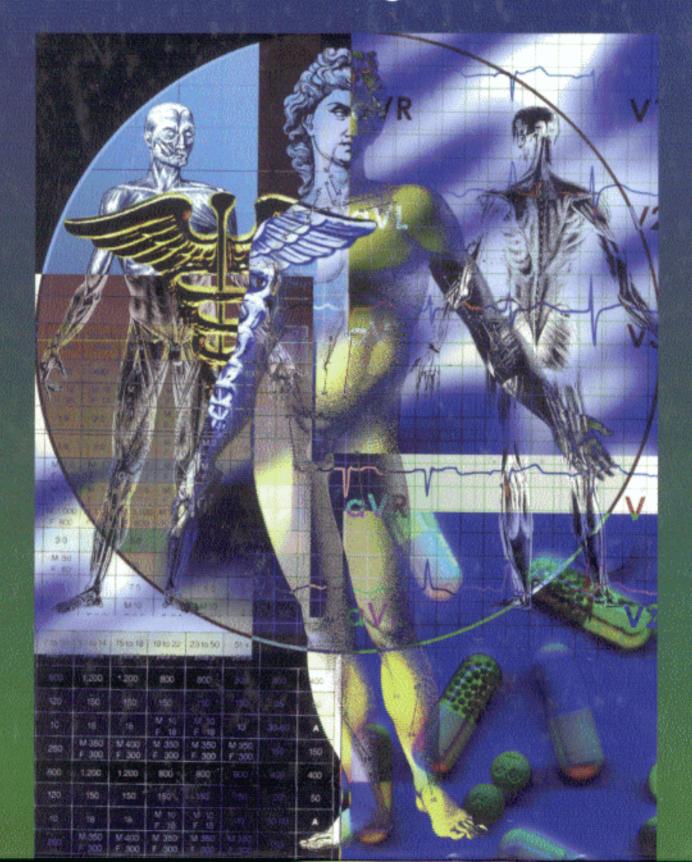
FOURTH EDITION

# MEDICAL BIOCHEMISTRY

N. V. Bhagavan



### **CONTENTS**

Contributors xxv  Preface xxvii  Acknowledgments xxix  CHAPTER 1  Water, Acids, Bases, and Buffers		1.4	H <sup>+</sup> Concentration and pH 15
		Supplemental Readings and References 16  Properties of Water 16  Acid-Base Chemistry and Respiratory Function of Hemoglobin 16  Nuclear Magnetic Resonance and Magnetic Resonance Imaging 16	
1.1	Properties of Water 1	CHAP	TER <b>2</b>
	Hydrogen Bonding 1 Physical Properties 2 Solutes Micelles and Hydrophobic	Am	ino Acids
	Solutes, Micelles, and Hydrophobic Interactions 2 Colligative Properties 3	2.1	L- $lpha$ -Amino Acids: Structure 17
1.2	Buffers 4  Henderson-Hasselbalch Equation 5  Buffer Systems of Blood and Exchange of O <sub>2</sub> and CO <sub>2</sub> 6  Blood Buffer Calculations 9  Nonbicarbonate Buffers in Blood 10	2.2	Classification 17  Nonpolar Amino Acids 18  Glycine 18  Alanine 20  Valine, Leucine, and Isoleucine 20  Phenylalanine 20  Tryptophan 20  Methionine 21
1.3	Measurement of pH 11		Proline 21
	Nuclear Magnetic Resonance and Magnetic Resonance Imaging 11 Gibbs-Donnan Equilibrium 13		Acidic Amino Acids 23  Aspartic Acid 23  Glutamic Acid 23

2.3

2.4

Selective Hydrolysis Methods 45

Peptide Sequence Confirmation 46 Fmoc Solid-Phase Peptide Synthesis 48

	Basic Amino Acids 23  Lysine 23  Histidine 24		Supplemental Readings and References 49
	Arginine 24 Neutral Amino Acids 24 Serine 24	CHAP	TER <b>4</b>
	Threonine 25 Cysteine 25 Tyrosine 25	of I	ree-Dimensional Structure Proteins
	Asparagine 25 Glutamine 26 Unusual Amino Acids 26 Amino Acids Used as Drugs 26	4.1	Attractive and Repulsive Forces in Proteins 52 Attractive Forces 52 Repulsive Forces 52
2.3 2.4	Electrolyte and Acid—Base Properties 27 Chemical Reactions of Amino Acids 31	4.2	Primary Structure 53 Peptide Bond 53
	Supplemental Readings and References 33	4.3	Secondary Structure 53 $\alpha$ -Helix 54 $\beta$ -Pleated Sheet 55 $\beta$ -Turns 56 Random Coil 56
Pro	otein Isolation and Determination  Amino Acid Sequence		Determination of Secondary Structure by Using Circular Dichroism (CD) Spectroscopy 56 Other Types of Secondary Structure 56
3.1	Quantitative Determination of Proteins 35	4.4 4.5	Tertiary Structure 57 Quaternary Structure 58
3.2	Determination of Primary Structure 36	4.6	Denaturation 58
3.3	Separation of Proteins 36 Separation by Molecular Size 37 Separation by Chromatography 37	4.7	Protein Folding and Associated Diseases 59
	Affinity Tag Chromatography 39 Separation by Electrophoresis 39		Supplemental Readings and References 64
3.4	Capillary Electrophoresis 41 Separation by Solubility 41		Protein Folding and Its Defects 64 Alzheimer's Disease, p53, and Prions 64
3.5	Amino Acid Composition 42	CUAD	TER <b>5</b>
3.6	Amino Acid Sequence Determination 43 Identification of the N-Terminal Residue 43 Identification of the C-Terminal Residue 44	Th	ermodynamics, Chemical Kinetics, d Energy Metabolism

5.1

Methods of Altering the Rate of Reactions 67

Com	onto		
5.2 5.3 5.4 5.5 5.6	Thermodynamics 68  Standard Free Energy of Hydrolysis of ATP 73  Chemical Kinetics 75  Energy Metabolism 77  Obesity 82  Biochemical Mediators of Obesity 82  Supplemental Readings and References 84		Kinetics of Ligand–Receptor Interaction 104  Mechanisms of Enzyme Action 105 Coenzymes, Prosthetic Groups, and Cofactors 106  Supplemental Readings and References 108
CHAP	TER <b>6</b>	En: 7.1	zymes II: Regulation  Types of Regulation 109
Enz Kir	zymes I: General Properties, netics, and Inhibition	7.2	Allosteric Enzyme Regulation 111  Kinetics of Allosteric Proteins 111  Examples of Allosteric Proteins 112  Theoretical Models for Allosteric Effect 117
6.1	Nomenclature 85		
6.2	Catalysis 86  Specificity of Enzyme Catalysis 86  Active Site and Enzyme—Substrate Complex 86  Factors Governing the Rate of Enzyme-Catalyzed Reactions 86  Effect of Temperature 87  Effect of pH 87  Effect of Concentration of Enzyme and Substrate 88	<u>CHAP</u>	Supplemental Readings and References 119  Enzyme Regulation (General) 119  Allosteric Properties of Aspartate Transcarbamoylase and Hemoglobin Aspartate Transcarbamoylase 119  Hemoglobin 119
	Michaelis–Menten Treatment of the Kinetic Properties of an Enzyme 88	En	zymes III: Clinical Applications
6.3	Linear Plots for Michaelis-Menten Expression 91  Kinetics of Enzymes Catalyzing Two-Substrate Reactions 92	8.1	Diagnosis and Prognosis of Disease 12 Factors Affecting Presence and Removal of Intracellular Enzymes from Plasma 122 Measurement of Enzyme Activity 124
6.4	Inhibition 92  Reversible Inhibition 92  Competitive Substrates in Treatment of Some Intoxications 96  Irreversible Inhibition 98  Inactivation and Reactivation of Cytochrome Oxidase 99	8.2	Serum Markers in the Diagnosis of Tissue Damage 126 Myocardium 126 Pancreas 127 Liver 127
	Proteinase Inhibitors and Their Clinical	8.3	Enzymes as Analytical Reagents 128
	Significance 102	8.4	Enzymes as Therapeutic Agents 130

## Supplemental Readings and References 132

### CHAPTER 9

### Simple Carbohydrates

#### 9.1 Classification 133

Monosaccharides 133

Some Physiologically Important Monosaccharide

Derivatives 139

Sugar Alcohols 139

Sugar Acids 140

Amino Sugars 141

Sugar Phosphates 142

Deoxy Sugars 142

Glycosides 143

Disaccharides 144

Polysaccharides 147

## Supplemental Readings and References 151

### CHAPTER 10

## Heteropolysaccharides I: Glycoproteins and Glycolipids

10.1 Glycoproteins 153

10.2 Cell Membrane Constituents 156

#### 10.3 Cell-Surface Glycoproteins 161

Red Blood Cell Membrane and Membrane Skeleton Proteins 163 Blood Group Antigens 166

#### 10.4 Serum Glycoproteins 168

### 10.5 Molecular Mimicry of Oligosaccharides and Host Susceptibility 170

## Supplemental Readings and References 170

Extracellular Matrix 170 Blood Group Antigens 170 Molecular Mimicry 171
Disorders of Red Blood Cell Membrane
Skeleton 171

### CHAPTER 11

### Heteropolysaccharides II: Proteoglycans and Peptidoglycans

#### 11.1 Protein Fibers and Proteoglycans 173

Collagen 173

Collagen Types 173

Structure and Function 174

Turnover of Collagen and Tissue Repair 178

Elastin 179

Structure and Function 179

Turnover of Elastin 181

Proteoglycans 182

Types, Structures, and Functions of

Glycosaminoglycans 182

Turnover of Proteoglycans and Role

of Lysosomes 186

Mucopolysaccharidoses 187

### 11.2 Peptidoglycans 188

Lysis of Peptidoglycans by Lysozymes 193

#### 11.3 Lectins 194

Supplemental Readings and References 195

### CHAPTER 12

## Gastrointestinal Digestion and Absorption

#### 12.1 Anatomy and Physiology of the GI Tract 197

Mouth and Esophagus 197

Stomach 198

Small Intestine 199

Formation, Secretion, and Composition

of Bile 199

Exocrine Pancreatic Secretion 201

CHAPTER 13

and TCA Cycle

13.1 Glycolysis 225

Carbohydrate Metabolism I: Glycolysis

	Composition of Pancreatic Juice 202 Large Intestine 202	Source and Entry of Glucose into Cells 225 Reactions of Glycolysis 226
		Phosphorylation of Glucose 226
12.2	Gastrointestinal Hormones 202 Gastrin 203	Isomerization of Glucose-6-Phosphate to Fructose-6-Phosphate 229
	Peptic Ulcer Disease 207 Cholecystokinin 208	Phosphorylation of Fructose-6-Phosphate to Fructose-1,6-Bisphosphate 229
	Secretin 208 Gastric Inhibitory Peptide 208	Cleavage of Fructose-1,6-Bisphosphate into Two Triose Phosphates 229
12 2	Digestion and Absorption of Major Food	Isomerization of Dihydroxyacetone Phosphate to Glyceraldehyde 3-Phosphate 229
12.5	Substances 208	Dehydrogenation of Glyceraldehyde 3-Phosphate 230
	Carbohydrates 208  Digestion of Starch 209	Phosphorylation of ADP from 1,3-Bisphosphoglycerate 231
	Brush-Border Surface Hydrolysis 211 Transport of Monosaccharides into	Isomerization of 3-Phosphoglycerate to 2-Phosphoglycerate 231
	the Enterocyte 211 Na+,K+-ATPase 212	Dehydration of 2-Phosphoglycerate to Phosphoenolpyruvate 232
	Disorders of Carbohydrate Digestion and Absorption 212	Phosphorylation of ADP from Phosphoenolpyruvate 232
	Proteins 214	Reduction of Pyruvate to Lactate 233
	Digestion 214	Alternative Substrates of Glycolysis 234
	Absorption of Amino Acids and Oligopeptides 215 Disorders of Protein Digestion and Absorption 216	Role of Anaerobic Glycolysis in Various Tissue and Cells 235
	Lipids 216 Intraluminal Phase 216	Glycolytic Enzyme Deficiencies in Erythrocytes 235
	Intracellular (Mucosal) Phase 218 Secretion 218	13.2 Pyruvate Metabolism 235
	Disorders of Lipid Digestion and Absorption 218	Lactic Acidemia and Lactic Acidosis 236
	General Malabsorptive Problems 218	D-Lactic Acidosis 236
12.5	Absorption of Mister and Electrolytes 222	Oxidation of Pyruvate to Acetyl-CoA 236
12.4	Absorption of Water and Electrolytes 222  Disorders of Fluid and Electrolyte  Absorption 222	Regulation of Pyruvate Dehydrogenase Activity Abnormalities of Pyruvate Dehydrogenase Complex 240
12.5	Thermic Effect of Food 224	13.3 Tricarboxylic Acid (TCA) Cycle 241
	Sunniamental Readings	Reactions of TCA Cycle 241
	Supplemental Readings and References 224	Condensation of Acetyl-CoA with Oxaloacetate to Form Citrate 241
		Isomerization of Citrate to Isocitrate 241

Oxidative Decarboxylation of Isocitrate to

Oxidative Decarboxylation of \alpha-Ketoglutarate to

Conversion of Succinyl-CoA to Succinate Coupled to

Dehydrogenation of Succinate to Fumarate 244

α-Ketoglutarate 243

Succinyl-CoA 243

Formation of GTP 243

Hydration of Fumarate to Malate 244

Dehydrogenation of Malate to Oxaloacetate 244

Stereochemical Aspects of the TCA Cycle 244

Amphibolic Aspects of the TCA Cycle 244

Regulation of the TCA Cycle 245

Energetics of the TCA Cycle 245

## Supplemental Readings and References 245

#### CHAPTER 14

## **Electron Transport and Oxidative Phosphorylation**

## 14.1 Mitochondrial Structure and Properties 248

Submitochondrial Particles 251

Components of the Electron Transport Chain 251

Electron Transport Complexes 251

Complex I 251

Complex II 253

Complex III 254

Complex IV 255

Organization of the Electron Transport Chain 256

#### 14.2 Oxidative Phosphorylation 257

Mechanisms of Oxidative Phosphorylation 257
Uncoupling Agents of Oxidative
Phosphorylation 261

#### 14.3 Mitochondrial Energy States 263

Energy-Linked Functions of Mitochondria Other Than ATP Synthesis 263 Transport of Cytoplasmic NADH to Mitochondria 264

#### 14.4 The Mitochondrial Genome 266

Mitochondrial Biogenesis 267 Expression of mtDNA 267

## 14.5 Nuclear Control of Respiratory Chain Expression 267

#### 14.6 Mitochondrial Diseases 268

Base Substitution Mutations 268
Transfer RNA (tRNA) Mutations 269
mtDNA Deletions and Duplications 270

## 14.7 Other Reducing-Equivalent Transport and Oxygen-Consuming Systems 270

Supplemental Readings and References 274

### CHAPTER 15

### Carbohydrate Metabolism II: Gluconeogenesis, Glycogen Synthesis and Breakdown, and Alternative Pathways

#### 15.1 Gluconeogenesis 275

Metabolic Role 275
Gluconeogenic Pathway 276
Gluconeogenic Precursors 278
Regulation of Gluconeogenesis 279
Carboxylation of Pyruvate to
Oxaloacetate 279
Conversion of Oxaloacetate to
Phosphoenolpyruvate 280
Conversion of Fructose-1,6-Bisphosphate to
Fructose-6-Phosphate 280
Conversion of Glucose-6-Phosphate
to Glucose 281
Abnormalities of Gluconeogenesis 282

#### 15.2 Glycogen Metabolism 283

Glycogen Synthesis 283
Glycogen Breakdown 285
Regulation of Glycogen
Metabolism 286
Muscle 286

Control of Glycogen Synthase 286 Control of Glycogen Phosphorylase 288 Integrated Regulation of Muscle Glycogen Metabolism 289

Liver 290

Control of Glycogen Synthase 290 Control of Glycogen Phosphorylase 290

Integrated Regulation of Live	r Glycogen
Metabolism 290	
Glycogen Storage Diseases	291

#### 15.3 Alternative Pathways of Glucose Metabolism and Hexose Interconversions 291

Glucuronic Acid Pathway 291
Fructose and Sorbitol Metabolism 296
Galactose Metabolism 297
Metabolism of Amino Sugars 298
Pentose Phosphate Pathway 298

Oxidative Phase 300

Nonoxidative Phase 300

Pentose Phosphate Pathway in

Red Blood Cells 301

Glucose-6-Phosphate Dehydrogenase

Deficiency 302

Phagocytosis and the Pentose Phosphate

## Supplemental Readings and References 305

Pathway 304

### CHAPTER 16

### Carbohydrate Metabolism III: Glycoproteins, Glycolipids, GPI Anchors, Proteoglycans, and Peptidoglycans

### 16.1 Biosynthesis of Glycoproteins 311

N-Glycan Asn-Linked Glycoproteins 312
Phosphorylation of Oligosaccharide Chains on Lysosomal Enzymes 315
Inhibitors of Glycoprotein Biosynthesis 315
O-Glycan Ser(Thr)-Linked Oligosaccharides 317
Biosynthesis of GPI-Anchored Proteins 318
Biosynthesis of Glycosphingolipids 320
Biosynthesis of Glycosaminoglycans 322

### 16.2 Biosynthesis of Peptidoglycans 324

Penicillins and Cephalosporins 327

## Supplemental Readings and References 329

General 329
Glycoproteins 329
GPI-Anchored Proteins 329
Glycosphingolipids 329
Glycosaminoglycans and
Proteoglycans 329

Peptidoglycans, Antibiotics, and Resistance 330

### CHAPTER 17

#### Protein and Amino Acid Metabolism

#### 17.1 Essential and Nonessential Amino Acids 331

Nitrogen Balance 332
Quality and Quantity of Dietary Protein
Requirement 332
Protein Energy Malnutrition 333
Transport of Amino Acids into Cells 333
General Reactions of Amino Acids 335
Deamination 335
Dehydrogenation of L-Glutamate 336
Transamination 337
Role of Specific Tissues in Amino Acid
Metabolism 338

#### 17.2 Metabolism of Ammonia 340

Urea Synthesis 340

Formation of Carbamoyl Phosphate 341

Formation of Citrulline 342

Formation of Argininosuccinate 342

Formation of Arginine and Fumarate 342

Formation of Urea and Ornithine 343

Energetics of Ureagenesis 343

Hyperammonemias 343

## 17.3 Metabolism of Some Individual Amino Acids 345

Arginine 345
Metabolism and Synthesis of Nitric Oxide 345
Isoforms (Also Known as Isozymes) of Nitric Oxide
Synthase 346

α-Oxidation 373

ω-Oxidation 374

Acids 374

Oxidation of Mono- and Polyunsaturated Fatty

	Signal Transduction of NO 346  Glycine 347  Disorders of Glycine Catabolism 348  Creatine and Related Compounds 348	18.2	Metabolism of Ketone Bodies 374  Physiological and Pathological Aspects of Metabolism of Ketone Bodies 376
	Use of Creatine as a Dietary Supplement 349	18.3	Metabolism of Ethanol 377
	Serine 349 Proline 349 Histidine 351 Branched-Chain Amino Acids 352 Sulfur-Containing Amino Acids 353 Methionine 353 Cysteine 354 Abnormalities Involving Sulfur-Containing Amino Acids 354	18.4	Synthesis of Long-Chain Saturated Fatty Acids 379 Functional Organization of Fatty Acid Synthase 383 Sources of NADPH for Fatty Acid Synthesis 384 Source and Transport of Acetyl-CoA 384 Regulation of Fatty Acid Synthase 384 Fatty Acid Elongation 385
	Homocysteine 354  Phenylalanine and Tyrosine 356  Phenylketonuria (PKU) 358  Melanin 360  Abnormalities of Tyrosine Metabolism 360  Tryptophan 361	18.5	Metabolism of Unsaturated Fatty Acids 386 Structure and Nomenclature of Unsaturated Fatty Acids 386 Functions of Unsaturated Fatty Acids 386
		18.6	Nonessential Fatty Acids 386
	Supplemental Readings and References 363	18.7	trans-Fatty Acids 388
	10	18.8	Essential Fatty Acids 388 Deficiency of Essential Fatty Acids 389
	ids I: Fatty Acids and Eicosanoids	18.9	Metabolism of Eicosanoids 389 Biological Properties of Prostanoids 395 Leukotrienes 396
18.1	Activation of Fatty Acids 366  Transport of Acyl-CoA to Mitochondrial Matrix 367		Supplemental Readings and References 398
	8-Oxidation 368 Energetics of $\beta$ -Oxidation 371 CHAP		er 19
	Regulation of Fatty Acid Oxidation 372 Peroxisomal Fatty Acid Oxidation 372 Other Pathways of Fatty Acid Oxidation 373  Propionyl-CoA Oxidation 373	—— Lipi	ds II: Phospholipids, cosphingolipids, and Cholesterol

19.1 Phospholipids 401

Phosphatidylcholines 401

Other Glycerophospholipids

Phosphosphingolipids 406

402

## 19.2 Phospholipids and Glycosphingolipids in Clinical Medicine 406

Pulmonary Surfactant Metabolism and
Respiratory Distress Syndrome 406
Biochemical Determinants of Fetal Lung
Maturity 408
Catabolism and Storage Disorders of
Sphingolipids 409
Alterations in Cell Surface
Glycosphingolipids 414

#### 19.3 Cholesterol 414

Conversion of Acetyl-CoA to HMG-CoA 415
Conversion of HMG-CoA to
Mevalonate 416
Conversion of Mevalonate to Isoprenyl
Pyrophosphate 419
Condensation of Isoprenyl Pyrophosphate to
Form Squalene 420
Conversion of Squalene to Lanosterol 420
Conversion of Lanosterol to Cholesterol 421
Utilization of Cholesterol 421

#### 19.4 Bile Acids 423

Regulation of Bile Acid Synthesis 424
Disposition of Bile Acids in the Intestines and
Their Enterohepatic Circulation 425
Bile Acid Metabolism and Clinical
Medicine 426

## Supplemental Readings and References 427

### CHAPTER 20

### Lipids III: Plasma Lipoproteins

#### 20.1 Structure and Composition 429

#### 20.2 Metabolism 433

Chylomicrons 434
Very-Low-Density Lipoproteins 435
Low-Density Lipoproteins 437
High-Density Lipoproteins 438

### 20.3 Lipoprotein-Associated Disorders 440

Hyperlipidemias 440

Hypertriacylglycerolemias 440

Hypercholesterolemias 441

Hypolipidemias 442

Atherosclerosis and Coronary Heart Disease 444

Lipid-Lowering Methods 448

## Supplemental Readings and References 450

### CHAPTER 21

## **Muscle and Nonmuscle Contractile Systems**

#### 21.1 Muscle Systems 454

Structure and Development of
Skeletal Muscle 454

Myofibrils 457

Thin Myofilaments 458

Thick Myofilaments 460

Organization and Properties of
Muscle Fibers 462

Contractile Properties 462

pH Dependence of Myosin ATPase
Activity 462

Metabolic Profile 463

Multigene Families Encode Muscle
Proteins 463

#### 21.2 Mechanism of Muscle Contraction: Overview 464

Mechanism of Contraction:
Excitation/Contraction Coupling 464
Mechanism of Contraction: Activation of
Contraction 466
Mechanism of Contraction: Cross-Bridge
Cycling 466

### 21.3 Energy Supply in Muscle 468

Phosphocreatine Shuttle 471
Regulation of Smooth and Cardiac
Muscle 472

#### 21.4 Inherited Diseases of Muscle 476

Degenerative Syndromes 478 Dynamic Syndromes 478

#### 21.5 Nonmuscle Systems 478

Actin 478 Cilia 480

#### 21.6 Drugs Affecting Microtubules 483

Immotile Cilia Syndrome 483 Kinesins 484

## Supplemental Readings and References 484

### CHAPTER 22

#### **Metabolic Homeostasis**

#### 22.1 Metabolic Homeostasis 485

#### 22.2 Metabolic Roles of Organs 487

Liver 487 Adipose Tissue 487 Skeletal Muscle 488 Brain 488

Heart 489 Kidneys 489

Gastrointestinal System 489

Blood and Other Body Fluids 489

Albumin 490 Lipoproteins 490

## 22.3 Endocrine Pancreas and Pancreatic Hormones 490

Insulin 490

Structure and Synthesis 490

Secretion 492

Biological Actions of Insulin 494

Insulin Receptor 494

Glucagon 495

Somatostatin 496

Pancreatic Polypeptide 496

#### 22.4 Stored Fuels 496

Appetite, Hunger, and Control of Food Intake 497

#### 22.5 Carbohydrate Homeostasis 497

Carbohydrate as a Food 497

Disposition of High Glucose Intake 498

Glucose Tolerance 499

Glucose Homeostasis during Fasting 499

Utilization of Hepatic Glycogen 500

Utilization of Skeletal Muscle Glycogen 501

Gluconeogenesis 502

Regulation of Gluconeogenesis 502

#### 22.6 Lipid Homeostasis 504

Lipid Digestion and Absorption 504
Disposition of Absorbed Triacylglycerol 504
Production of Triacylglycerol from
Carbohydrate 505
Release of Lipid from Adipose Tissue Stores 505
Tissue Utilization of Fatty Acids 506
Ketone Body Production and Utilization 506

## 22.7 Protein Synthesis and Nitrogen Homeostasis 508

Protein Synthesis and Proteins as Energy
Source 508

Nitrogen Balance 508

Ammonia Toxicity 509

Nitrogen Transfer between Compounds and
Tissues 509

Methods for Directly Transferring
Nitrogen 509

Reactions in Which Ammonia Is
Released 509

Reactions That "Fix" Ammonia 509

Disposition of Dietary Intake of Protein 509 Protein Catabolism during Starvation 510

## 22.8 Abnormalities of Metabolic Homeostasis 511

Diabetes Mellitus 511

Etiologic Classification of Diabetes Mellitus 512

Obesity 515

<b>22.9</b>	Metabolic	Homeostasis	during
	Exercise	517	

Exercise Generating Maximum Power 517 High-Intensity Endurance Exercise 517 Low-Level Nonfatiguing Exercise 518

## Supplemental Readings and References 518

### CHAPTER 23

## Nucleic Acid Structure and Properties of DNA

### 23.1 Components of Nucleic Acids 521

Base Pairing and Base Composition 522
Tautomerization of Bases 523
Methylation of Bases 524

## 23.2 Physical and Chemical Structure of DNA 524

The Watson-Crick DNA Structure 524
Alternative DNA Structures 526
Plasmid DNA 526
Circular and Supercoiled DNA 526

- 23.3 Denaturation of DNA 527
- 23.4 Renaturation of DNA 528
- 23.5 Repetitive DNA Sequences 530

### 23.6 Degradation of DNA 530

Nucleases 530 Restriction Enzymes 530

## 23.7 Diagnostic and Clinical Applications of DNA 532

DNA Probes 532
Southern Blot Analysis 532
Polymorphisms 533
Forensic DNA Analysis 535
Sequencing DNA 535
Gene Therapy 536

#### 23.8 DNA Vaccines 537

Antibodies to DNA 537

### 23.9 The Human Genome Project 538

#### 23.10 Genomics and Proteomics 542

## Supplemental Readings and References 542

Structure of DNA 542
Sequencing DNA 542
Properties of DNA 542
Gene Therapy 543
Human Genome Project 543

### CHAPTER 24

## DNA Replication, Repair, and Mutagenesis

#### 24.1 DNA Replication 546

Problems of Replication 546
Semiconservative Replication 546
Origin and Direction of DNA Replication 546
Replicons 546
Discontinuous DNA Replication 547

### 24.2 Enzymology of DNA Replication 548

DNA Polymerases 548

Exonuclease Activities of Polymerase I 550

Polymerase III 551

Eukaryotic Polymerases 552

#### 24.3 The Replication Fork 552

Inhibitors of DNA Replication 553 Topoisomerase I Inhibitors 553

#### 24.4 Chromosome Replication 554

Replication of DNA in Chromosomes 555
Replication at the Ends of Chromosomes 555

#### 24,5 DNA Repair 556

Mismatch Repair and Methylation of DNA 556

Glycosylases 556
Alterations of DNA Molecules 557
General Mechanisms for Repair of DNA 557
Photoreactivation 557
Excision Repair 557
Recombination Repair 558
SOS Repair 559
Human Diseases and DNA Repair Deficiency 559

#### 24.6 DNA Mutation 559

Types of Mutations 559
Triplet Repeats and Fragile Sites 560

Supplemental Readings and References 562

### CHAPTER 25

### **RNA and Protein Synthesis**

# 25.1 Structure of RNA 564 Ribosomal RNA (rRNA) 564 Transfer RNA (tRNA) 564

- 25.2 Messenger RNA 564
- 25.3 Enzymatic Synthesis of RNA 566
- 25.4 Prokaryotic Transcription 566
  Lifetime of Prokaryotic mRNA 568

# **25.5 Transcription in Eukaryotes 568**Eukaryotic RNA Polymerases 568 RNA Polymerase II Promoters 569

Eukaryotic mRNA Synthesis 569
Capping and Polyadenylylation 569
Splicing of RNA in Eukaryotes 570

RNA Polymerase III Promoters 569

Splicing and Ribozymes 571

#### 25.6 Genetic Code 571

"Universal" Genetic Code 571 Genetic Code of Mitochondria 572

## 25.7 Attachment of Amino Acid to tRNA Molecule 574

## 25.8 Initiator tRNA Molecules and Selection of Initiation Codon 574

#### **25.9 Ribosomes 575**

Chemical Composition of Prokaryotic Ribosomes 575 Ribosomes Are Ribozymes 575 Chemical Composition of Eukaryotic Ribosomes 576

#### 25.10 Protein Synthesis 576

Stages of Protein Synthesis 576
Role of GTP 579
Posttranslational Modification of Proteins 579
Coupled Transcription and Translation 580
Endoplasmic Reticulum 580
Compartment Disorders 581
Inhibitors of Protein Synthesis and Related Disorders 584

#### 25.11 Collagen Biosynthesis and Its Disorders 585

Transcription and Translation of Collagen Polypeptides 586 Intracellular Posttranslational Modifications 587 Hydroxylations of Selected Prolyl and Lysyl Residues 587 Glycosylation of Hydroxylysyl Residues 588 Formation of Disulfide Linkages and Assembly of Procollagen Polypeptides into a Triple Helix 588 Translocation and Secretion of Procollagen 589 Extracellular Posttranslational Modification 589 Formation of Collagen Fibrils from Ordered Aggregation of Collagen Molecules 589

## Supplemental Readings and References 590

CHAPTER	26
OFIATILA	

### **Regulation of Gene Expression**

#### 26.1 Regulation of mRNA 593

#### 26.2 Gene Regulation in Prokaryotes 594

Lactose (lac) Operon 594

Tryptophan (trp) Operon 595

Temporal mRNA Regulation in Phage
Systems 598

Regulons 599

#### 26.3 Gene Regulation in Eukaryotes 599

Housekeeping Genes and RNases 600 Gene Families 600

### 26.4 Mechanisms of Gene Regulation in Eukaryotes 601

Transcription Factors 601
Steroid Receptors 603
G-Protein Diseases 604
Regulation of Transcription by Methylation 604
Genomic Imprinting 606
Regulation of RNA Processing 606
Alternative RNA Splicing and Editing 607
Regulation of Iron Utilization in Cells 607
Polyproteins 608
Translational Regulation 608
Regulation of Protein Activity 608

### 26.5 Regulation of Cell Death: Apoptosis 609

### 26.6 Regulation of Cell Proliferation: Oncogenes 609

#### 26.7 Retroviruses and AIDS 612

Supplemental Readings and References 613

### CHAPTER 27

#### **Nucleotide Metabolism**

#### 27.1 One-Carbon Metabolism 615

Inhibitors of Dihydrofolate Reductase 617

Formation of One-Carbon Derivatives of Folate 617

## 27.2 Formation of 5-Phosphoribosyl-1-Pyrophosphate 619

### 27.3 Biosynthesis of Purine Nucleotides 620

De Novo Synthesis 620 Salvage Pathways 622 Dietary Purines 623

## 27.4 Conversion of Nucleoside Monophosphates to Diphosphates and Triphosphates 624

## 27.5 Formation of Purine Deoxyribonucleotides 624

#### 27.6 Regulation of Purine Biosynthesis 625

PRPP Synthetase Reaction 625
Amidophosphoribosyltransferase Reaction 625
Regulation of Formation of AMP and GMP
from IMP 626

#### 27.7 Inhibitors of Purine Biosynthesis 626

Inhibitors of Folate Biosynthesis 626
Inhibitors of Formation of IMP 626
Inhibitors of Formation of AMP and GMP 626
Inhibitors of Multiple Steps—Purine
Analogues 627
Inhibition of Conversion of Ribonucleoside
Diphosphate to Deoxyribonucleoside
Diphosphate 628

#### 27.8 Catabolism of Purine Nucleotides 628

Xanthine Oxidase Reaction 629
Disorders of Purine Nucleotide Metabolism 630
Gout 630

Overproduction of PRPP 631

Treatment 631

Dietary and Lifestyle Factors 633

Lesch-Nyhan Syndrome 633

Adenine Phosphoribosyltransferase (APRT)

Deficiency 634

Adenosine Deaminase (ADA) Deficiency and Purine Nucleoside Phosphorylase (PNP) Deficiency 634

Myoadenylate Deaminase Deficiency 636 Xanthine Oxidase Deficiency 637 xviii Contents

## 27.9 Biosynthesis of Pyrimidine Nucleotides 637

Salvage Pathways 638

De Novo Synthesis 638

Formation of UMP 638

Formation of Other Pyrimidine

Nucleotides 639

Synthesis of Cytidine Nucleotides 640

Synthesis of Thymidine Nucleotides 640

Pyrimidine Analogues 641

Regulation of de Novo Pyrimidine

Biosynthesis 641

## 27.10 Coordination of Purine and Pyrimidine Nucleotide Biosynthesis 642

## 27.11 Catabolism of Pyrimidine Nucleotides 643

## 27.12 Abnormalities of Pyrimidine Metabolism 644

Supplemental Readings and References 644

### CHAPTER 28

### Hemoglobin

#### 28.1 Structure of Hemoglobins 645

Globin Chains 645 Heme Group 646

### 28.2 Functional Aspects of Hemoglobin 646

Oxygen Transport 646

Mechanism of Oxygenation 650

Function, Metabolism, and Regulation of Organic

Phosphates in Erythrocytes 652

CO<sub>2</sub> Transport 655

Nitric Oxide (NO) Binding to Hemoglobin 656

Erythropoietin 656

## 28.3 Inherited Disorders of Hemoglobin Structure and Synthesis 657

Normal Hemoglobins 657 Thalassemias 659 α-Thalassemias 660

Thalassemias of the  $\beta$ -Globin Gene Family 662

 δ-β Thalassemias, Lepore Hemoglobins, and Hereditary Persistence of Fetal Hemoglobin (HPFH) 662

Hemoglobinopathies 664

Molecular Pathology 664

Unstable Hemoglobins 667

Secondary Polycythemia Syndromes 667

Congenital Methemoglobinemias and

Cyanosis 668

Hemoglobin S and Sickling Disorders 668

 $\gamma$ - and  $\delta$ -Globin Mutants 670

Screening and Prenatal Diagnosis 670

#### 28.4 Derivatives of Hemoglobin 67

Carbon Monoxide-Hemoglobin 671

Carbaminohemoglobin 672

Methemoglobin 672

Sulfhemoglobin 673

Cyanmethemoglobin 673

Glycated Hemoglobins 674

## Supplemental Readings and References 674

### CHAPTER 29

#### Metabolism of Iron and Heme

#### 29.1 Iron Metabolism 675

Absorption of Iron from the Diet 675

Plasma Iron Transport 679

Storage of Iron 679

Coordinate Regulation of Iron Uptake and Storage

in Non-Erythroid Cells 679

Alterations of Plasma Transferrin

Concentration 680

Disorders of Iron Metabolism 681

Iron Deficiency Anemia 681

Iron-Storage Disorders 682

Hereditary Hemochromatosis 683

#### 29.2 Heme Biosynthesis 684

Formation of δ-Aminolevulinic Acid 684

Formation of Porphobilinogen 684

Formation of Uroporphyrinogen III 685

Formation of Coproporphyrinogen III 685

Formation of Protoporphyrinogen IX 685

Formation of Protoporphyrin IX and Heme 685

Disorders of Heme Biosynthesis 686

Hepatic Porphyrias 687

Erythropoietic Porphyrias 688

#### 29.3 Heme Catabolism 689

Formation of Bilirubin 690
Circulatory Transport of Bilirubin 691
Hepatic Uptake, Conjugation, and Secretion of Bilirubin 692
Bilirubin 692
Bilirubin in the Intestinal Tract 694
Disorders of Bilirubin Metabolism 694
Unconjugated Hyperbilirubinemias 694
Conjugated Hyperbilirubinemias 694
Neonatal Hyperbilirubinemia 696

## Supplemental Readings and References 696

### CHAPTER 30

### Endocrine Metabolism I: Introduction

- 30.1 Hormonal Amines 700
- 30.2 Peptide, Protein, and Glycoprotein Hormones 701
- 30.3 Steroid Hormones 702

The  $\Delta^4$  Pathway:  $3\beta HSD - 705$ Directional Flow Valve: CYP17 - 705 The Corticosteroid Pathway Is Initiated by 21-Hydroxylase (CYP21) - 705 The Sex Steroid Pathway Is Initiated by  $17\alpha$ -Hydroxylase/17,20-Lyase (CYP17) - 706 Synthesis of Androgens: 17,20-Lyase - 706 Synthesis of Estrogens: Aromatase (CYP19) - 706 Steroid-Binding Serum Proteins - 707 Eicosanoids - 709

#### 30.4 Mechanism of Hormone Action 709

### 30.5 Types of Hormone Receptors 710

Nuclear Receptors 710
Thyroid Hormone Receptors 710
Steroid Hormone Receptors 711
Cell Surface Receptors 713

G-Protein-Coupled Adenylate Cyclase-cAMP System 713

Abnormalities in Initiation of G-Protein Signal 717

G-Protein-Coupled Phosphatidylinositol- Ca<sup>2+</sup> Pathway 718

Mechanism of the Calcium Messenger System 718

Receptors for Insulin and Growth Factors 721
Receptors for Growth Hormone and
Prolactin 722

### 30.6 Organization of the Endocrine System 722

Supplemental Readings and References 726

### CHAPTER 31

### Endocrine Metabolism II: Hypothalamus and Pituitary

### 31.1 Hypothalamus 729

Hypophysiotropic Peptides (Table 31-1) 730
Neurohypophyseal Peptides 733
Neuroregulatory Peptides 733
Brain-Gut Peptides 733
Endogenous Opiates 735

### 31.2 Pituitary Gland (Hypophysis) 736

Somatomammotropin Family 737
Growth Hormone (GH Somatotropin) 737
Actions of GH 738
Regulation of GH Release 739
Insulin-like Growth Factors (IGFs) 739
Disturbances in GH and IGF 740
Prolactin 741
Disturbances in Prolactin 742

The Opiomelanocortin Family 742 Glycoprotein Hormones 744 Neural Regulation of Anterior Pituitary Function 745

### Supplemental Readings and References 746

### CHAPTER 32

## **Endocrine Metabolism III: Adrenal Glands**

#### 32.1 Adrenal Cortex 749

Synthesis of Corticosteroids (See Chapter 30) 750

Regulation of Corticosteroid

Secretion 752

Regulation of Aldosterone

Secretion 752

Regulation of Cortisol Secretion 753

Metabolism of Corticosteroids 754

Synthetic Corticosteroids 754

Biological Actions of Aldosterone 754

Mechanism of Action 754

Physiological Effects of Aldosterone 755

Biological Actions of Cortisol 755

Mechanism of Action 755

Physiological Effects of Cortisol 755

Pharmacological Effects of Glucocorticoids 756

Adrenal Androgen, Dehydroepiandrosterone (DHEA) 757

Disturbances in Adrenocortical Function 757

Deficiency 757

#### 32.2 Adrenal Medulia 760

Regulation of Release 760

Synthesis of Epinephrine 761

Regulation of Catecholamine Secretion 761

Regulation of Synthesis 761

Regulation of Release 763

Transport and Metabolism of

Catecholamines 763

Biological Actions of Catecholamines 763

Mechanism of Action 763

Dopamine Receptors 763

Adrenergic Receptors 763

Biological Effects of Epinephrine and

Norepinephrine (Table 32-3) 765

Cardiovascular, Pulmonary, and Renal Effects 765

Pulmonary Respiratory System 765

Renal Urinary System 765

Metabolic, Endocrine, and Thermogenic

Effects 766

Disturbances in Adrenal Medullary

Function 767

## Supplemental Readings and References 767

### CHAPTER 33

## **Endocrine Metabolism IV:** Thyroid Gland

## 33.1 Structure-Activity of Thyroid Hormones 769

#### 33.2 Thyroid Hormone Synthesis 770

Regulation of Thyroid Hormone Synthesis 772

Thyroid-Stimulating Hormone (TSH) 772

Iodine 773

#### 33.3 Transport and Metabolism of Thyroid Hormones 774

## 33.4 Biological Actions of Thyroid Hormones 776

Mechanism of Action and Latency Period 776

Physiological Effects 776

Cardiovascular System 776

Intermediary Metabolism 777

Growth and Maturation 777

Reproductive System 778

Pharmacological Effects 778

## Supplemental Readings and References 779

	34
CHAPTER	34

### Endocrine Metabolism V: Reproductive System

#### 34.1 Testes 782

Regulation of Spermatogenesis:
Sertoli-Neuroendocrine Axis 782

Regulation of Testicular Steroidogenesis: Leydig-Neuroendocrine Axis 784

Metabolism of Testosterone 785

Biological Effects of Androgens 785

Reproductive (Androgenic)

Effects 787

Nonreproductive Effects 787

Pharmacological Inhibition of Spermatogenesis or Fertility (Male Contraception) 789

#### 34.2 Ovaries 790

Menstrual Cycle 790

**Endocrine Control of** 

Folliculogenesis 790

Hormonal Control of Follicle Growth 790

Hormonal Control of Luteal

Function 792

Pregnancy 792

Human Chorionic Gonadotropin (hCG) 792

Placental Steroids 793

Human Placental Lactogen (hPL) 793

Decidual Prolactin 794

Relaxin 794

Parturition 794

Lactation 794

Biological Effects of Estrogens 795

Metabolism of Estrogen 797

Selective Estrogen Receptor Modulators

(SERM) 797

Biological Effects of Progesterone 798

Pharmacological Enhancement of

Fertility 799

Pharmacological Prevention of Pregnancy

(Female Contraception) 799

### Supplemental Readings and References 801

### CHAPTER 35

#### **Molecular Immunology**

- 35.1 Innate Immunity 803
- 35.2 Acquired or Adaptive Immunity 808
- 35.3 Antibody-Dependent Cell-Mediated Cytotoxicity 811
- 35.4 Distinguishing Self from Nonself 811
- 35.5 Molecules and Chemical Processes of the Immune System 811

## 35.6 Immunoglobulin Structure and Function 812

Antigen-Antibody Reactions 818

Monoclonal Antibodies: Diagnostic Tools and

Therapeutic Agents 819

Recognition of Infected Cells by Cell

Receptors 820

### 35.7 B-Cell Clonal Selection and Proliferation 823

#### 35.8 Antibody Diversity and Immunoglobulin Genes 824

Class (Isotype) Switching 826

## 35.9 Major Histocompatibility Complex (MHC) Genes 827

#### 35.10 Complement 827

The Alternative Pathway 831
The Classical Pathway 831
The Lectin Pathway 832

#### 35.11 Cytokines 832

#### 35.12 Vaccines 833

Supplemental Readings and References 837

### CHAPTER 36

### **Biochemistry of Hemostasis**

#### 36.1 Primary Hemostasis 840

#### 36.2 Secondary Hemostasis 841

Clot Dissolution—Fibrinolysis 841
Thrombosis: A Dark Side of Hemostatic
System Function 842

### 36.3 Functional Properties and Structures of the Hemostatic System Factors (Proteins) 842

Proteinase Precursors 842
Proteinase Domain Structures 848
Amino Terminal Domain Structures and Structural Motifs 848
Cofactor Proteins 848
Proteinase Inhibitors 849
Other Proteins of the Hemostatic System 850
Membrane Phospholipid Surfaces 851

#### 36.4 Clotting 851

## 36.5 The Procoagulant Subsystem of Coagulation 852

Activation Complexes 852
The Prothrombin Activation Complex (Prothrombinase) 853
Activation of Prothrombin 853

#### 36.6 The Extrinsic Pathway 854

Initiation of the Procoagulant Subsystem and Activation of Factor VII 854 Activation of Factor X by Factor VII(VIIa) 855

#### 36.7 The Intrinsic Pathway 856

Activation of Factor X 856

Activation of Factor IX by Factor VIIa and Tissue Factor 856

Activation of Factor IX by Factor XIa 856

The Contact Phase of the *in Vitro* Intrinsic Pathway of Coagulation 857

#### 36.8 Anticoagulant Subsystem—Activation of Protein C and Inactivation of Factors Va and VIIIa 857

Anticoagulant Subsystem—Proteinase
Inhibitors 858

Mechanism of Action of Heparin as a Therapeutic
Anticoagulant 859

Inhibitors of the Contact Phase
Proteinases 859

#### 36.9 Fibrinolytic Subsystem 859

Plasminogen Activation 859
Degradation of Fibrin (Fibrinolysis) 861

### 36.10 Vitamin K, Oral Anticoagulants, and Their Mechanisms of Action 861

Action of Warfarin and Other Vitamin K Antagonists 862

#### 36.11 Coagulation Factor Measurements 863

Deficiencies 863
Laboratory Assessment of Coagulation System
Functions 864
Prothrombin Time 864
Thrombin Time 864
Activated Partial Thromboplastin Time 864
Specific Factor Assays 870
Assay of Heparin 870

#### **36.12 Case Studies 870**

Fibrinogen 870

Factor XIII 870

Activated Protein C Resistance 870

Antibiotic-Induced Vitamin K Deficiency 871

Hemophilia 871

Von Willebrand Disease 871

Laboratory-Created Artifacts 871

## Supplemental Readings and References 872

### CHAPTER 37

#### Mineral Metabolism

#### 37.1 Calcium and Phosphorus 873

Distribution and Function 873

Bone Structure, Formation, and Turnover 875

Calcium and Phosphate Homeostasis 876
Calcium and Phosphase in the Diet 876
Vitamin D Metabolism and Function 880
Parathyroid Hormone-Related Protein 887
Disorders of Calcium and Phosphorus
Homeostasis 888

#### 37.2 Magnesium 890

#### 37.3 Nonessential Trace Elements 891

Cadmium 891
Lead 894
Aluminum 894
Other Trace Elements 894

#### 37.4 Metallothioneins 894

#### 37.5 Essential Trace Elements 894

Copper 895 Zinc 897

## Supplemental Readings and References 899

### CHAPTER 38

#### Vitamin Metabolism

General Considerations 901

#### 38.1 Fat-Soluble Vitamins 904

Vitamin A 904

Nutrition and Chemistry 904

Absorption, Transport, and Metabolism 905

Function 906

Hypo- and Hypervitaminosis A 907

Vision and Vitamin A 908

Vitamin E 912

Nutrition and Chemistry 912

Absorption, Transport, and Metabolism 913

Function 913

#### 38.2 Water-Soluble Vitamins 914

Hypo- and Hypervitaminosis E 913

Thiamine (Vitamin B<sub>1</sub>) 914

Nutrition and Chemistry 914

Absorption, Transport, and Metabolism 915
Function 915
Hypo- and Hypervitaminosis 915
Riboflavin (Vitamin B<sub>2</sub>) 915
Pyridoxine (Vitamin B<sub>6</sub>) 916
Cobalamin (Vitamin B<sub>12</sub>) 918
Folic Acid (Pteroylglutamic Acid) 922
Niacin 924
Pantothenic Acid (Pantoyl-β-Alanine) 924
Biotin 924
Ascorbic Acid (Vitamin C) 925

## 38.3 Vitamin-Responsive Inherited Metabolic Disorders 926

## 38.4 Vitamin-like Substances 927

Supplemental Readings and References 928

### CHAPTER 39

## Water, Electrolytes, and Acid-Base Balance

39.1 Water Metabolism 929

39.2 Homeostatic Controls 930

39.3 Water and Osmolality Controls 931

#### 39.4 Electrolyte Balance 933

Sodium 933 Potassium 934 Chloride 934

#### 39.5 Acid-Base Balance 934

Disorders of Acid-Base Balance 935

## Supplemental Readings and References 938

Appendixes 939 Index 979