

Contents in Brief

Preface	viii
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	187
7 Carbohydrates and Glycobiology	241
8 Nucleotides and Nucleic Acids	279
9 DNA-Based Information Technologies	319
10 Lipids	361
11 Biological Membranes and Transport	387
12 Biosignaling	437
II BIOENERGETICS AND METABOLISM	491
13 Bioenergetics and Biochemical Reaction Types	495
14 Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway	533
15 Principles of Metabolic Regulation	575
16 The Citric Acid Cycle	619
17 Fatty Acid Catabolism	649
18 Amino Acid Oxidation and the Production of Urea	675
19 Oxidative Phosphorylation	711
20 Photosynthesis and Carbohydrate Synthesis in Plants	755
21 Lipid Biosynthesis	811
22 Biosynthesis of Amino Acids, Nucleotides, and Related Molecules	859
23 Hormonal Regulation and Integration of Mammalian Metabolism	907
III INFORMATION PATHWAYS	955
24 Genes and Chromosomes	957
25 DNA Metabolism	987
26 RNA Metabolism	1035
27 Protein Metabolism	1077
28 Regulation of Gene Expression	1127
Abbreviated Solutions to Problems	AS-1
Glossary	G-1
Index	I-1

Contents

1 The Foundations of Biochemistry	1
1.1 Cellular Foundations	3
Cells Are the Structural and Functional Units of All Living Organisms	3
Cellular Dimensions Are Limited by Diffusion	3
Organisms Belong to Three Distinct Domains of Life	4
Organisms Differ Widely in Their Sources of Energy and Biosynthetic Precursors	5
Bacterial and Archaeal Cells Share Common Features but Differ in Important Ways	6
Eukaryotic Cells Have a Variety of Membranous Organelles, Which Can Be Isolated for Study	7
The Cytoplasm Is Organized by the Cytoskeleton and Is Highly Dynamic	7
Cells Build Supramolecular Structures	9
In Vitro Studies May Overlook Important Interactions among Molecules	11
1.2 Chemical Foundations	12
Biomolecules Are Compounds of Carbon with a Variety of Functional Groups	12
BOX 1-1 Molecular Weight, Molecular Mass, and Their Correct Units	13
Cells Contain a Universal Set of Small Molecules	13
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: <i>In Vino, Veritas</i>	18
Interactions between Biomolecules Are Stereospecific	19
1.3 Physical Foundations	21
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	29
1.4 Genetic Foundations	29
Genetic Continuity Is Vested in Single DNA Molecules	30
The Structure of DNA Allows Its Replication and Repair with Near-Perfect Fidelity	31
The Linear Sequence in DNA Encodes Proteins with Three-Dimensional Structures	31
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	37
Molecular Anatomy Reveals Evolutionary Relationships	37
Functional Genomics Shows the Allocations of Genes to Specific Cellular Processes	39
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 Solute	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
Solute 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 75

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	88

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 Help 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 116

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
BOX 4-1 METHODS Knowing the Right Hand from the Left	121
Amino Acid Sequence Affects Stability of the α Helix	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	125
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
Some Proteins or Protein Segments Are Intrinsically Disordered	138
Protein Motifs Are the Basis for Protein Structural Classification	139
Protein Quaternary Structures Range from Simple Dimers to Large Complexes	141
4.4 Protein Denaturation and Folding	142
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	147
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	160
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	164
Hemoglobin Binds Oxygen Cooperatively	165
Cooperative Ligand Binding Can Be Described Quantitatively	166
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 Includes 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	177
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	179
Myosin Thick Filaments Slide along Actin Thin Filaments	182
6 Enzymes	187
6.1 An Introduction to Enzymes	187
Most Enzymes Are Proteins	188
Enzymes Are Classified by the Reactions They Catalyze	188
6.2 How Enzymes Work	190
Enzymes Affect Reaction Rates, Not Equilibria	190
Reaction Rates and Equilibria Have Precise Thermodynamic Definitions	192
A Few Principles Explain the Catalytic Power and Specificity of Enzymes	192
Weak Interactions between Enzyme and Substrate Are Optimized in the Transition State	193
Binding Energy Contributes to Reaction Specificity and Catalysis	195
Specific Catalytic Groups Contribute to Catalysis	197
6.3 Enzyme Kinetics as an Approach to Understanding Mechanism	198
Substrate Concentration Affects the Rate of Enzyme-Catalyzed Reactions	198
The Relationship between Substrate Concentration and Reaction Rate Can Be Expressed Quantitatively	200
Kinetic Parameters Are Used to Compare Enzyme Activities	201
BOX 6-1 Transformations of the Michaelis-Menten Equation: The Double-Reciprocal Plot	202
Many Enzymes Catalyze Reactions with Two or More Substrates	204
Enzyme Activity Depends on pH	205
Pre-Steady State Kinetics Can Provide Evidence for Specific Reaction Steps	206
Enzymes Are Subject to Reversible or Irreversible Inhibition	206

BOX 6-2 Kinetic Tests for Determining Inhibition Mechanisms	209	Glycosaminoglycans Are Heteropolysaccharides of the Extracellular Matrix	258
BOX 6-3 MEDICINE Curing African Sleeping Sickness with a Biochemical Trojan Horse	211	7.3 Glycoconjugates: Proteoglycans, Glycoproteins, and Glycosphingolipids	261
6.4 Examples of Enzymatic Reactions	213	Proteoglycans Are Glycosaminoglycan-Containing Macromolecules of the Cell Surface and Extracellular Matrix	261
The Chymotrypsin Mechanism Involves Acylation and Deacylation of a Ser Residue	213	BOX 7-3 MEDICINE Defects in the Synthesis or Degradation of Sulfated Glycosaminoglycans Can Lead to Serious Human Disease	264
An Understanding of Protease Mechanisms Leads to New Treatments for HIV Infections	215	Glycoproteins Have Covalently Attached Oligosaccharides	265
Hexokinase Undergoes Induced Fit on Substrate Binding	218	Glycolipids and Lipopolysaccharides Are Membrane Components	266
The Enolase Reaction Mechanism Requires Metal Ions	220	7.4 Carbohydrates as Informational Molecules: The Sugar Code	267
Lysozyme Uses Two Successive Nucleophilic Displacement Reactions	220	Lectins Are Proteins That Read the Sugar Code and Mediate Many Biological Processes	268
An Understanding of Enzyme Mechanism Produces Useful Antibiotics	223	Lectin-Carbohydrate Interactions Are Highly Specific and Often Multivalent	271
6.5 Regulatory Enzymes	225	7.5 Working with Carbohydrates	272
Allosteric Enzymes Undergo Conformational Changes in Response to Modulator Binding	226	8 Nucleotides and Nucleic Acids	279
The Kinetic Properties of Allosteric Enzymes Diverge from Michaelis-Menten Behavior	227	8.1 Some Basics	279
Some Enzymes Are Regulated by Reversible Covalent Modification	228	Nucleotides and Nucleic Acids Have Characteristic Bases and Pentoses	279
Phosphoryl Groups Affect the Structure and Catalytic Activity of Enzymes	229	Phosphodiester Bonds Link Successive Nucleotides in Nucleic Acids	282
Multiple Phosphorylations Allow Exquisite Regulatory Control	230	The Properties of Nucleotide Bases Affect the Three-Dimensional Structure of Nucleic Acids	284
Some Enzymes and Other Proteins Are Regulated by Proteolytic Cleavage of an Enzyme Precursor	230	8.2 Nucleic Acid Structure	285
A Cascade of Proteolytically Activated Zymogens Leads to Blood Coagulation	232	DNA Is a Double Helix That Stores Genetic Information	285
Some Regulatory Enzymes Use Several Regulatory Mechanisms	235	DNA Can Occur in Different Three-Dimensional Forms	288
7 Carbohydrates and Glycobiology	241	Certain DNA Sequences Adopt Unusual Structures	289
7.1 Monosaccharides and Disaccharides	241	Messenger RNAs Code for Polypeptide Chains	290
The Two Families of Monosaccharides Are Aldoses and Ketoses	242	Many RNAs Have More Complex Three-Dimensional Structures	292
Monosaccharides Have Asymmetric Centers	242	8.3 Nucleic Acid Chemistry	295
The Common Monosaccharides Have Cyclic Structures	243	Double-Helical DNA and RNA Can Be Denatured	295
Organisms Contain a Variety of Hexose Derivatives	247	Nucleotides and Nucleic Acids Undergo Nonenzymatic Transformations	297
BOX 7-1 MEDICINE Blood Glucose Measurements in the Diagnosis and Treatment of Diabetes	248	Some Bases of DNA Are Methylated	299
Monosaccharides Are Reducing Agents	249	The Chemical Synthesis of DNA Has Been Automated	301
Disaccharides Contain a Glycosidic Bond	250	Gene Sequences Can Be Amplified with the Polymerase Chain Reaction	301
BOX 7-2 Sugar Is Sweet, and So Are . . . a Few Other Things	252	The Sequences of Long DNA Strands Can Be Determined	302
7.2 Polysaccharides	252	BOX 8-1 A Potent Weapon in Forensic Medicine	304
Some Homopolysaccharides Are Storage Forms of Fuel	253	DNA Sequencing Technologies Are Advancing Rapidly	306
Some Homopolysaccharides Serve Structural Roles	254	8.4 Other Functions of Nucleotides	310
Steric Factors and Hydrogen Bonding Influence Homopolysaccharide Folding	256	Nucleotides Carry Chemical Energy in Cells	310
Bacterial and Algal Cell Walls Contain Structural Heteropolysaccharides	258	Adenine Nucleotides Are Components of Many Enzyme Cofactors	311

Some Nucleotides Are Regulatory Molecules	311	Waxes Serve as Energy Stores and Water Repellents	365
Adenine Nucleotides Also Serve as Signals	312		
9 DNA-Based Information Technologies	319	10.2 Structural Lipids in Membranes	366
9.1 Studying Genes and Their Products	320	Glycerophospholipids Are Derivatives of Phosphatidic Acid	367
Genes Can Be Isolated by DNA Cloning	320	Some Glycerophospholipids Have Ether-Linked Fatty Acids	369
Restriction Endonucleases and DNA Ligases Yield Recombinant DNA	321	Chloroplasts Contain Galactolipids and Sulfolipids	369
Cloning Vectors Allow Amplification of Inserted DNA Segments	324	Archaea Contain Unique Membrane Lipids	369
Cloned Genes Can Be Expressed to Amplify Protein Production	327	Sphingolipids Are Derivatives of Sphingosine	370
Many Different Systems Are Used to Express Recombinant Proteins	328	Sphingolipids at Cell Surfaces Are Sites of Biological Recognition	371
Alteration of Cloned Genes Produces Altered Proteins	330	Phospholipids and Sphingolipids Are Degraded in Lysosomes	372
Terminal Tags Provide Handles for Affinity Purification	332	Sterols Have Four Fused Carbon Rings	372
The Polymerase Chain Reaction Can Be Adapted for Convenient Cloning	332	BOX 10-1 MEDICINE Abnormal Accumulations of Membrane Lipids: Some Inherited Human Diseases	373
9.2 Using DNA-Based Methods to Understand Protein Function	335	10.3 Lipids as Signals, Cofactors, and Pigments	374
DNA Libraries Are Specialized Catalogs of Genetic Information	335	Phosphatidylinositols and Sphingosine Derivatives Act as Intracellular Signals	374
Sequence or Structural Relationships Provide Information on Protein Function	335	Eicosanoids Carry Messages to Nearby Cells	375
Fusion Proteins and Immunofluorescence Can Reveal the Location of Proteins in Cells	336	Steroid Hormones Carry Messages between Tissues	376
Protein-Protein Interactions Can Help Elucidate Protein Function	338	Vascular Plants Produce Thousands of Volatile Signals	376
DNA Microarrays Reveal RNA Expression Patterns and Other Information	341	Vitamins A and D Are Hormone Precursors	377
Inactivating or Altering a Gene with CRISPR Can Reveal Gene Function	342	Vitamins E and K and the Lipid Quinones Are Oxidation-Reduction Cofactors	378
9.3 Genomics and the Human Story	344	Dolichols Activate Sugar Precursors for Biosynthesis	380
BOX 9-1 MEDICINE Personalized Genomic Medicine	345	Many Natural Pigments Are Lipidic Conjugated Dienes	380
Annotation Provides a Description of the Genome	346	Polyketides Are Natural Products with Potent Biological Activities	381
The Human Genome Contains Many Types of Sequences	346	10.4 Working with Lipids	381
Genome Sequencing Informs Us about Our Humanity	348	Lipid Extraction Requires Organic Solvents	382
Genome Comparisons Help Locate Genes Involved in Disease	350	Adsorption Chromatography Separates Lipids of Different Polarity	382
Genome Sequences Inform Us about Our Past and Provide Opportunities for the Future	353	Gas Chromatography Resolves Mixtures of Volatile Lipid Derivatives	382
BOX 9-2 Getting to Know Humanity's Next of Kin	353	Specific Hydrolysis Aids in Determination of Lipid Structure	383
10 Lipids	361	Mass Spectrometry Reveals Complete Lipid Structure	383
10.1 Storage Lipids	361	Lipidomics Seeks to Catalog All Lipids and Their Functions	384
Fatty Acids Are Hydrocarbon Derivatives	361	11 Biological Membranes and Transport	387
Triacylglycerols Are Fatty Acid Esters of Glycerol	364	11.1 The Composition and Architecture of Membranes	388
Triacylglycerols Provide Stored Energy and Insulation	364	Each Type of Membrane Has Characteristic Lipids and Proteins	388
Partial Hydrogenation of Cooking Oils Improves Their Stability but Creates Fatty Acids with Harmful Health Effects	365	All Biological Membranes Share Some Fundamental Properties	389
		A Lipid Bilayer Is the Basic Structural Element of Membranes	389

Three Types of Membrane Proteins Differ in the Nature of Their Association with the Membrane 391

Many Integral Membrane Proteins Span the Lipid Bilayer 392

Hydrophobic Regions of Integral Proteins Associate with Membrane Lipids 393

The Topology of an Integral Membrane Protein Can Often Be Predicted from Its Sequence 394

Covalently Attached Lipids Anchor Some Membrane Proteins 395

Amphitropic Proteins Associate Reversibly with the Membrane 397

11.2 Membrane Dynamics 397

Acyl Groups in the Bilayer Interior Are Ordered to Varying Degrees 397

Transbilayer Movement of Lipids Requires Catalysis 398

Lipids and Proteins Diffuse Laterally in the Bilayer 399

Sphingolipids and Cholesterol Cluster Together in Membrane Rafts 401

Membrane Curvature and Fusion Are Central to Many Biological Processes 402

Integral Proteins of the Plasma Membrane Are Involved in Surface Adhesion, Signaling, and Other Cellular Processes 405

11.3 Solute Transport across Membranes 405

Transport May Be Passive or Active 406

Transporters and Ion Channels Share Some Structural Properties but Have Different Mechanisms 406

The Glucose Transporter of Erythrocytes Mediates Passive Transport 408

The Chloride-Bicarbonate Exchanger Catalyzes Electroneutral Cotransport of Anions across the Plasma Membrane 410

BOX 11-1 MEDICINE Defective Glucose and Water Transport in Two Forms of Diabetes 411

Active Transport Results in Solute Movement against a Concentration or Electrochemical Gradient 412

P-Type ATPases Undergo Phosphorylation during Their Catalytic Cycles 413

V-Type and F-Type ATPases Are ATP-Driven Proton Pumps 416

ABC Transporters Use ATP to Drive the Active Transport of a Wide Variety of Substrates 417

Ion Gradients Provide the Energy for Secondary Active Transport 418

BOX 11-2 MEDICINE A Defective Ion Channel in Cystic Fibrosis 419

Aquaporins Form Hydrophilic Transmembrane Channels for the Passage of Water 423

Ion-Selective Channels Allow Rapid Movement of Ions across Membranes 425

Ion-Channel Function Is Measured Electrically 425

The Structure of a K⁺ Channel Reveals the Basis for Its Specificity 426

Gated Ion Channels Are Central in Neuronal Function 427

Defective Ion Channels Can Have Severe Physiological Consequences 430

12 Biosignaling 437

12.1 General Features of Signal Transduction 437

12.2 G Protein-Coupled Receptors and Second Messengers 440

The β -Adrenergic Receptor System Acts through the Second Messenger cAMP 441

BOX 12-1 G Proteins: Binary Switches in Health and Disease 444

Several Mechanisms Cause Termination of the β -Adrenergic Response 447

The β -Adrenergic Receptor Is Desensitized by Phosphorylation and by Association with Arrestin 448

Cyclic AMP Acts as a Second Messenger for Many Regulatory Molecules 449

Diacylglycerol, Inositol Trisphosphate, and Ca²⁺ Have Related Roles as Second Messengers 451

BOX 12-2 METHODS FRET: Biochemistry Visualized in a Living Cell 452

Calcium Is a Second Messenger That Is Localized in Space and Time 452

12.3 GPCRs in Vision, Olfaction, and Gustation 456

The Vertebrate Eye Uses Classic GPCR Mechanisms 456

BOX 12-3 MEDICINE Color Blindness: John Dalton's Experiment from the Grave 458

Vertebrate Olfaction and Gustation Use Mechanisms Similar to the Visual System 459

All GPCR Systems Share Universal Features 459

12.4 Receptor Tyrosine Kinases 461

Stimulation of the Insulin Receptor Initiates a Cascade of Protein Phosphorylation Reactions 461

The Membrane Phospholipid PIP₃ Functions at a Branch in Insulin Signaling 463

Cross Talk among Signaling Systems Is Common and Complex 465

12.5 Receptor Guanylyl Cyclases, cGMP, and Protein Kinase G 466

12.6 Multivalent Adaptor Proteins and Membrane Rafts 467

Protein Modules Bind Phosphorylated Tyr, Ser, or Thr Residues in Partner Proteins 468

Membrane Rafts and Caveolae Segregate Signaling Proteins 470

12.7 Gated Ion Channels 471

Ion Channels Underlie Electrical Signaling in Excitable Cells 471

Voltage-Gated Ion Channels Produce Neuronal Action Potentials 472

Neurons Have Receptor Channels That Respond to Different Neurotransmitters 473

Toxins Target Ion Channels 473

12.8 Regulation of Transcription by Nuclear Hormone Receptors 473

12.9	Signaling in Microorganisms and Plants	475
	Bacterial Signaling Entails Phosphorylation in a Two-Component System	475
	Signaling Systems of Plants Have Some of the Same Components Used by Microbes and Mammals	476
12.10	Regulation of the Cell Cycle by Protein Kinases	476
	The Cell Cycle Has Four Stages	476
	Levels of Cyclin-Dependent Protein Kinases Oscillate	477
	CDKs Regulate Cell Division by Phosphorylating Critical Proteins	479
12.11	Oncogenes, Tumor Suppressor Genes, and Programmed Cell Death	481
	Oncogenes Are Mutant Forms of the Genes for Proteins That Regulate the Cell Cycle	481
	BOX 12-4 MEDICINE Development of Protein Kinase Inhibitors for Cancer Treatment	482
	Defects in Certain Genes Remove Normal Restraints on Cell Division	484
	Apoptosis Is Programmed Cell Suicide	485
II	BIOENERGETICS AND METABOLISM	491
13	Bioenergetics and Biochemical Reaction Types	495
13.1	Bioenergetics and Thermodynamics	496
	Biological Energy Transformations Obey the Laws of Thermodynamics	496
	Cells Require Sources of Free Energy	497
	Standard Free-Energy Change Is Directly Related to the Equilibrium Constant	497
	Actual Free-Energy Changes Depend on Reactant and Product Concentrations	499
	Standard Free-Energy Changes Are Additive	500
13.2	Chemical Logic and Common Biochemical Reactions	501
	Biochemical and Chemical Equations Are Not Identical	506
13.3	Phosphoryl Group Transfers and ATP	507
	The Free-Energy Change for ATP Hydrolysis Is Large and Negative	507
	Other Phosphorylated Compounds and Thioesters Also Have Large Free Energies of Hydrolysis	509
	ATP Provides Energy by Group Transfers, Not by Simple Hydrolysis	511
	ATP Donates Phosphoryl, Pyrophosphoryl, and Adenylyl Groups	513
	Assembly of Informational Macromolecules Requires Energy	514
	ATP Energizes Active Transport and Muscle Contraction	514
	BOX 13-1 Firefly Flashes: Glowing Reports of ATP	515
	Transphosphorylations between Nucleotides Occur in All Cell Types	516

	Inorganic Polyphosphate Is a Potential Phosphoryl Group Donor	516
13.4	Biological Oxidation-Reduction Reactions	517
	The Flow of Electrons Can Do Biological Work	518
	Oxidation-Reductions Can Be Described as Half-Reactions	518
	Biological Oxidations Often Involve Dehydrogenation	519
	Reduction Potentials Measure Affinity for Electrons	520
	Standard Reduction Potentials Can Be Used to Calculate Free-Energy Change	521
	Cellular Oxidation of Glucose to Carbon Dioxide Requires Specialized Electron Carriers	522
	A Few Types of Coenzymes and Proteins Serve as Universal Electron Carriers	522
	NADH and NADPH Act with Dehydrogenases as Soluble Electron Carriers	522
	NAD Has Important Functions in Addition to Electron Transfer	524
	Dietary Deficiency of Niacin, the Vitamin Form of NAD and NADP, Causes Pellagra	525
	Flavin Nucleotides Are Tightly Bound in Flavoproteins	525

14	Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway	533
14.1	Glycolysis	534
	An Overview: Glycolysis Has Two Phases	534
	The Preparatory Phase of Glycolysis Requires ATP	538
	The Payoff Phase of Glycolysis Yields ATP and NADH	540
	The Overall Balance Sheet Shows a Net Gain of ATP	545
	Glycolysis Is under Tight Regulation	545
	BOX 14-1 MEDICINE High Rate of Glycolysis in Tumors Suggests Targets for Chemotherapy and Facilitates Diagnosis	546
	Glucose Uptake Is Deficient in Type 1 Diabetes Mellitus	548
14.2	Feeder Pathways for Glycolysis	548
	Dietary Polysaccharides and Disaccharides Undergo Hydrolysis to Monosaccharides	548
	Endogenous Glycogen and Starch Are Degraded by Phosphorolysis	550
	Other Monosaccharides Enter the Glycolytic Pathway at Several Points	551
14.3	Fates of Pyruvate under Anaerobic Conditions: Fermentation	553
	Pyruvate Is the Terminal Electron Acceptor in Lactic Acid Fermentation	553
	BOX 14-2 Athletes, Alligators, and Coelacanths: Glycolysis at Limiting Concentrations of Oxygen	554
	Ethanol Is the Reduced Product in Ethanol Fermentation	555
	Thiamine Pyrophosphate Carries “Active Acetaldehyde” Groups	555

BOX 14-3 Ethanol Fermentations: Brewing Beer and Producing Biofuels	556	Metabolic Control Analysis Suggests a General Method for Increasing Flux through a Pathway	588
Fermentations Are Used to Produce Some Common Foods and Industrial Chemicals	556		
14.4 Gluconeogenesis	558	15.3 Coordinated Regulation of Glycolysis and Gluconeogenesis	589
Conversion of Pyruvate to Phosphoenolpyruvate Requires Two Exergonic Reactions	560	Hexokinase Isozymes of Muscle and Liver Are Affected Differently by Their Product, Glucose 6-Phosphate	590
Conversion of Fructose 1,6-Bisphosphate to Fructose 6-Phosphate Is the Second Bypass	562	BOX 15-2 Isozymes: Different Proteins That Catalyze the Same Reaction	590
Conversion of Glucose 6-Phosphate to Glucose Is the Third Bypass	563	Hexokinase IV (Glucokinase) and Glucose 6-Phosphatase Are Transcriptionally Regulated	592
Gluconeogenesis Is Energetically Expensive, but Essential	563	Phosphofructokinase-1 and Fructose 1,6-Bisphosphatase Are Reciprocally Regulated	592
Citric Acid Cycle Intermediates and Some Amino Acids Are Glucogenic	563	Fructose 2,6-Bisphosphate Is a Potent Allosteric Regulator of PFK-1 and FBPase-1	593
Mammals Cannot Convert Fatty Acids to Glucose	564	Xylulose 5-Phosphate Is a Key Regulator of Carbohydrate and Fat Metabolism	593
Glycolysis and Gluconeogenesis Are Reciprocally Regulated	564	The Glycolytic Enzyme Pyruvate Kinase Is Allosterically Inhibited by ATP	595
14.5 Pentose Phosphate Pathway of Glucose Oxidation	565	The Gluconeogenic Conversion of Pyruvate to Phosphoenolpyruvate Is under Multiple Types of Regulation	595
The Oxidative Phase Produces Pentose Phosphates and NADPH	565	Transcriptional Regulation of Glycolysis and Gluconeogenesis Changes the Number of Enzyme Molecules	596
BOX 14-4 MEDICINE Why Pythagoras Wouldn't Eat Falafel: Glucose 6-Phosphate Dehydrogenase Deficiency	566	BOX 15-3 MEDICINE Genetic Mutations That Lead to Rare Forms of Diabetes	599
The Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate	567	15.4 The Metabolism of Glycogen in Animals	601
Wernicke-Korsakoff Syndrome Is Exacerbated by a Defect in Transketolase	569	Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase	601
Glucose 6-Phosphate Is Partitioned between Glycolysis and the Pentose Phosphate Pathway	570	Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose	601
15 Principles of Metabolic Regulation	575	The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis	603
15.1 Regulation of Metabolic Pathways	576	BOX 15-4 Carl and Gerty Cori: Pioneers in Glycogen Metabolism and Disease	604
Cells and Organisms Maintain a Dynamic Steady State	577	Glycogenin Primes the Initial Sugar Residues in Glycogen	607
Both the Amount and the Catalytic Activity of an Enzyme Can Be Regulated	577	15.5 Coordinated Regulation of Glycogen Breakdown and Synthesis	608
Reactions Far from Equilibrium in Cells Are Common Points of Regulation	580	Glycogen Phosphorylase Is Regulated Allosterically and Hormonally	608
Adenine Nucleotides Play Special Roles in Metabolic Regulation	582	Glycogen Synthase Is Also Regulated by Phosphorylation and Dephosphorylation	609
15.2 Analysis of Metabolic Control	584	Glycogen Synthase Kinase 3 Mediates Some of the Actions of Insulin	611
The Contribution of Each Enzyme to Flux through a Pathway Is Experimentally Measurable	584	Phosphoprotein Phosphatase 1 Is Central to Glycogen Metabolism	612
The Flux Control Coefficient Quantifies the Effect of a Change in Enzyme Activity on Metabolite Flux through a Pathway	585	Allosteric and Hormonal Signals Coordinate Carbohydrate Metabolism Globally	612
The Elasticity Coefficient Is Related to an Enzyme's Responsiveness to Changes in Metabolite or Regulator Concentrations	585	Carbohydrate and Lipid Metabolism Are Integrated by Hormonal and Allosteric Mechanisms	614
BOX 15-1 METHODS Metabolic Control Analysis: Quantitative Aspects	586	16 The Citric Acid Cycle	619
The Response Coefficient Expresses the Effect of an Outside Controller on Flux through a Pathway	587	16.1 Production of Acetyl-CoA (Activated Acetate)	619
Metabolic Control Analysis Has Been Applied to Carbohydrate Metabolism, with Surprising Results	588	Pyruvate Is Oxidized to Acetyl-CoA and CO ₂	620

The Pyruvate Dehydrogenase Complex Employs Five Coenzymes	621		
The Pyruvate Dehydrogenase Complex Consists of Three Distinct Enzymes	621		
In Substrate Channeling, Intermediates Never Leave the Enzyme Surface	623		
16.2 Reactions of the Citric Acid Cycle	624		
The Sequence of Reactions in the Citric Acid Cycle Makes Chemical Sense	624		
The Citric Acid Cycle Has Eight Steps	626		
BOX 16-1 Moonlighting Enzymes: Proteins with More Than One Job	628		
BOX 16-2 Synthases and Synthetases; Ligases and Lyases; Kinases, Phosphatases, and Phosphorylases: Yes, the Names Are Confusing!	631		
The Energy of Oxidations in the Cycle Is Efficiently Conserved	633		
BOX 16-3 Citrate: A Symmetric Molecule That Reacts Asymmetrically	634		
Why Is the Oxidation of Acetate So Complicated?	635		
Citric Acid Cycle Components Are Important Biosynthetic Intermediates	636		
Anaplerotic Reactions Replenish Citric Acid Cycle Intermediates	636		
Biotin in Pyruvate Carboxylase Carries CO ₂ Groups	638		
16.3 Regulation of the Citric Acid Cycle	640		
Production of Acetyl-CoA by the Pyruvate Dehydrogenase Complex Is Regulated by Allosteric and Covalent Mechanisms	640		
The Citric Acid Cycle Is Regulated at Its Three Exergonic Steps	641		
Substrate Channeling through Multienzyme Complexes May Occur in the Citric Acid Cycle	641		
Some Mutations in Enzymes of the Citric Acid Cycle Lead to Cancer	642		
17 Fatty Acid Catabolism	649		
17.1 Digestion, Mobilization, and Transport of Fats	650		
Dietary Fats Are Absorbed in the Small Intestine	650		
Hormones Trigger Mobilization of Stored Triacylglycerols	651		
Fatty Acids Are Activated and Transported into Mitochondria	652		
17.2 Oxidation of Fatty Acids	654		
The β Oxidation of Saturated Fatty Acids Has Four Basic Steps	655		
The Four β -Oxidation Steps Are Repeated to Yield Acetyl-CoA and ATP	656		
Acetyl-CoA Can Be Further Oxidized in the Citric Acid Cycle	657		
BOX 17-1 A Long Winter's Nap: Oxidizing Fats during Hibernation	658		
Oxidation of Unsaturated Fatty Acids Requires Two Additional Reactions	659		
Complete Oxidation of Odd-Number Fatty Acids Requires Three Extra Reactions	660		
Fatty Acid Oxidation Is Tightly Regulated	661		
BOX 17-2 Coenzyme B₁₂: A Radical Solution to a Perplexing Problem	662		
Transcription Factors Turn on the Synthesis of Proteins for Lipid Catabolism	664		
Genetic Defects in Fatty Acyl-CoA Dehydrogenases Cause Serious Disease	664		
Peroxisomes Also Carry Out β Oxidation	664		
The β -Oxidation Enzymes of Different Organelles Have Diverged during Evolution	665		
The ω Oxidation of Fatty Acids Occurs in the Endoplasmic Reticulum	666		
Phytanic Acid Undergoes α Oxidation in Peroxisomes	667		
17.3 Ketone Bodies	668		
Ketone Bodies, Formed in the Liver, Are Exported to Other Organs as Fuel	668		
Ketone Bodies Are Overproduced in Diabetes and during Starvation	670		
18 Amino Acid Oxidation and the Production of Urea	675		
18.1 Metabolic Fates of Amino Groups	676		
Dietary Protein Is Enzymatically Degraded to Amino Acids	677		
Pyridoxal Phosphate Participates in the Transfer of α -Amino Groups to α -Ketoglutarate	679		
Glutamate Releases Its Amino Group as Ammonia in the Liver	680		
Glutamine Transports Ammonia in the Bloodstream	682		
Alanine Transports Ammonia from Skeletal Muscles to the Liver	683		
Ammonia Is Toxic to Animals	683		
18.2 Nitrogen Excretion and the Urea Cycle	684		
Urea Is Produced from Ammonia in Five Enzymatic Steps	684		
The Citric Acid and Urea Cycles Can Be Linked	686		
The Activity of the Urea Cycle Is Regulated at Two Levels	687		
BOX 18-1 MEDICINE Assays for Tissue Damage	688		
Pathway Interconnections Reduce the Energetic Cost of Urea Synthesis	688		
Genetic Defects in the Urea Cycle Can Be Life-Threatening	688		
18.3 Pathways of Amino Acid Degradation	690		
Some Amino Acids Are Converted to Glucose, Others to Ketone Bodies	691		
Several Enzyme Cofactors Play Important Roles in Amino Acid Catabolism	691		
Six Amino Acids Are Degraded to Pyruvate	694		
Seven Amino Acids Are Degraded to Acetyl-CoA	697		
Phenylalanine Catabolism Is Genetically Defective in Some People	697		
Five Amino Acids Are Converted to α -Ketoglutarate	700		
Four Amino Acids Are Converted to Succinyl-CoA	701		
Branched-Chain Amino Acids Are Not Degraded in the Liver	702		

Asparagine and Aspartate Are Degraded to Oxaloacetate	703	ATP-Producing Pathways Are Coordinately Regulated	743
BOX 18-2 MEDICINE Scientific Sleuths Solve a Murder Mystery	704	19.4 Mitochondria in Thermogenesis, Steroid Synthesis, and Apoptosis	744
19. Oxidative Phosphorylation	711	Uncoupled Mitochondria in Brown Adipose Tissue Produce Heat	744
19.1 The Mitochondrial Respiratory Chain	712	Mitochondrial P-450 Monooxygenases Catalyze Steroid Hydroxylations	744
Electrons Are Funneled to Universal Electron Acceptors	712	Mitochondria Are Central to the Initiation of Apoptosis	745
Electrons Pass through a Series of Membrane-Bound Carriers	714	19.5 Mitochondrial Genes: Their Origin and the Effects of Mutations	746
Electron Carriers Function in Multienzyme Complexes	717	Mitochondria Evolved from Endosymbiotic Bacteria	746
Mitochondrial Complexes Associate in Respirasomes	722	Mutations in Mitochondrial DNA Accumulate throughout the Life of the Organism	747
Other Pathways Donate Electrons to the Respiratory Chain via Ubiquinone	723	Some Mutations in Mitochondrial Genomes Cause Disease	748
BOX 19-1 METHODS Determining Three-Dimensional Structures of Large Macromolecular Complexes by Single-Particle Cryo-Electron Microscopy	724	A Rare Form of Diabetes Results from Defects in the Mitochondria of Pancreatic β Cells	749
The Energy of Electron Transfer Is Efficiently Conserved in a Proton Gradient	724	20 Photosynthesis and Carbohydrate Synthesis in Plants	755
Reactive Oxygen Species Are Generated during Oxidative Phosphorylation	726	20.1 Light Absorption	756
Plant Mitochondria Have Alternative Mechanisms for Oxidizing NADH	727	Chloroplasts Are the Site of Light-Driven Electron Flow and Photosynthesis in Plants	756
BOX 19-2 Hot, Stinking Plants and Alternative Respiratory Pathways	728	Chlorophylls Absorb Light Energy for Photosynthesis	759
19.2 ATP Synthesis	728	Accessory Pigments Extend the Range of Light Absorption	759
In the Chemiosmotic Model, Oxidation and Phosphorylation Are Obligately Coupled	729	Chlorophylls Funnel Absorbed Energy to Reaction Centers by Exciton Transfer	761
ATP Synthase Has Two Functional Domains, F_0 and F_1	731	20.2 Photochemical Reaction Centers	763
ATP Is Stabilized Relative to ADP on the Surface of F_1	732	Photosynthetic Bacteria Have Two Types of Reaction Center	763
The Proton Gradient Drives the Release of ATP from the Enzyme Surface	732	Kinetic and Thermodynamic Factors Prevent the Dissipation of Energy by Internal Conversion	766
Each β Subunit of ATP Synthase Can Assume Three Different Conformations	733	In Plants, Two Reaction Centers Act in Tandem	766
Rotational Catalysis Is Key to the Binding-Change Mechanism for ATP Synthesis	735	The Cytochrome b_6f Complex Links Photosystems II and I	770
How Does Proton Flow through the F_0 Complex Produce Rotary Motion?	735	Cyclic Electron Flow between PSI and the Cytochrome b_6f Complex Increases the Production of ATP Relative to NADPH	771
BOX 19-3 Atomic Force Microscopy to Visualize Membrane Proteins	737	State Transitions Change the Distribution of LHClI between the Two Photosystems	771
Chemiosmotic Coupling Allows Nonintegral Stoichiometries of O_2 Consumption and ATP Synthesis	738	Water Is Split by the Oxygen-Evolving Complex	773
The Proton-Motive Force Energizes Active Transport	738	20.3 ATP Synthesis by Photophosphorylation	774
Shuttle Systems Indirectly Convey Cytosolic NADH into Mitochondria for Oxidation	739	A Proton Gradient Couples Electron Flow and Phosphorylation	774
19.3 Regulation of Oxidative Phosphorylation	741	The Approximate Stoichiometry of Photophosphorylation Has Been Established	775
Oxidative Phosphorylation Is Regulated by Cellular Energy Needs	741	The ATP Synthase of Chloroplasts Resembles That of Mitochondria	775
An Inhibitory Protein Prevents ATP Hydrolysis during Hypoxia	741	20.4 Evolution of Oxygenic Photosynthesis	776
Hypoxia Leads to ROS Production and Several Adaptive Responses	742	Chloroplasts Evolved from Ancient Photosynthetic Bacteria	776

In <i>Halobacterium</i> , a Single Protein Absorbs Light and Pumps Protons to Drive ATP Synthesis	778	Fatty Acid Biosynthesis Is Tightly Regulated	818
20.5 Carbon-Assimilation Reactions	780	Long-Chain Saturated Fatty Acids Are Synthesized from Palmitate	820
Carbon Dioxide Assimilation Occurs in Three Stages	780	Desaturation of Fatty Acids Requires a Mixed-Function Oxidase	821
Synthesis of Each Triose Phosphate from CO ₂ Requires Six NADPH and Nine ATP	786	BOX 21-1 MEDICINE Oxidases, Oxygenases, Cytochrome P-450 Enzymes, and Drug Overdoses	822
A Transport System Exports Triose Phosphates from the Chloroplast and Imports Phosphate	788	Eicosanoids Are Formed from 20- and 22-Carbon Polyunsaturated Fatty Acids	824
Four Enzymes of the Calvin Cycle Are Indirectly Activated by Light	790	21.2 Biosynthesis of Triacylglycerols	826
20.6 Photorespiration and the C₄ and CAM Pathways	792	Triacylglycerols and Glycerophospholipids Are Synthesized from the Same Precursors	826
Photorespiration Results from Rubisco's Oxygenase Activity	792	Triacylglycerol Biosynthesis in Animals Is Regulated by Hormones	827
The Salvage of Phosphoglycolate Is Costly	793	Adipose Tissue Generates Glycerol 3-Phosphate by Glyceroneogenesis	829
In C ₄ Plants, CO ₂ Fixation and Rubisco Activity Are Spatially Separated	794	Thiazolidinediones Treat Type 2 Diabetes by Increasing Glyceroneogenesis	829
BOX 20-1 Will Genetic Engineering of Photosynthetic Organisms Increase Their Efficiency?	796	21.3 Biosynthesis of Membrane Phospholipids	830
In CAM Plants, CO ₂ Capture and Rubisco Action Are Temporally Separated	798	Cells Have Two Strategies for Attaching Phospholipid Head Groups	830
20.7 Biosynthesis of Starch, Sucrose, and Cellulose	798	Phospholipid Synthesis in <i>E. coli</i> Employs CDP-Diacylglycerol	831
ADP-Glucose Is the Substrate for Starch Synthesis in Plant Plastids and for Glycogen Synthesis in Bacteria	798	Eukaryotes Synthesize Anionic Phospholipids from CDP-Diacylglycerol	833
UDP-Glucose Is the Substrate for Sucrose Synthesis in the Cytosol of Leaf Cells	799	Eukaryotic Pathways to Phosphatidylserine, Phosphatidylethanolamine, and Phosphatidylcholine Are Interrelated	833
Conversion of Triose Phosphates to Sucrose and Starch Is Tightly Regulated	799	Plasmalogen Synthesis Requires Formation of an Ether-Linked Fatty Alcohol	834
The Glyoxylate Cycle and Gluconeogenesis Produce Glucose in Germinating Seeds	800	Sphingolipid and Glycerophospholipid Synthesis Share Precursors and Some Mechanisms	835
Cellulose Is Synthesized by Supramolecular Structures in the Plasma Membrane	802	Polar Lipids Are Targeted to Specific Cellular Membranes	835
20.8 Integration of Carbohydrate Metabolism in Plants	804	21.4 Cholesterol, Steroids, and Isoprenoids: Biosynthesis, Regulation, and Transport	837
Pools of Common Intermediates Link Pathways in Different Organelles	804	Cholesterol Is Made from Acetyl-CoA in Four Stages	838
21 Lipid Biosynthesis	811	Cholesterol Has Several Fates	842
21.1 Biosynthesis of Fatty Acids and Eicosanoids	811	Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins	842
Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate	811	BOX 21-2 MEDICINE ApoE Alleles Predict Incidence of Alzheimer Disease	844
Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence	812	Cholesteryl Esters Enter Cells by Receptor-Mediated Endocytosis	846
The Mammalian Fatty Acid Synthase Has Multiple Active Sites	814	HDL Carries Out Reverse Cholesterol Transport	847
Fatty Acid Synthase Receives the Acetyl and Malonyl Groups	814	Cholesterol Synthesis and Transport Are Regulated at Several Levels	847
The Fatty Acid Synthase Reactions Are Repeated to Form Palmitate	816	Dysregulation of Cholesterol Metabolism Can Lead to Cardiovascular Disease	849
Fatty Acid Synthesis Is a Cytosolic Process in Many Organisms but Takes Place in the Chloroplasts in Plants	817	Reverse Cholesterol Transport by HDL Counters Plaque Formation and Atherosclerosis	850
Acetate Is Shuttled out of Mitochondria as Citrate	817	BOX 21-3 MEDICINE The Lipid Hypothesis and the Development of Statins	851
		Steroid Hormones Are Formed by Side-Chain Cleavage and Oxidation of Cholesterol	852
		Intermediates in Cholesterol Biosynthesis Have Many Alternative Fates	853

22	Biosynthesis of Amino Acids, Nucleotides, and Related Molecules	859			
22.1	Overview of Nitrogen Metabolism	860			
	The Nitrogen Cycle Maintains a Pool of Biologically Available Nitrogen	860			
	Nitrogen Is Fixed by Enzymes of the Nitrogenase Complex	861			
	BOX 22-1 Unusual Lifestyles of the Obscure but Abundant	862			
	Ammonia Is Incorporated into Biomolecules through Glutamate and Glutamine	866			
	Glutamine Synthetase Is a Primary Regulatory Point in Nitrogen Metabolism	867			
	Several Classes of Reactions Play Special Roles in the Biosynthesis of Amino Acids and Nucleotides	868			
22.2	Biosynthesis of Amino Acids	869			
	α -Ketoglutarate Gives Rise to Glutamate, Glutamine, Proline, and Arginine	870			
	Serine, Glycine, and Cysteine Are Derived from 3-Phosphoglycerate	872			
	Three Nonessential and Six Essential Amino Acids Are Synthesized from Oxaloacetate and Pyruvate	873			
	Chorismate Is a Key Intermediate in the Synthesis of Tryptophan, Phenylalanine, and Tyrosine	876			
	Histidine Biosynthesis Uses Precursors of Purine Biosynthesis	876			
	Amino Acid Biosynthesis Is under Allosteric Regulation	877			
22.3	Molecules Derived from Amino Acids	880			
	Glycine Is a Precursor of Porphyrins	880			
	Heme Degradation Has Multiple Functions	882			
	BOX 22-2 MEDICINE On Kings and Vampires	884			
	Amino Acids Are Precursors of Creatine and Glutathione	884			
	D-Amino Acids Are Found Primarily in Bacteria	885			
	Aromatic Amino Acids Are Precursors of Many Plant Substances	886			
	Biological Amines Are Products of Amino Acid Decarboxylation	886			
	Arginine Is the Precursor for Biological Synthesis of Nitric Oxide	887			
22.4	Biosynthesis and Degradation of Nucleotides	888			
	De Novo Purine Nucleotide Synthesis Begins with PRPP	890			
	Purine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition	892			
	Pyrimidine Nucleotides Are Made from Aspartate, PRPP, and Carbamoyl Phosphate	893			
	Pyrimidine Nucleotide Biosynthesis Is Regulated by Feedback Inhibition	893			
	Nucleoside Monophosphates Are Converted to Nucleoside Triphosphates	894			
	Ribonucleotides Are the Precursors of Deoxyribonucleotides	894			
	Thymidylate Is Derived from dCDP and dUMP	898			
	Degradation of Purines and Pyrimidines Produces Uric Acid and Urea, Respectively	898			
	Purine and Pyrimidine Bases Are Recycled by Salvage Pathways	900			
	Excess Uric Acid Causes Gout	900			
	Many Chemotherapeutic Agents Target Enzymes in Nucleotide Biosynthetic Pathways	901			
23	Hormonal Regulation and Integration of Mammalian Metabolism	907			
23.1	Hormones: Diverse Structures for Diverse Functions	907			
	The Detection and Purification of Hormones Requires a Bioassay	908			
	BOX 23-1 MEDICINE How Is a Hormone Discovered? The Arduous Path to Purified Insulin	909			
	Hormones Act through Specific High-Affinity Cellular Receptors	910			
	Hormones Are Chemically Diverse	911			
	Hormone Release Is Regulated by a “Top-Down” Hierarchy of Neuronal and Hormonal Signals	915			
	“Bottom-Up” Hormonal Systems Send Signals Back to the Brain and to Other Tissues	916			
23.2	Tissue-Specific Metabolism: The Division of Labor	918			
	The Liver Processes and Distributes Nutrients	919			
	Adipose Tissues Store and Supply Fatty Acids	922			
	Brown and Beige Adipose Tissues Are Thermogenic	923			
	Muscles Use ATP for Mechanical Work	925			
	BOX 23-2 Creatine and Creatine Kinase: Invaluable Diagnostic Aids and the Muscle Builder’s Friends	926			
	The Brain Uses Energy for Transmission of Electrical Impulses	928			
	Blood Carries Oxygen, Metabolites, and Hormones	929			
23.3	Hormonal Regulation of Fuel Metabolism	930			
	Insulin Counters High Blood Glucose	931			
	Pancreatic β Cells Secrete Insulin in Response to Changes in Blood Glucose	932			
	Glucagon Counters Low Blood Glucose	934			
	During Fasting and Starvation, Metabolism Shifts to Provide Fuel for the Brain	935			
	Epinephrine Signals Impending Activity	937			
	Cortisol Signals Stress, Including Low Blood Glucose	937			
	Diabetes Mellitus Arises from Defects in Insulin Production or Action	938			
23.4	Obesity and the Regulation of Body Mass	939			
	Adipose Tissue Has Important Endocrine Functions	939			
	Leptin Stimulates Production of Anorexigenic Peptide Hormones	941			
	Leptin Triggers a Signaling Cascade That Regulates Gene Expression	941			
	The Leptin System May Have Evolved to Regulate the Starvation Response	942			

Insulin Also Acts in the Arcuate Nucleus to Regulate Eating and Energy Conservation	942	DNA Is Degraded by Nucleases	991
Adiponectin Acts through AMPK to Increase Insulin Sensitivity	942	DNA Is Synthesized by DNA Polymerases	991
AMPK Coordinates Catabolism and Anabolism in Response to Metabolic Stress	943	Replication Is Very Accurate	993
The mTORC1 Pathway Coordinates Cell Growth with the Supply of Nutrients and Energy	944	<i>E. coli</i> Has at Least Five DNA Polymerases	994
Diet Regulates the Expression of Genes Central to Maintaining Body Mass	945	DNA Replication Requires Many Enzymes and Protein Factors	995
Short-Term Eating Behavior Is Influenced by Ghrelin, PYY ₃₋₃₆ , and Cannabinoids	946	Replication of the <i>E. coli</i> Chromosome Proceeds in Stages	997
Microbial Symbionts in the Gut Influence Energy Metabolism and Adipogenesis	947	Replication in Eukaryotic Cells Is Similar but More Complex	1003
23.5 Obesity, Metabolic Syndrome, and Type 2 Diabetes	949	Viral DNA Polymerases Provide Targets for Antiviral Therapy	1005
In Type 2 Diabetes the Tissues Become Insensitive to Insulin	949	25.2 DNA Repair	1005
Type 2 Diabetes Is Managed with Diet, Exercise, Medication, and Surgery	950	Mutations Are Linked to Cancer	1005
III INFORMATION PATHWAYS	955	All Cells Have Multiple DNA Repair Systems	1006
24 Genes and Chromosomes	957	The Interaction of Replication Forks with DNA Damage Can Lead to Error-Prone Translesion DNA Synthesis	1012
24.1 Chromosomal Elements	957	BOX 25-1 MEDICINE DNA Repair and Cancer	1015
Genes Are Segments of DNA That Code for Polypeptide Chains and RNAs	958	25.3 DNA Recombination	1016
DNA Molecules Are Much Longer Than the Cellular or Viral Packages That Contain Them	958	Bacterial Homologous Recombination Is a DNA Repair Function	1017
Eukaryotic Genes and Chromosomes Are Very Complex	962	Eukaryotic Homologous Recombination Is Required for Proper Chromosome Segregation during Meiosis	1019
24.2 DNA Supercoiling	963	Recombination during Meiosis Is Initiated with Double-Strand Breaks	1021
Most Cellular DNA Is Underwound	964	BOX 25-2 MEDICINE Why Proper Segregation of Chromosomes Matters	1023
DNA Underwinding Is Defined by Topological Linking Number	965	Some Double-Strand Breaks Are Repaired by Nonhomologous End Joining	1024
Topoisomerases Catalyze Changes in the Linking Number of DNA	967	Site-Specific Recombination Results in Precise DNA Rearrangements	1025
BOX 24-1 MEDICINE Curing Disease by Inhibiting Topoisomerases	970	Transposable Genetic Elements Move from One Location to Another	1027
DNA Compaction Requires a Special Form of Supercoiling	970	Immunoglobulin Genes Assemble by Recombination	1029
24.3 The Structure of Chromosomes	972	26 RNA Metabolism	1035
Chromatin Consists of DNA and Proteins	972	26.1 DNA-Dependent Synthesis of RNA	1036
Histones Are Small, Basic Proteins	973	RNA Is Synthesized by RNA Polymerases	1036
Nucleosomes Are the Fundamental Organizational Units of Chromatin	973	RNA Synthesis Begins at Promoters	1038
Nucleosomes Are Packed into Highly Condensed Chromosome Structures	975	Transcription Is Regulated at Several Levels	1039
BOX 24-2 METHODS Epigenetics, Nucleosome Structure, and Histone Variants	976	BOX 26-1 METHODS RNA Polymerase Leaves Its Footprint on a Promoter	1040
Condensed Chromosome Structures Are Maintained by SMC Proteins	979	Specific Sequences Signal Termination of RNA Synthesis	1041
Bacterial DNA Is Also Highly Organized	979	Eukaryotic Cells Have Three Kinds of Nuclear RNA Polymerases	1042
25 DNA Metabolism	987	RNA Polymerase II Requires Many Other Protein Factors for Its Activity	1042
25.1 DNA Replication	989	DNA-Dependent RNA Polymerase Undergoes Selective Inhibition	1046
DNA Replication Follows a Set of Fundamental Rules	989	26.2 RNA Processing	1047
		Eukaryotic mRNAs Are Capped at the 5' End	1048
		Both Introns and Exons Are Transcribed from DNA into RNA	1048
		RNA Catalyzes the Splicing of Introns	1049

Eukaryotic mRNAs Have a Distinctive 3' End Structure	1053	Stage 5: Newly Synthesized Polypeptide Chains Undergo Folding and Processing	1110
A Gene Can Give Rise to Multiple Products by Differential RNA Processing	1054	Ribosome Profiling Provides a Snapshot of Cellular Translation	1111
Ribosomal RNAs and tRNAs Also Undergo Processing	1055	Protein Synthesis Is Inhibited by Many Antibiotics and Toxins	1112
Special-Function RNAs Undergo Several Types of Processing	1059	27.3 Protein Targeting and Degradation	1114
RNA Enzymes Are the Catalysts of Some Events in RNA Metabolism	1060	Posttranslational Modification of Many Eukaryotic Proteins Begins in the Endoplasmic Reticulum	1114
Cellular mRNAs Are Degraded at Different Rates	1062	Glycosylation Plays a Key Role in Protein Targeting	1115
Polynucleotide Phosphorylase Makes Random RNA-like Polymers	1063	Signal Sequences for Nuclear Transport Are Not Cleaved	1118
26.3 RNA-Dependent Synthesis of RNA and DNA	1063	Bacteria Also Use Signal Sequences for Protein Targeting	1118
Reverse Transcriptase Produces DNA from Viral RNA	1064	Cells Import Proteins by Receptor-Mediated Endocytosis	1119
Some Retroviruses Cause Cancer and AIDS	1066	Protein Degradation Is Mediated by Specialized Systems in All Cells	1121
Many Transposons, Retroviruses, and Introns May Have a Common Evolutionary Origin	1066	<hr/>	
BOX 26-2 MEDICINE Fighting AIDS with Inhibitors of HIV Reverse Transcriptase	1067	28 Regulation of Gene Expression	1127
Telomerase Is a Specialized Reverse Transcriptase	1067	28.1 Principles of Gene Regulation	1128
Some RNAs Are Replicated by RNA-Dependent RNA Polymerase	1070	RNA Polymerase Binds to DNA at Promoters	1128
RNA Synthesis Provides Clues to the Origin of Life in an RNA World	1070	Transcription Initiation Is Regulated by Proteins and RNAs	1129
BOX 26-3 METHODS The SELEX Method for Generating RNA Polymers with New Functions	1072	Many Bacterial Genes Are Clustered and Regulated in Operons	1131
<hr/>		The <i>lac</i> Operon Is Subject to Negative Regulation	1131
27 Protein Metabolism	1077	Regulatory Proteins Have Discrete DNA-Binding Domains	1133
27.1 The Genetic Code	1078	Regulatory Proteins Also Have Protein-Protein Interaction Domains	1135
The Genetic Code Was Cracked Using Artificial mRNA Templates	1078	28.2 Regulation of Gene Expression in Bacteria	1138
BOX 27-1 Exceptions That Prove the Rule: Natural Variations in the Genetic Code	1082	The <i>lac</i> Operon Undergoes Positive Regulation	1138
Wobble Allows Some tRNAs to Recognize More than One Codon	1084	Many Genes for Amino Acid Biosynthetic Enzymes Are Regulated by Transcription Attenuation	1139
The Genetic Code Is Mutation-Resistant	1085	Induction of the SOS Response Requires Destruction of Repressor Proteins	1142
Translational Frameshifting and RNA Editing Affect How the Code Is Read	1085	Synthesis of Ribosomal Proteins Is Coordinated with rRNA Synthesis	1143
27.2 Protein Synthesis	1088	The Function of Some mRNAs Is Regulated by Small RNAs in Cis or in Trans	1144
Protein Biosynthesis Takes Place in Five Stages	1088	Some Genes Are Regulated by Genetic Recombination	1146
The Ribosome Is a Complex Supramolecular Machine	1090	28.3 Regulation of Gene Expression in Eukaryotes	1147
Transfer RNAs Have Characteristic Structural Features	1092	Transcriptionally Active Chromatin Is Structurally Distinct from Inactive Chromatin	1148
Stage 1: Aminoacyl-tRNA Synthetases Attach the Correct Amino Acids to Their tRNAs	1092	Most Eukaryotic Promoters Are Positively Regulated	1149
Stage 2: A Specific Amino Acid Initiates Protein Synthesis	1096	DNA-Binding Activators and Coactivators Facilitate Assembly of the Basal Transcription Factors	1150
BOX 27-2 Natural and Unnatural Expansion of the Genetic Code	1098	The Genes of Galactose Metabolism in Yeast Are Subject to Both Positive and Negative Regulation	1153
Stage 3: Peptide Bonds Are Formed in the Elongation Stage	1103	Transcription Activators Have a Modular Structure	1154
Stage 4: Termination of Polypeptide Synthesis Requires a Special Signal	1107		
BOX 27-3 Induced Variation in the Genetic Code: Nonsense Suppression	1107		

Eukaryotic Gene Expression Can Be Regulated by Intercellular and Intracellular Signals 1155

Regulation Can Result from Phosphorylation of Nuclear Transcription Factors 1157

Many Eukaryotic mRNAs Are Subject to Translational Repression 1157

Posttranscriptional Gene Silencing Is Mediated by RNA Interference 1158

RNA-Mediated Regulation of Gene Expression Takes Many Forms in Eukaryotes 1159

Development Is Controlled by Cascades of Regulatory Proteins 1160

Stem Cells Have Developmental Potential That Can Be Controlled 1165

BOX 28-1 Of Fins, Wings, Beaks, and Things 1168

Abbreviated Solutions to Problems AS-1

Glossary G-1

Index I-1

Protein Degradation Is Mediated by Specialized Systems in All Cells 1171

Endocytosis 1171

Cells Import Proteins by Receptor-Mediated Targeting 1178

Bacteria Also Use Signal Sequences for Nuclear Transport and Cleavage 1178

28 Regulation of Gene Expression

28.1 Principles of Gene Regulation

RNA Polymerase Binds to DNA at Promoters 1178

Chromosomes

Transcription Initiation Is Regulated by Transcription Factors and RNA Polymerase 1179

Many Bacterial Genes Are Clustered and Regulated in Operons 1181

The *lac* Operon Is Subject to Negative Regulation by Repressor Proteins Having DNA-Binding Domains 1181

Regulatory Proteins Also Have Protein-Protein Interaction Domains 1184

28.2 Regulation of Gene Expression in Bacteria

The *lac* Operon Undergoes Positive Regulation by Many Genes for Amino Acid Biosynthesis 1188

Enzymes Are Regulated by Transcription Attenuation 1189

Induction of the SOS Response Requires Destruction of Repressor Proteins 1192

Synthesis of Ribosomal Proteins Is Coordinated with rRNA Synthesis 1198

The Function of Some Bacterial Genes Is Regulated by Small RNAs in *Gyrodinium aureolum* 1144

Some Genes Are Regulated by Genetically Incompatible Elements 1148

28.3 Regulation of Gene Expression in Eukaryotes

Transcriptionally Active Chromatin Is Structurally Distinct from Inactive Chromatin 1148

Most Eukaryotic Promoters Are Positively Regulated 1149

DNA-Binding Activators and Corepressors Facilitate Assembly of the Basal Transcription Factors 1150

The Genes of Glucose Metabolism Are Subject to Both Positive and Negative Regulation 1152

Transcription Activators Have a Modular Structure 1154

RNA-Dependent Synthesis of RNA and DNA 1083

Reverse Transcriptase Produces cDNA from Viral RNA 1084

Some Retroviruses Cause Cancer and AIDS 1086

Many Transposons, Retroviruses, and Intons May Have a Common Evolutionary Origin 1088

BOXES

of HIV Reverse Transcriptase 1072

Telomerase Is a Specialized Reverse Transcriptase 1077

Some RNAs Are Replicated by RNA-Dependent RNA Polymerases 1070

RNA Synthesis Provides Clues to the Origin of Life on RNA Worlds 1070

BOXES

METHOD: The SELEX Method for Generating RNA Polymers with New Functions 1073

27 Protein Metabolism

27.1 The Genetic Code

The Genetic Code Was Cracked Using Artificial mRNA Templates 1078

BOXES

Exceptions That Prove the Rule: Natural Variations in the Genetic Code 1082

Wobble Allows Some tRNAs to Recognize More Than One Codon 1084

The Genetic Code Is Mutation-Resistant 1087

26 RNA Metabolism

Translational Frameshifting and RNA Editing Affect How the Genetic Code Is Used 1092

27.2 Protein Synthesis

Protein Biosynthesis Takes Place in Five Stages 1088

The Ribosome Is a Complex Subunit of a Catalytic Assemblage 1090

Transfer RNAs Have Characteristic Structures 1092

Stage 1: Anticodon-tRNA Synthetases Attach the Correct Amino Acids to Their tRNAs 1092

Stage 2: A Specific Amino Acid Initiates Protein Synthesis 1098

BOXES

Natural and Unnatural Expansion of the Genetic Code 1098

Stage 3: Peptide Bonds Are Formed in the Elongation Stage 1401

Stage 4: Termination of Polypeptide Synthesis Requires a Special Signal 1107

BOXES

Induced Variation in the Genetic Code: Nonense Suppression 1107

25 DNA

Regulation of Gene Expression in Eukaryotes 1147

Structurally Distinct from Inactive Chromatin 1148

Most Eukaryotic Promoters Are Positively Regulated 1149

DNA-Binding Activators and Corepressors Facilitate Assembly of the Basal Transcription Factors 1150

The Genes of Glucose Metabolism Are Subject to Both Positive and Negative Regulation 1152

Transcription Activators Have a Modular Structure 1154