Stages	484
Levels of Cyclin-Dependent Protein Kinases Oscillate	484
CDKs Regulate Cell Division by Phosphorylating Critical Proteins	487
12.12 Oncogenes, Tumor Suppressor Genes, and Programmed Cell Death	488
Oncogenes Are Mutant Forms of the Genes for Proteins That Regulate the Cell Cycle	489
Defects in Certain Genes Remove Normal Restraints on Cell Division	489
BOX 12-5 MEDICINE: Development of Protein Kinase Inhibitors for Cancer Treatment	490
Apoptosis Is Programmed Cell Suicide	492

II BIOENERGETICS AND METABOLISM 501

13 Bioenergetics and Biochemical Reaction Types	505
13.1 Bioenergetics and Thermodynamics	506
Biological Energy Transformations Obey the Laws of Thermodynamics	506
Cells Require Sources of Free Energy	507
Standard Free-Energy Change Is Directly Related to the Equilibrium Constant	507
Actual Free-Energy Changes Depend on Reactant and Product Concentrations	509
Standard Free-Energy Changes Are Additive	510
13.2 Chemical Logic and Common Biochemical Reactions	511
Biochemical and Chemical Equations Are Not Identical	517
13.3 Phosphoryl Group Transfers and ATP	517
The Free-Energy Change for ATP Hydrolysis Is Large and Negative	518
Other Phosphorylated Compounds and Thioesters Also Have Large Free Energies of Hydrolysis	520
ATP Provides Energy by Group Transfers, Not by	

Simple Hydrolysis	522
ATP Donates Phosphoryl, Pyrophosphoryl, and Adenylyl Groups	523
Assembly of Informational Macromolecules Requires Energy	524
BOX 13-1 Firefly Flashes: Glowing Reports of ATP	525
ATP Energizes Active Transport and Muscle Contraction	525
Transphosphorylations between Nucleotides Occur in All Cell Types	526
Inorganic Polyphosphate Is a Potential Phosphoryl Group Donor	527
13.4 Biological Oxidation-Reduction Reactions	528
The Flow of Electrons Can Do Biological Work	528
Oxidation-Reductions Can Be Described as Half-Reactions	528
Biological Oxidations Often Involve Dehydrogenation	529
Reduction Potentials Measure Affinity for Electrons	530
Standard Reduction Potentials Can Be Used to Calculate Free-Energy Change	531
Cellular Oxidation of Glucose to Carbon Dioxide Requires Specialized Electron Carriers	532
A Few Types of Coenzymes and Proteins Serve as Universal Electron Carriers	532
NADH and NADPH Act with Dehydrogenases as Soluble Electron Carriers	532
Dietary Deficiency of Niacin, the Vitamin Form of NAD and NADP, Causes Pellagra	535
Flavin Nucleotides Are Tightly Bound in Flavoproteins	535
14 Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway	543
14.1 Glycolysis	544
An Overview: Glycolysis Has Two Phases	544
The Preparatory Phase of Glycolysis Requires ATP	548
The Payoff Phase of Glycolysis Yields ATP and NADH	550
The Overall Balance Sheet Shows a Net Gain of ATP	555
Glycolysis Is under Tight Regulation	555
BOX 14-1 MEDICINE: High Rate of Glycolysis in Tumors Suggests Targets for Chemotherapy and Facilitates Diagnosis	556
Glucose Uptake Is Deficient in Type 1 Diabetes Mellitus	558
14.2 Feeder Pathways for Glycolysis	558
Dietary Polysaccharides and Disaccharides Undergo Hydrolysis to Monosaccharides	558
Endogenous Glycogen and Starch Are Degraded by Phosphorolysis	560
Other Monosaccharides Enter the Glycolytic Pathway at Several Points	561
14.3 Fates of Pyruvate under Anaerobic Conditions: Fermentation	563
Pyruvate Is the Terminal Electron Acceptor in Lactic Acid Fermentation	563
BOX 14-2 Athletes, Alligators, and Coelacanths:	

BOX 14-2 Athletes, Alligators, and Coelacanths: Glycolysis at Limiting Concentrations of Oxygen	564
Ethanol Is the Reduced Product in Ethanol Fermentation	565
Thiamine Pyrophosphate Carries "Active Acetaldehyde" Groups	565
BOX 14-3 Ethanol Fermentations: Brewing Beer and Producing Biofuels	566
Fermentations Are Used to Produce Some Common Foods and Industrial Chemicals	566
14.4 Gluconeogenesis	568
Conversion of Pyruvate to Phosphoenolpyruvate Requires Two Exergonic Reactions	570
Conversion of Fructose 1,6-Bisphosphate to Fructose 6-Phosphate Is the Second Bypass	572
Conversion of Glucose 6-Phosphate to Glucose Is the Third Bypass	573
Gluconeogenesis Is Energetically Expensive, but Essential	573
Citric Acid Cycle Intermediates and Some Amino Acids Are Glucogenic	574
Mammals Cannot Convert Fatty Acids to Glucose	574
Glycolysis and Gluconeogenesis Are Reciprocally Regulated	574
14.5 Pentose Phosphate Pathway of Glucose Oxidation	575
The Oxidative Phase Produces Pentose Phosphates and NADPH	575
BOX 14-4 MEDICINE: Why Pythagoras Wouldn't Eat Falafel: Glucose 6-Phosphate Dehydrogenase Deficiency	576
The Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate	577
Wernicke-Korsakoff Syndrome Is Exacerbated by a Defect in Transketolase	580
Glucose 6-Phosphate Is Partitioned between Glycolysis and the Pentose Phosphate Pathway	580
15 Principles of Metabolic Regulation	587
15.1 Regulation of Metabolic Pathways	588
Cells and Organisms Maintain a Dynamic Steady State	589
Both the Amount and the Catalytic Activity of an Enzyme Can Be Regulated	589
Reactions Far from Equilibrium in Cells Are Common Points of Regulation	592
Adenine Nucleotides Play Special Roles in Metabolic Regulation	594
15.2 Analysis of Metabolic Control	596
The Contribution of Each Enzyme to Flux through a Pathway Is Experimentally Measurable	596
The Flux Control Coefficient Quantifies the Effect of a Change in Enzyme Activity on Metabolite Flux through a Pathway	597
The Elasticity Coefficient Is Related to an Enzyme's Responsiveness to Changes in Metabolite or Regulator Concentrations	597
BOX 15-1 METHODS: Metabolic Control Analysis: Quantitative Aspects	598

The Response Coefficient Expresses the Effect of an Outside Controller on Flux through a Pathway	598
Metabolic Control Analysis Has Been Applied to Carbohydrate Metabolism, with Surprising Results	599
Metabolic Control Analysis Suggests a General Method for Increasing Flux through a Pathway	600
15.3 Coordinated Regulation of Glycolysis and Gluconeogenesis	601
Hexokinase Isozymes of Muscle and Liver Are Affected Differently by Their Product, Glucose 6-Phosphate	602
BOX 15-2 Isozymes: Different Proteins That Catalyze the Same Reaction	602
Hexokinase IV (Glucokinase) and Glucose 6-Phosphatase Are Transcriptionally Regulated	603
Phosphofructokinase-1 and Fructose 1,6-Bisphosphatase Are Reciprocally Regulated	604
Fructose 2,6-Bisphosphate Is a Potent Allosteric Regulator of PFK-1 and FBPase-1	605
Xylulose 5-Phosphate Is a Key Regulator of Carbohydrate and Fat Metabolism	606
The Glycolytic Enzyme Pyruvate Kinase Is Allosterically Inhibited by ATP	606
The Gluconeogenic Conversion of Pyruvate to Phosphoenol Pyruvate Is Under Multiple Types of Regulation	608
Transcriptional Regulation of Glycolysis and Gluconeogenesis Changes the Number of Enzyme Molecules	608
BOX 15-3 MEDICINE: Genetic Mutations That Lead to Rare Forms of Diabetes	611
15.4 The Metabolism of Glycogen in Animals	612
Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase	613
Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose	614
The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis	615
BOX 15-4 Carl and Gerty Cori: Pioneers in Glycogen Metabolism and Disease	616
Glycogenin Primes the Initial Sugar Residues in Glycogen	619
15.5 Coordinated Regulation of Glycogen Synthesis and Breakdown	620
Glycogen Phosphorylase Is Regulated Allosterically and Hormonally	621
Glycogen Synthase Is Also Regulated by Phosphorylation and Dephosphorylation	623
Glycogen Synthase Kinase 3 Mediates Some of the Actions of Insulin	624
Phosphoprotein Phosphatase 1 Is Central to Glycogen Metabolism	624
Allosteric and Hormonal Signals Coordinate Carbohydrate Metabolism Globally	624
Carbohydrate and Lipid Metabolism Are Integrated by Hormonal and Allosteric Mechanisms	626

16 The Citric Acid Cycle	633
16.1 Production of Acetyl-CoA (Activated Acetate)	633
Pyruvate Is Oxidized to Acetyl-CoA and CO ₂	634
The Pyruvate Dehydrogenase Complex Requires Five Coenzymes	634
The Pyruvate Dehydrogenase Complex Consists of Three Distinct Enzymes	635
In Substrate Channeling, Intermediates Never Leave the Enzyme Surface	636
16.2 Reactions of the Citric Acid Cycle	638
The Sequence of Reactions in the Citric Acid Cycle Makes Chemical Sense	638
The Citric Acid Cycle Has Eight Steps	640
BOX 16-1 Moonlighting Enzymes: Proteins with More Than One Job	642
BOX 16-2 Synthases and Synthetases; Ligases and Lyases; Kinases, Phosphatases, and Phosphorylases: Yes, the Names Are Confusing!	646
The Energy of Oxidations in the Cycle Is Efficiently Conserved	647
BOX 16-3 Citrate: A Symmetric Molecule That Reacts Asymmetrically	648
Why Is the Oxidation of Acetate So Complicated? Citric Acid Cycle Components Are Important	649
Biosynthetic Intermediates	650
Anaplerotic Reactions Replenish Citric Acid Cycle Intermediates	650
Biotin in Pyruvate Carboxylase Carries CO ₂ Groups	651
16.3 Regulation of the Citric Acid Cycle	653
Production of Acetyl-CoA by the Pyruvate Dehydrogenase Complex Is Regulated by Allosteric and Covalent Mechanisms	654
The Citric Acid Cycle Is Regulated at Its Three Exergonic Steps	655
Substrate Channeling through Multienzyme Complexes May Occur in the Citric Acid Cycle	655
Some Mutations in Enzymes of the Citric Acid Cycle Lead to Cancer	656
16.4 The Glyoxylate Cycle	656
The Glyoxylate Cycle Produces Four-Carbon Compounds from Acetate	657
The Citric Acid and Glyoxylate Cycles Are Coordinately Regulated	658
17 Fatty Acid Catabolism	667
17.1 Digestion, Mobilization, and Transport of Fats	668
Dietary Fats Are Absorbed in the Small Intestine	668
Hormones Trigger Mobilization of Stored Triacylglycerols	669
Fatty Acids Are Activated and Transported into Mitochondria	670
17.2 Oxidation of Fatty Acids	672
The β Oxidation of Saturated Fatty Acids Has Four Basic Steps	673
The Four β -Oxidation Steps Are Repeated to Yield Acetyl-CoA and ATP	674

Acetyl-CoA Can Be Further Oxidized in the Citric Acid Cycle	675
BOX 17-1 Fat Bears Carry Out β Oxidation in Their Sleep	676
Oxidation of Unsaturated Fatty Acids Requires Two Additional Reactions	677
Complete Oxidation of Odd-Number Fatty Acids Requires Three Extra Reactions	677
Fatty Acid Oxidation Is Tightly Regulated	678
Transcription Factors Turn on the Synthesis of Proteins for Lipid Catabolism	679
BOX 17-2 Coenzyme B₁₂: A Radical Solution to a Perplexing Problem	680
Genetic Defects in Fatty Acyl-CoA Dehydrogenases Cause Serious Disease	682
Peroxisomes Also Carry Out β Oxidation	682
Plant Peroxisomes and Glyoxysomes Use Acetyl-CoA from β Oxidation as a Biosynthetic Precursor	683
The β -Oxidation Enzymes of Different Organelles Have Diverged during Evolution	683
The ω Oxidation of Fatty Acids Occurs in the Endoplasmic Reticulum	684
Phytanic Acid Undergoes α Oxidation in Peroxisomes	685
17.3 Ketone Bodies	686
Ketone Bodies, Formed in the Liver, Are Exported to Other Organs as Fuel	686
Ketone Bodies Are Overproduced in Diabetes and during Starvation	688
18 Amino Acid Oxidation and the Production of Urea	695
18.1 Metabolic Fates of Amino Groups	696
Dietary Protein Is Enzymatically Degraded to Amino Acids	697
Pyridoxal Phosphate Participates in the Transfer of α -Amino Groups to α -Ketoglutarate	699
Glutamate Releases Its Amino Group As Ammonia in the Liver	700
Glutamine Transports Ammonia in the Bloodstream	702
Alanine Transports Ammonia from Skeletal Muscles to the Liver	703
Ammonia Is Toxic to Animals	703
18.2 Nitrogen Excretion and the Urea Cycle	704
Urea Is Produced from Ammonia in Five Enzymatic Steps	704
The Citric Acid and Urea Cycles Can Be Linked	706
The Activity of the Urea Cycle Is Regulated at Two Levels	708
Pathway Interconnections Reduce the Energetic Cost of Urea Synthesis	708
BOX 18-1 MEDICINE: Assays for Tissue Damage	708
Genetic Defects in the Urea Cycle Can Be Life-Threatening	709
18.3 Pathways of Amino Acid Degradation	710
Some Amino Acids Are Converted to Glucose, Others to Ketone Bodies	711
Several Enzyme Cofactors Play Important Roles in Amino Acid Catabolism	712

Six Amino Acids Are Degraded to Pyruvate	715
Seven Amino Acids Are Degraded to Acetyl-CoA	717
Phenylalanine Catabolism Is Genetically Defective in Some People	719
Five Amino Acids Are Converted to α -Ketoglutarate	721
Four Amino Acids Are Converted to Succinyl-CoA	722
Branched-Chain Amino Acids Are Not Degraded in the Liver	723
BOX 18-2 MEDICINE: Scientific Sleuths Solve a Murder Mystery	724
Asparagine and Aspartate Are Degraded to Oxaloacetate	724
19 Oxidative Phosphorylation and Photophosphorylation	731
OXIDATIVE PHOSPHORYLATION	732
19.1 Electron-Transfer Reactions in Mitochondria	732
Electrons Are Funneled to Universal Electron Acceptors	734
Electrons Pass through a Series of Membrane-Bound Carriers	735
Electron Carriers Function in Multienzyme Complexes	737
Mitochondrial Complexes May Associate in Respirasomes	743
The Energy of Electron Transfer Is Efficiently Conserved in a Proton Gradient	743
Reactive Oxygen Species Are Generated during Oxidative Phosphorylation	745
BOX 19-1 Hot, Stinking Plants and Alternative Respiratory Pathways	746
Plant Mitochondria Have Alternative Mechanisms for Oxidizing NADH	746
19.2 ATP Synthesis	747
ATP Synthase Has Two Functional Domains, F_0 and F_1	750
ATP Is Stabilized Relative to ADP on the Surface of F_1	750
The Proton Gradient Drives the Release of ATP from the Enzyme Surface	751
Each β Subunit of ATP Synthase Can Assume Three Different Conformations	752
Rotational Catalysis Is Key to the Binding-Change Mechanism for ATP Synthesis	752
How Does Proton Flow through the F_0 Complex Produce Rotary Motion?	755
Chemiosmotic Coupling Allows Nonintegral Stoichiometries of O_2 Consumption and ATP Synthesis	755
BOX 19-2 METHODS: Atomic Force Microscopy to Visualize Membrane Proteins	756
The Proton-Motive Force Energizes Active Transport	757
Shuttle Systems Indirectly Convey Cytosolic NADH into Mitochondria for Oxidation	758
19.3 Regulation of Oxidative Phosphorylation	759
Oxidative Phosphorylation Is Regulated by Cellular Energy Needs	760
An Inhibitory Protein Prevents ATP Hydrolysis during Hypoxia	760

Hypoxia Leads to ROS Production and Several Adaptive Responses	760
ATP-Producing Pathways Are Coordinately Regulated	761
19.4 Mitochondria in Thermogenesis, Steroid Synthesis, and Apoptosis	762
Uncoupled Mitochondria in Brown Adipose Tissue Produce Heat	762
Mitochondrial P-450 Oxygenases Catalyze Steroid Hydroxylations	763
Mitochondria Are Central to the Initiation of Apoptosis	764
19.5 Mitochondrial Genes: Their Origin and the Effects of Mutations	765
Mitochondria Evolved from Endosymbiotic Bacteria	765
Mutations in Mitochondrial DNA Accumulate throughout the Life of the Organism	766
Some Mutations in Mitochondrial Genomes Cause Disease	767
Diabetes Can Result from Defects in the Mitochondria of Pancreatic β Cells	768
PHOTOSYNTHESIS: HARVESTING LIGHT ENERGY	769
19.6 General Features of Photophosphorylation	769
Photosynthesis in Plants Takes Place in Chloroplasts	769
Light Drives Electron Flow in Chloroplasts	770
19.7 Light Absorption	771
Chlorophylls Absorb Light Energy for Photosynthesis	771
Accessory Pigments Extend the Range of Light Absorption	773
Chlorophyll Funnel the Absorbed Energy to Reaction Centers by Exciton Transfer	774
19.8 The Central Photochemical Event: Light-Driven Electron Flow	776
Bacteria Have One of Two Types of Single Photochemical Reaction Center	776
Kinetic and Thermodynamic Factors Prevent the Dissipation of Energy by Internal Conversion	778
In Plants, Two Reaction Centers Act in Tandem	779
Antenna Chlorophylls Are Tightly Integrated with Electron Carriers	781
The Cytochrome b_6f Complex Links Photosystems II and I	782
Cyclic Electron Flow between PSI and the Cytochrome b_6f Complex Increases the Production of ATP Relative to NADPH	783
State Transitions Change the Distribution of LHCII between the Two Photosystems	783
Water Is Split by the Oxygen-Evolving Complex	784
19.9 ATP Synthesis by Photophosphorylation	786
A Proton Gradient Couples Electron Flow and Phosphorylation	786
The Approximate Stoichiometry of Photophosphorylation Has Been Established	787
The ATP Synthase of Chloroplasts Is Like That of Mitochondria	787

19.10 The Evolution of Oxygenic Photosynthesis	788
Chloroplasts Evolved from Ancient Photosynthetic Bacteria	788
In <i>Halobacterium</i> , a Single Protein Absorbs Light and Pumps Protons to Drive ATP Synthesis	789
20 Carbohydrate Biosynthesis in Plants and Bacteria	799
20.1 Photosynthetic Carbohydrate Synthesis	799
Plastids Are Organelles Unique to Plant Cells and Algae	800
Carbon Dioxide Assimilation Occurs in Three Stages	801
Synthesis of Each Triose Phosphate from CO_2 Requires Six NADPH and Nine ATP	808
A Transport System Exports Triose Phosphates from the Chloroplast and Imports Phosphate	809
Four Enzymes of the Calvin Cycle Are Indirectly Activated by Light	810
20.2 Photorespiration and the C_4 and CAM Pathways	812
Photorespiration Results from Rubisco's Oxygenase Activity	812
The Salvage of Phosphoglycolate Is Costly	813
In C_4 Plants, CO_2 Fixation and Rubisco Activity Are Spatially Separated	815
BOX 20-1 Will Genetic Engineering of Photosynthetic Organisms Increase Their Efficiency?	816
In CAM Plants, CO_2 Capture and Rubisco Action Are Temporally Separated	818
20.3 Biosynthesis of Starch and Sucrose	818
ADP-Glucose Is the Substrate for Starch Synthesis in Plant Plastids and for Glycogen Synthesis in Bacteria	818
UDP-Glucose Is the Substrate for Sucrose Synthesis in the Cytosol of Leaf Cells	819
Conversion of Triose Phosphates to Sucrose and Starch Is Tightly Regulated	820
20.4 Synthesis of Cell Wall Polysaccharides: Plant Cellulose and Bacterial Peptidoglycan	821
Cellulose Is Synthesized by Supramolecular Structures in the Plasma Membrane	822
Lipid-Linked Oligosaccharides Are Precursors for Bacterial Cell Wall Synthesis	823
20.5 Integration of Carbohydrate Metabolism in the Plant Cell	825
Gluconeogenesis Converts Fats and Proteins to Glucose in Germinating Seeds	825
Pools of Common Intermediates Link Pathways in Different Organelles	826
21 Lipid Biosynthesis	833
21.1 Biosynthesis of Fatty Acids and Eicosanoids	833
Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate	833
Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence	834
The Mammalian Fatty Acid Synthase Has Multiple Active Sites	834

Fatty Acid Synthase Receives the Acetyl and Malonyl Groups	836
The Fatty Acid Synthase Reactions Are Repeated to Form Palmitate	838
Fatty Acid Synthesis Occurs in the Cytosol of Many Organisms but in the Chloroplasts of Plants	839
Acetate Is Shuttled out of Mitochondria as Citrate	840
Fatty Acid Biosynthesis Is Tightly Regulated	840
Long-Chain Saturated Fatty Acids Are Synthesized from Palmitate	842
Desaturation of Fatty Acids Requires a Mixed-Function Oxidase	842
BOX 21-1 MEDICINE: Mixed-Function Oxidases, Cytochrome P-450 Enzymes, and Drug Overdoses	844
Eicosanoids Are Formed from 20-Carbon Polyunsaturated Fatty Acids	845
21.2 Biosynthesis of Triacylglycerols	848
Triacylglycerols and Glycerophospholipids Are Synthesized from the Same Precursors	848
Triacylglycerol Biosynthesis in Animals Is Regulated by Hormones	849
Adipose Tissue Generates Glycerol 3-phosphate by Glyceroneogenesis	850
Thiazolidinediones Treat Type 2 Diabetes by Increasing Glyceroneogenesis	852
21.3 Biosynthesis of Membrane Phospholipids	852
Cells Have Two Strategies for Attaching Phospholipid Head Groups	852
Phospholipid Synthesis in <i>E. coli</i> Employs CDP-Diacylglycerol	853
Eukaryotes Synthesize Anionic Phospholipids from CDP-Diacylglycerol	855
Eukaryotic Pathways to Phosphatidylserine, Phosphatidylethanolamine, and Phosphatidylcholine Are Interrelated	855
Plasmalogen Synthesis Requires Formation of an Ether-Linked Fatty Alcohol	856
Sphingolipid and Glycerophospholipid Synthesis Share Precursors and Some Mechanisms	857
Polar Lipids Are Targeted to Specific Cellular Membranes	857
21.4 Cholesterol, Steroids, and Isoprenoids: Biosynthesis, Regulation, and Transport	859
Cholesterol Is Made from Acetyl-CoA in Four Stages	860
Cholesterol Has Several Fates	864
Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins	864
BOX 21-2 MEDICINE: ApoE Alleles Predict Incidence of Alzheimer Disease	866
Cholesteryl Esters Enter Cells by Receptor-Mediated Endocytosis	868
HDL Carries Out Reverse Cholesterol Transport	869
Cholesterol Synthesis and Transport Is Regulated at Several Levels	869
Dysregulation of Cholesterol Metabolism Can Lead to Cardiovascular Disease	871
BOX 21-3 MEDICINE: The Lipid Hypothesis and the Development of Statins	872
Reverse Cholesterol Transport by HDL Counters Plaque Formation and Atherosclerosis	873

Steroid Hormones Are Formed by Side-Chain Cleavage and Oxidation of Cholesterol	874	Degradation of Purines and Pyrimidines Produces Uric Acid and Urea, Respectively	920
Intermediates in Cholesterol Biosynthesis Have Many Alternative Fates	874	Purine and Pyrimidine Bases Are Recycled by Salvage Pathways	922
		Excess Uric Acid Causes Gout	922
		Many Chemotherapeutic Agents Target Enzymes in the Nucleotide Biosynthetic Pathways	923
22 Biosynthesis of Amino Acids, Nucleotides, and Related Molecules	881	23 Hormonal Regulation and Integration of Mammalian Metabolism	929
22.1 Overview of Nitrogen Metabolism	881	23.1 Hormones: Diverse Structures for Diverse Functions	929
The Nitrogen Cycle Maintains a Pool of Biologically Available Nitrogen	882	The Detection and Purification of Hormones Requires a Bioassay	930
Nitrogen Is Fixed by Enzymes of the Nitrogenase Complex	882	BOX 23-1 MEDICINE: How Is a Hormone Discovered? The Arduous Path to Purified Insulin	931
BOX 22-1 Unusual Lifestyles of the Obscure but Abundant	884	Hormones Act through Specific High-Affinity Cellular Receptors	932
Ammonia Is Incorporated into Biomolecules through Glutamate and Glutamine	888	Hormones Are Chemically Diverse	933
Glutamine Synthetase Is a Primary Regulatory Point in Nitrogen Metabolism	889	Hormone Release Is Regulated by a Hierarchy of Neuronal and Hormonal Signals	936
Several Classes of Reactions Play Special Roles in the Biosynthesis of Amino Acids and Nucleotides	890	23.2 Tissue-Specific Metabolism: The Division of Labor	939
22.2 Biosynthesis of Amino Acids	891	The Liver Processes and Distributes Nutrients	939
α -Ketoglutarate Gives Rise to Glutamate, Glutamine, Proline, and Arginine	892	Adipose Tissues Store and Supply Fatty Acids	943
Serine, Glycine, and Cysteine Are Derived from 3-Phosphoglycerate	892	Brown Adipose Tissue Is Thermogenic	944
Three Nonessential and Six Essential Amino Acids Are Synthesized from Oxaloacetate and Pyruvate	895	Muscles Use ATP for Mechanical Work	944
Chorismate Is a Key Intermediate in the Synthesis of Tryptophan, Phenylalanine, and Tyrosine	898	BOX 23-2 Creatine and Creatine Kinase: Invaluable Diagnostic Aids and the Muscle Builder's Friends	946
Histidine Biosynthesis Uses Precursors of Purine Biosynthesis	898	The Brain Uses Energy for Transmission of Electrical Impulses	948
Amino Acid Biosynthesis Is under Allosteric Regulation	899	Blood Carries Oxygen, Metabolites, and Hormones	949
22.3 Molecules Derived from Amino Acids	902	23.3 Hormonal Regulation of Fuel Metabolism	951
Glycine Is a Precursor of Porphyrins	902	Insulin Counters High Blood Glucose	951
Heme Is the Source of Bile Pigments	904	Pancreatic β Cells Secrete Insulin in Response to Changes in Blood Glucose	953
BOX 22-2 MEDICINE: On Kings and Vampires	906	Glucagon Counters Low Blood Glucose	955
Amino Acids Are Precursors of Creatine and Glutathione	906	During Fasting and Starvation, Metabolism Shifts to Provide Fuel for the Brain	956
D-Amino Acids Are Found Primarily in Bacteria	907	Epinephrine Signals Impending Activity	958
Aromatic Amino Acids Are Precursors of Many Plant Substances	908	Cortisol Signals Stress, Including Low Blood Glucose	958
Biological Amines Are Products of Amino Acid Decarboxylation	908	Diabetes Mellitus Arises from Defects in Insulin Production or Action	959
Arginine Is the Precursor for Biological Synthesis of Nitric Oxide	909	23.4 Obesity and the Regulation of Body Mass	960
22.4 Biosynthesis and Degradation of Nucleotides	910	Adipose Tissue Has Important Endocrine Functions	960
De Novo Purine Nucleotide Synthesis Begins with PRPP	912	Leptin Stimulates Production of Anorexigenic Peptide Hormones	962
Purine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition	914	Leptin Triggers a Signaling Cascade That Regulates Gene Expression	962
Pyrimidine Nucleotides Are Made from Aspartate, PRPP, and Carbamoyl Phosphate	915	The Leptin System May Have Evolved to Regulate the Starvation Response	963
Pyrimidine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition	916	Insulin Acts in the Arcuate Nucleus to Regulate Eating and Energy Conservation	963
Nucleoside Monophosphates Are Converted to Nucleoside Triphosphates	916	Adiponectin Acts through AMPK to Increase Insulin Sensitivity	964
Ribonucleotides Are the Precursors of Deoxyribonucleotides	917	mTORC1 Activity Coordinates Cell Growth with the Supply of Nutrients and Energy	965
Thymidylate Is Derived from dCDP and dUMP	920	Diet Regulates the Expression of Genes Central to Maintaining Body Mass	965
		Short-Term Eating Behavior Is Influenced by Ghrelin and PYY ₃₋₃₆	966

Microbial Symbionts in the Gut Influence Energy Metabolism and Adipogenesis	968	25.2 DNA Repair	1027
23.5 Obesity, the Metabolic Syndrome, and Type 2 Diabetes	968	Mutations Are Linked to Cancer	1027
In Type 2 Diabetes the Tissues Become Insensitive to Insulin	968	All Cells Have Multiple DNA Repair Systems	1028
Type 2 Diabetes Is Managed with Diet, Exercise, and Medication	970	The Interaction of Replication Forks with DNA Damage Can Lead to Error-Prone Translesion DNA Synthesis	1034
		BOX 25-1 MEDICINE: DNA Repair and Cancer	1037
III INFORMATION PATHWAYS	977	25.3 DNA Recombination	1038
24 Genes and Chromosomes	979	Bacterial Homologous Recombination Is a DNA Repair Function	1039
24.1 Chromosomal Elements	979	Eukaryotic Homologous Recombination Is Required for Proper Chromosome Segregation during Meiosis	1041
Genes Are Segments of DNA That Code for Polypeptide Chains and RNAs	979	Recombination during Meiosis Is Initiated with Double-Strand Breaks	1043
DNA Molecules Are Much Longer Than the Cellular or Viral Packages That Contain Them	980	BOX 25-2 MEDICINE: Why Proper Chromosomal Segregation Matters	1045
Eukaryotic Genes and Chromosomes Are Very Complex	984	Site-Specific Recombination Results in Precise DNA Rearrangements	1046
24.2 DNA Supercoiling	985	Transposable Genetic Elements Move from One Location to Another	1049
Most Cellular DNA Is Underwound	986	Immunoglobulin Genes Assemble by Recombination	1049
DNA Underwinding Is Defined by Topological Linking Number	988	26 RNA Metabolism	1057
Topoisomerases Catalyze Changes in the Linking Number of DNA	989	26.1 DNA-Dependent Synthesis of RNA	1058
DNA Compaction Requires a Special Form of Supercoiling	990	RNA Is Synthesized by RNA Polymerases	1058
BOX 24-1 MEDICINE: Curing Disease by Inhibiting Topoisomerases	992	RNA Synthesis Begins at Promoters	1060
24.3 The Structure of Chromosomes	994	Transcription Is Regulated at Several Levels	1061
Chromatin Consists of DNA and Proteins	994	BOX 26-1 METHODS: RNA Polymerase Leaves Its Footprint on a Promoter	1062
Histones Are Small, Basic Proteins	995	Specific Sequences Signal Termination of RNA Synthesis	1063
Nucleosomes Are the Fundamental Organizational Units of Chromatin	995	Eukaryotic Cells Have Three Kinds of Nuclear RNA Polymerases	1064
Nucleosomes Are Packed into Successively Higher-Order Structures	997	RNA Polymerase II Requires Many Other Protein Factors for Its Activity	1064
BOX 24-2 MEDICINE: Epigenetics, Nucleosome Structure, and Histone Variants	998	DNA-Dependent RNA Polymerase Undergoes Selective Inhibition	1068
Condensed Chromosome Structures Are Maintained by SMC Proteins	1000	26.2 RNA Processing	1069
Bacterial DNA Is Also Highly Organized	1002	Eukaryotic mRNAs Are Capped at the 5' End	1070
25 DNA Metabolism	1009	Both Introns and Exons Are Transcribed from DNA into RNA	1070
25.1 DNA Replication	1011	RNA Catalyzes the Splicing of Introns	1070
DNA Replication Follows a Set of Fundamental Rules	1011	Eukaryotic mRNAs Have a Distinctive 3' End Structure	1075
DNA Is Degraded by Nucleases	1013	A Gene Can Give Rise to Multiple Products by Differential RNA Processing	1075
DNA Is Synthesized by DNA Polymerases	1013	Ribosomal RNAs and tRNAs Also Undergo Processing	1077
Replication Is Very Accurate	1015	Special-Function RNAs Undergo Several Types of Processing	1081
<i>E. coli</i> Has at Least Five DNA Polymerases	1016	RNA Enzymes Are the Catalysts of Some Events in RNA Metabolism	1082
DNA Replication Requires Many Enzymes and Protein Factors	1017	Cellular mRNAs Are Degraded at Different Rates	1084
Replication of the <i>E. coli</i> Chromosome Proceeds in Stages	1019	Polynucleotide Phosphorylase Makes Random RNA-Like Polymers	1085
Replication in Eukaryotic Cells Is Similar but More Complex	1025	26.3 RNA-Dependent Synthesis of RNA and DNA	1085
Viral DNA Polymerases Provide Targets for Antiviral Therapy	1026	Reverse Transcriptase Produces DNA from Viral RNA	1086
		Some Retroviruses Cause Cancer and AIDS	1088

Many Transposons, Retroviruses, and Introns May Have a Common Evolutionary Origin	1088	Protein Degradation Is Mediated by Specialized Systems in All Cells	1147
BOX 26-2 MEDICINE: Fighting AIDS with Inhibitors of HIV Reverse Transcriptase	1089	28 Regulation of Gene Expression	1155
Telomerase Is a Specialized Reverse Transcriptase	1089	28.1 Principles of Gene Regulation	1156
Some Viral RNAs Are Replicated by RNA-Dependent RNA Polymerase	1092	RNA Polymerase Binds to DNA at Promoters	1156
RNA Synthesis Offers Important Clues to Biochemical Evolution	1092	Transcription Initiation Is Regulated by Proteins That Bind to or near Promoters	1157
BOX 26-3 METHODS: The SELEX Method for Generating RNA Polymers with New Functions	1095	Many Bacterial Genes Are Clustered and Regulated in Operons	1158
BOX 26-4 An Expanding RNA Universe Filled with TUF RNAs	1096	The <i>lac</i> Operon Is Subject to Negative Regulation	1159
27 Protein Metabolism	1103	Regulatory Proteins Have Discrete DNA-Binding Domains	1160
27.1 The Genetic Code	1103	Regulatory Proteins Also Have Protein-Protein Interaction Domains	1163
The Genetic Code Was Cracked Using Artificial mRNA Templates	1104	28.2 Regulation of Gene Expression in Bacteria	1165
BOX 27-1 Exceptions That Prove the Rule: Natural Variations in the Genetic Code	1108	The <i>lac</i> Operon Undergoes Positive Regulation	1165
Wobble Allows Some tRNAs to Recognize More than One Codon	1108	Many Genes for Amino Acid Biosynthetic Enzymes Are Regulated by Transcription Attenuation	1167
The Genetic Code Is Mutation-Resistant	1110	Induction of the SOS Response Requires Destruction of Repressor Proteins	1169
Translational Frameshifting and RNA Editing Affect How the Code Is Read	1111	Synthesis of Ribosomal Proteins Is Coordinated with rRNA Synthesis	1170
27.2 Protein Synthesis	1113	The Function of Some mRNAs Is Regulated by Small RNAs in Cis or in Trans	1171
Protein Biosynthesis Takes Place in Five Stages	1114	Some Genes Are Regulated by Genetic Recombination	1173
The Ribosome Is a Complex Supramolecular Machine	1115	28.3 Regulation of Gene Expression in Eukaryotes	1175
BOX 27-2 From an RNA World to a Protein World	1117	Transcriptionally Active Chromatin Is Structurally Distinct from Inactive Chromatin	1175
Transfer RNAs Have Characteristic Structural Features	1118	Most Eukaryotic Promoters Are Positively Regulated	1176
Stage 1: Aminoacyl-tRNA Synthetases Attach the Correct Amino Acids to Their tRNAs	1119	DNA-Binding Activators and Coactivators Facilitate Assembly of the General Transcription Factors	1177
Proofreading by Aminoacyl-tRNA Synthetases	1121	The Genes of Galactose Metabolism in Yeast Are Subject to Both Positive and Negative Regulation	1180
Interaction between an Aminoacyl-tRNA Synthetase and a tRNA: A "Second Genetic Code"	1122	Transcription Activators Have a Modular Structure	1181
BOX 27-3 Natural and Unnatural Expansion of the Genetic Code	1124	Eukaryotic Gene Expression Can Be Regulated by Intercellular and Intracellular Signals	1182
Stage 2: A Specific Amino Acid Initiates Protein Synthesis	1127	Regulation Can Result from Phosphorylation of Nuclear Transcription Factors	1184
Stage 3: Peptide Bonds Are Formed in the Elongation Stage	1129	Many Eukaryotic mRNAs Are Subject to Translational Repression	1184
Stage 4: Termination of Polypeptide Synthesis Requires a Special Signal	1134	Posttranscriptional Gene Silencing Is Mediated by RNA Interference	1185
BOX 27-4 Induced Variation in the Genetic Code: Nonsense Suppression	1134	RNA-Mediated Regulation of Gene Expression Takes Many Forms in Eukaryotes	1186
Stage 5: Newly Synthesized Polypeptide Chains Undergo Folding and Processing	1136	Development Is Controlled by Cascades of Regulatory Proteins	1186
Protein Synthesis Is Inhibited by Many Antibiotics and Toxins	1138	Stem Cells Have Developmental Potential That Can Be Controlled	1191
27.3 Protein Targeting and Degradation	1139	BOX 28-1 Of Fins, Wings, Beaks, and Things	1194
Posttranslational Modification of Many Eukaryotic Proteins Begins in the Endoplasmic Reticulum	1140	Abbreviated Solutions to Problems	AS-1
Glycosylation Plays a Key Role in Protein Targeting	1141	Glossary	G-1
Signal Sequences for Nuclear Transport Are Not Cleaved	1143	Credits	C-0
Bacteria Also Use Signal Sequences for Protein Targeting	1145	Index	I-1
Cells Import Proteins by Receptor-Mediated Endocytosis	1146		

The Foundations of Biochemistry

1.1 Cellular Foundations	2
1.2 Chemical Foundations	11
1.3 Physical Foundations	20
1.4 Genetic Foundations	29
1.5 Evolutionary Foundations	32

About fourteen billion years ago, the universe arose as a cataclysmic explosion of hot, energy-rich subatomic particles. Within seconds, the simplest elements (hydrogen and helium) were formed. As the universe expanded and cooled, material condensed under the influence of gravity to form stars. Some stars became enormous and then exploded as supernovae, releasing the energy needed to fuse simpler atomic nuclei into the more complex elements. Atoms and molecules formed swirling masses of dust particles, and their accumulation led eventually to the formation of rocks, planetoids, and planets. Thus were produced, over billions of years, Earth itself and the chemical elements found on Earth today. About four billion years ago, life arose—simple microorganisms with the ability to extract energy from chemical compounds and, later, from sunlight, which they used to make a vast array of more complex **biomolecules** from the simple elements and compounds on the Earth's surface. We and all other living organisms are made of stardust.

Biochemistry asks how the remarkable properties of living organisms arise from the thousands of different biomolecules. When these molecules are isolated and examined individually, they conform to all the physical and chemical laws that describe the behavior of inanimate matter—as do all the processes occurring in living organisms. The study of biochemistry shows how the collections of inanimate molecules that constitute living organisms interact to maintain and perpetuate life animated solely by the physical and chemical laws that govern the nonliving universe.

Yet organisms possess extraordinary attributes, properties that distinguish them from other collections

of matter. What are these distinguishing features of living organisms?

A high degree of chemical complexity and microscopic organization. Thousands of different molecules make up a cell's intricate internal structures (**Fig. 1-1a**). These include very long polymers, each with its characteristic sequence of subunits, its unique three-dimensional structure, and its highly specific selection of binding partners in the cell.

Systems for extracting, transforming, and using energy from the environment (Fig. 1-1b), enabling organisms to build and maintain their intricate structures and to do mechanical, chemical, osmotic, and electrical work. This counteracts the tendency of all matter to decay toward a more disordered state, to come to equilibrium with its surroundings.

Defined functions for each of an organism's components and regulated interactions among them. This is true not only of macroscopic structures, such as leaves and stems or hearts and lungs, but also of microscopic intracellular structures and individual chemical compounds. The interplay among the chemical components of a living organism is dynamic; changes in one component cause coordinating or compensating changes in another, with the whole ensemble displaying a character beyond that of its individual parts. The collection of molecules carries out a program, the end result of which is reproduction of the program and self-perpetuation of that collection of molecules—in short, life.

Mechanisms for sensing and responding to alterations in their surroundings. Organisms constantly adjust to these changes by adapting their internal chemistry or their location in the environment.

A capacity for precise self-replication and self-assembly (Fig. 1-1c). A single bacterial cell placed in a sterile nutrient medium can give rise to