# **BIOCHEMISTRY**

# A CASE-ORIENTED APPROACH

REX MONTGOMERY, Ph.D., D.Sc. ROBERT L. DRYER, Ph.D. THOMAS W. CONWAY, Ph.D. ARTHUR A. SPECTOR, M.D.

THIRD EDITION

# **BIOCHEMISTRY**

# A CASE-ORIENTED APPROACH

REX MONTGOMERY, Ph.D., D.Sc. ROBERT L. DRYER, Ph.D. THOMAS W. CONWAY, Ph.D. ARTHUR A. SPECTOR, M.D.

Department of Biochemistry, The University of Iowa College of Medicine, Iowa City, Iowa

#### THIRD EDITION

With 276 illustrations



The C. V. Mosby Company

ST. LOUIS • TORONTO • LONDON 1

#### THIRD EDITION

#### Copyright © 1980 by The C. V. Mosby Company

All rights reserved. No part of this book may be reproduced in any manner without written permission of the publisher.

Previous editions copyrighted 1974, 1977

Printed in the United States of America

The C. V. Mosby Company 11830 Westline Industrial Drive, St. Louis, Missouri 63141

### Library of Congress Cataloging in Publication Data

Main entry under title:

Biochemistry.

Bibliography: p. Includes index.

1. Biological chemistry. 2. Physiology,

Pathological. I. Montgomery, Rex. [DNLM: 1. Biochemistry. QU4 B6155] 612'.015 80-11370 QP514.2.B56 1980

ISBN 0-8016-3470-9

# **PREFACE**

Over the course of the two previous editions the biochemical information in this book has continued to increase, both in the presentation of basic concepts and in the application of these concepts to analyses of health-related problems. As a result, the biochemical content of the third edition is self-standing and appropriate for a one-semester course in biochemistry. It is, however, organized in a manner less traditional than that found in most textbooks, since significant information on biochemical principles has been incorporated, where it seemed appropriate, into the detailed statements that comprise solutions to the case problems associated with each chapter. The text thus continues to serve a dual function: first, to make students aware of biochemical principles and, second, to provide opportunities to use these principles in analyzing commonly occurring health-related problems. We believe that the second goal is the ultimate objective of biochemical education for the health science student.

At first glance the chapter titles of this book are much like those of other biochemistry texts. Indeed, the first part of each chapter contains material that by itself is of a scope suitable for a one-semester course in general biochemistry. These biochemical principles are needed to understand the chemical and molecular aspects of health science problems. The second part of each chapter amplifies these principles, sometimes adding others as may be particularly relevant to the health-related problem at hand, and applies these facts and concepts to the stated solutions of health-related problems. While the purpose of the case presentations is to illustrate the application of biochemistry to health problems, students are often curious to know more about the physiologic or pathologic aspects of the clinical material. This curiosity can be satisfied by reading the references given after each case. Generally, students realize that the purpose of the text is to teach biochemistry, to demonstrate why biochemistry is important in the health sciences, and to show how biochemical principles are involved in day-to-day professional practice. Experience has shown us that students grasp concepts more clearly when they see a relation between those concepts and their own professional goals. Learning also seems to be more enjoyable when the applications are made evident.

Selected clinical case descriptions and biochemical questions about them are provided with and without written analysis. Those without analysis as well as a series of shorter additional questions at the end of each chapter are meant to be solved by the students. Many of the questions can be answered with a knowledge of the basic biochemistry presented in the first portion of the chapter. Sufficient references are given to answer the questions that are indicated by arrows and not answered in the main body of the text. Similarly, brief unsolved clinical problems are marked by arrows, indicating that outside reading will be required to compose a suitable solution. These questions are included because it is imperative that students become accustomed to the method and value of bibliographic research. The knowledge gained by study of the principles in the first part of the chapter can be extended by independent study of other source materials.

The format of this book allows considerable flexibility. For some students the language statements plus the solved case problems may be sufficient. Others may wish to use the unsolved case problems or the questions for additional study. The last chapter, entitled Comprehensive Case Analysis, represents more of a challenge than the earlier ones and requires that the student have a reasonably good grasp of the preceding material. It also adds considerably to details of some areas of biochemistry not previously treated, such as iron metabolism, defects in collagen synthesis and metabolism, hormone receptors, and receptor binding. This chapter, in particular, requires reference to the original literature to answer certain questions.

As in the past editions we have selected nutrition as the first topic in order to introduce from the very beginning the case-oriented method of study. Many students have been exposed to this subject in their everyday living and in previous schooling. Knowledge of the properties of proteins (Chapter 2) follows, since this material is so essential for later chapters. Chapter 3 deals with enzymes, also essential for understanding of later material. Because errors of fluid and electrolyte regulation are such frequent components of so many diseases, this topic is introduced as Chapter 4. Early introduction to these topics then permits selection of a wide range of case-oriented discussions. The remaining chapters may be covered in virtually any order, but we have found the sequence presented here to be satisfactory. Each chapter has been kept reasonably limited and self-contained, but we have made an effort by cross-references to keep the student's thoughts holistic.

In our one-semester courses, Chapters 1 through 13 are covered in a 14-week periodfor the most part, one chapter per week. The chapters that sometimes require a slightly longer time for completion are Acid-Base, Fluid, and Electrolyte Control (Chapter 4), Carbohydrate Metabolism (Chapter 7), and Hormonal Regulation of Metabolism (Chapter 13). Weekly contact involves 5 lecture hours for the class as a whole and 2 hours of discussion and review in small groups. All 5 lecture hours are usually devoted to coverage of the basic biochemistry section of the particular chapter. In some instances, however, one of these lectures is employed to present greater amplification of some important biochemical feature taken from the clinical examples section of the text. For example, phenylketonuria in Chapter 6, diabetes mellitus in Chapter 7, and hyperlipidemia in Chapter 10 have been highlighted by special lecture time devoted to recent developments. About 1½ hours of the small-group discussions are devoted to the clinical examples section of each chapter. This section begins with a general discussion of the clinical cases that have been worked out in the text, in an attempt to strengthen correlation of that information with the basic principles enunciated in the earlier part of the given chapter. Following this, students are asked to present one or more of the cases and additional problems not worked out in the text, either in oral or written presentations. Chapter 14 may be covered during the final week of independent study, with daily 2-hour tutorial sessions scheduled on a voluntary attendance basis.

It is recommended that examinations be based entirely on the analysis of cases. We have employed questions requiring short answers, multiple choices, and brief calculations. Our examinations are largely designed to be machine graded. In all instances the questions should be based on clinical situations, real or not, designed to gauge the student's capacity to deal with applications of basic biochemistry.

The third edition benefits from continued refinement of this teaching program for students of medicine, which is now in its ninth year at the University of Iowa. The program based on this approach has been extended to physicians' assistant students, and it has been used for students of dentistry. Elsewhere this book has been used in colleges of allied health sciences, medicine, nursing, osteopathic medicine, pharmacy, and veterinary medicine. In some instances it is used, as at Iowa, as the sole instructional source. In others it is used, in association with a more classic text, as a source of enrichment in learning.

This edition has been extensively revised and enlarged. Perhaps the most notable change is the use of SI units. In May, 1977, the Thirtieth World Health Assembly endorsed the use of the Système Internationale d'Unites (SI) in medicine. These units have

since been adopted in most countries, and the process of change is underway in some publications and in some health care institutions in the United States. The advantages for the scientific community of a uniform system for expressing molar concentrations, pressures, temperatures, and other physical properties is clear, but the implementation in the health sciences may be delayed by the need to maintain communication with those now in clinical practice. This places a burden on the basic sciences, where new health sciences students first must be prepared for the eventual change to SI units. For this reason the present edition of this text frequently presents both units, the SI units and, in parentheses, the presently used units, with the hope that students can learn in either system but be prepared to communicate in the SI system. A more complete description of the SI system is found in Appendix E with a table of the more common measures given inside the back cover of the book. We look on this editorial change as an experiment and will appreciate some expression of reader reaction.

Certain other changes are worth noting. From experience we have found that particular problems have had a higher teaching value than others. The good ones have been retained and updated, whereas those of lesser value have been replaced. A larger number of case problems have been worked out. More pertinent references to both solved and unsolved case problems have been included for the benefit of student and teacher alike. In the basic biochemistry sections of the text, more extensive discussion of such important topics as cell membranes, the theory of oxidative phosphorylation, biosynthesis of glycoproteins, lipoproteins, prostaglandins, DNA sequencing, and RNA splicing can be found. Complex figures have been broken down into more numerous, simpler ones for easier study and comprehension. A list of biochemical topics contained in the case problems has been added to the table of contents.

Past editions of this book benefited from advice and criticism of numerous friends and colleagues. Their efforts are reflected in this edition. We here expess our deep appreciation to new friends, including A. Arnone, J. E. Donelson, H. E. Hamilton, P. Hinkle, C. A. Hogben, T. C. Kisker, W. J. Lennarz, B. J. McCabe, M. Osborne, E. Racker, P. M. Seebohm, D. E. Shaw, and D. C. Zavala.

Rex Montgomery Robert L. Dryer Thomas W. Conway Arthur A. Spector

# CONTENTS

#### 1 NUTRITION, 1

Homeostasis, 1

Body water, 2

Principal food components, 2

Proteins, 2

Lipids, 3

Carbohydrates, 4

Overall view of metabolism of principal dietary components, 5

Lipids, 5

Carbohydrates and amino acids, 5

Krebs cycle and adenosine triphosphate, 6

Modifications in response to stress, 7

General nutritional requirements, 8

Practical daily food plan, 8

Recommended daily dietary allowances (RDA), 9

Energy requirements, 9

Lipid requirements, 13

Carbohydrate requirements, 14

Protein requirements, 14

Vitamin requirements, 16

Mineral requirements, 21

Special problems in nutritional maintenance, 23

Parenteral nutrition, 23

Total parenteral nutrition (hyperalimentation), 24

Gavage feeding, 24

Weight changes, 24

Clinical examples, 26

Case 1: Ascorbic acid deficiency, 26

Case 2: Obesity, 27

Case 3: Vitamin A deficiency and night blindness, 33

Case 4: Obesity, 35

Case 5: Ulcerative colitis, 35

Case 6: Niacin deficiency and pellagra, 35

Case 7: Adult celiac disease, 35

Case 8: Vitamin D toxicity, 36

Case 9: Nutrition for burn patients, 36

Case 10: Liquid protein diets, 37

Case 11: Iron overload, 37

#### 2 PROTEIN STRUCTURE, 39

General properties of amino acids and proteins, 39

Amino acids, 39

Peptide bond, 44

Conformational segments of polypeptide chains, 47

Protein conformation, 49

Properties of proteins in solution, 50

Ionic properties of amino acids, peptides, and polypeptides, 52

Structural aspects of specific proteins, 59

Plasma proteins, 59

Fibrous proteins, 63

Myoglobin and hemoglobin, 67

Specific binding of molecules to proteins, 75

Protein turnover, 77

Genetic basis of protein structure, 78

Clinical examples, 80

Case 1: False positive test for hemoglobin S, 80

Case 2: Rheumatoid factors in rheumatoid arthritis, 84

Case 3: Oral manifestation of hemoglobinopathy, 86

Case 4: Scar formation, 87

Case 5: Aspirin-induced alteration of human serum albumin, 88

Case 6: Monoclonal immunoglobulinemia, 88

Case 7: Red blood cells and surgery involving a heart-lung bypass, 89

Case 8: Insulin resistance, 90

# 3 ENZYMES AND BIOLOGIC CATALYSIS, 92

What are enzymes? 92

Enzyme structure, 93

Enzyme cofactors, 93

Vitamins and coenzymes, 96

Protein domains, 96

Nucleotide fold and affinity chromatography, 96

Enzyme and cofactor turnover, 98

Enzyme classification, 98

Intracellular location of enzymes, 98

General enzyme properties, 101

Effect of temperature on enzymes, 102

pH and ionic dependence of enzymes, 102

Active catalytic site, 104

Isomeric enzymes, or isozymes, 104

Enzyme specificity, 106

Mechanism of enzyme catalysis, 106

Catalytic mechanism of enzyme action, 106

Nature of enzyme catalysis, 107

Quantitative analysis of single-substrate enzyme kinetics, 109

Analysis from concentrations and reaction velocities, 111

Turnover number, 112

Enzymatic activity, 112

Kinetic analysis of enzyme inhibition, 112

Noncompetitive inhibition, 112

Two-substrate kinetics, 115

Clinically important enzyme inhibitors, 116

Coenzyme analogues as drugs, 117

Enzyme regulation and control, 117

Allosteric enzymes, 117

Product inhibition, 120

Feedback control, 121

Constitutive and inducible enzymes, 122

Regulation by covalent modification, 123

Enzyme cascades, 123

Blood clotting, 124

Summary, 126

Integration of enzymes into metabolic pathways, 127

Heme biosynthesis, 127

Bilirubin glucuronide and bile pigment metabolism, 130

Bilirubin metabolism and jaundice, 132

Clinical applications of enzymes, 133

Use of enzymes as reagents, 133

Use of enzymes as labeling reagents, 133

Immobilized enzymes, 133

What is a valid enzyme assay? 134

Problems of enzyme assays, 136

Clinical examples, 138

Case 1: Lead poisoning, 138

Case 2: Acute pancreatitis, 140

Case 3: Creatine kinase and myocardial infarction, 142

Case 4: Serum amylase in the diagnosis of pancreatitis, 144

Case 5: Antibiotics as enzyme inhibitors, 145

Case 6: Serum hepatitis, 147

Case 7: Muscle injury, 148

Case 8: Wilson's disease, 148

## 4 ACID-BASE, FLUID, AND ELECTROLYTE CONTROL, 150

Buffers, 150

Bicarbonate buffer, 153

Control of pH in the body, 156

Respiratory control of blood pH, 157

Transport of oxygen and carbon dioxide in blood, 157

Renal regulation of pH, water, and electrolytes, 159

Osmotic pressure, 160

Transport across membranes, 160

Kidney function, 161

Reabsorption of ions and water, 162

Renal threshold, 164

Renal control of acid-base balance, 165

Factors affecting bicarbonate concentration in blood, 165

Mechanisms of H+ excretion, 166

Summary of general movement of ions and water in the nephron, 166

Regulation of volume and concentration of body fluids, 167

Water distribution in the body, 167

Electrolyte regulation, 168

Diuretic agents, 168

Metabolic and respiratory disturbances of acid-base balance, 170

Gamblegrams, 171

Respiratory acidosis, 172

Respiratory alkalosis, 172

Metabolic acidosis, 172

Metabolic alkalosis, 172

Mixed disturbances of acid-base balance, 173

#### xii Contents

Clinical examples, 174

Case 1: Narcotic overdose, 174

Case 2: Idiopathic hyperventilation, 175

Case 3: Diabetes and diabetic ketoacidosis, 176

Case 4: Poliomyelitis, 177

Case 5: Encephalitis, 179

Case 6: Déhydration, 181

Case 7: Emphysema, 183

Case 8: Pulmonary embolism, 183

Case 9: Pneumonia, 183

Case 10: Pulmonary edema, 184

Case 11: Hyponatremia, 185

Case 12: Oxygen toxicity, 185

Case 13: Whipple's disease, 186

#### 5 ENERGETICS AND COUPLED SYSTEMS, 188

Energy changes in chemical reactions, 188

Fundamental laws of energy flux, 189

Free energy, 190

Qualitative evaluation of reaction energetics, 190

Standard state, 190

Coupled reaction systems, 191

Quantitative expressions of  $\Delta G$ , 192

Effect of concentrations on oxiuation-reduction reactions, 195

Summary of energetics, 196

Respiratory chain, 196

Major components of the respiratory chain, 198

Structural summary, 200

Respiratory chains of the endoplasmic reticulum, 200

High-energy compounds, 201

Oxidative phosphorylation, 203

Control of oxidative phosphorylation, 203

Concept of energy charge, 204

Inhibition and uncoupling of oxidative phosphorylation, 205

Structure of the mitochondrial inner membrane, 207

Reconstitution experiments, 208

Mechanism of oxidative phosphorylation, 209

Mitochondrial ion translocation, 210

Sodium-potassium pump, 211

Muscle contraction, 212

Contractile proteins, 214

Actins in noncontractile tissues, 218

Oxygen toxicity, superoxide radical, and superoxide dismutases, 218

Clinical examples, 219

Case 1: Hypophosphatemia, 219

Case 2: Halothane intoxication, 223

Case 3: Snake venoms as uncoupling agents, 226

Case 4: Chronic alcoholism, death induced by the acetaldehyde syndrome, 227

Case 5: Zellweger's disease (cerebrohepatorenal syndrome), 228

Case 6: Hypermetabolism, 228

Case 7: Acute bacteremia, 229

Case 8: Mental retardation with congenital methemoglobinemia, 229

Case 9: Pyruvate kinase deficiency, 230

#### 6 KREBS CYCLE, 232

Cellular location of the Krebs cycle, 233

Nature of cycle components, 233

Pyruvate decarboxylation, 233

Regulation of the pyruvate dehydrogenase complex, 236

Condensing reaction, 237

Isomerization of citrate, 237

First decarboxylation, 239

Second decarboxylation, 239

Substrate-level phosphorylation, 240

Final stages, 240

Recapitulation of Krebs cycle energetics, 241

Entry of amino acids into Krebs cycle, 242

Transamination of amino acids, 242

Entry of other amino acids into the Krebs cycle, 244

Mechanism of methylmalonyl CoA mutase, 244

Summary, 245

Anaplerotic reactions, 245

Mitochondrial compartmentalization, 245

Nature of translocases, 247

Representation of translocases, 247

Metabolic regulation of translocases, 249

Mitochondrial function in lipogenesis, 251

Mitochondrial function in gluconeogenesis, 253

Transfer of reducing equivalents, 255

The closed road: why fat is not converted to glucose, 256

Summary, 258

Clinical examples, 258

Case 1: Hepatic coma in late cirrhosis, 258

Case 2: Phenylketonuria and pyruvate metabolism, 260

Case 3: Myocardial infarction, 261

Case 4: Congenital defect of pyruvate dehydrogenase, 263

Case 5: Diagnostic problems resulting from laboratory methodologies, 266

Case 6: Methylmalonic aciduria, 268

Case 7: Citrate synthesis by isolated leukemic lymphocytes, 268

Case 8: Mitochondrial metabolism in posthepatic jaundice, 269

Case 9: Mitochondrial myopathy, 269

· Case 10: Stroke and cerebral ischemia, 270

Case 11: Granulomatosis and polymorphonuclear leukocytes, 271

#### 7 CARBOHYDRATE METABOLISM, 273

Nomenclature, 273

Ring structures, 275

Sugar derivatives, 277

Glycosides, 277

Disaccharides, 277

Oligosaccharides and polysaccharides, 278

Other naturally occurring sugar derivatives, 280

Digestion of carbohydrates, 281

Absorption of carbohydrates from intestine, 283

Rate of glucose absorption, 283

Interconversion of D-glucose, D-galactose, and D-fructose, 284

Utilization of D-glucose, 284

Utilization of D-fructose, 286

Utilization of D-galactose, 288

Nucleoside diphosphate sugars and carbohydrate biosyntheses, 290

Control of glycogen metabolism, 291

Metabolic interrelationships, 291

Control of glycogen metabolism in different tissues, 293

Cyclic AMP and adenylate cyclase, 295

Role of n-glucose 6-phosphate and AMP, 297

Abnormal glycogen metabolism, 298

Glycolysis, 298

Pathway of glycolysis, 298

Regulation and energetics, 303

Gluconeogenesis, 304

Regulation of gluconeogenesis, 304

Hormonal interaction to control glucose metabolism, 306

Pentose phosphate pathway (hexose monophosphate shunt), 306

Regulation of the pentose phosphate pathway, 308

D-Glucuronate and polyol pathways, 310

Biopolymers containing carbohydrate, 312

Glycoproteins, 313

Proteoglycans (mucopolysaccharides), 319

Clinical examples, 323

Case 1: Hypoglycemia, 323

Case 2: Diabetes mellitus and obesity, 325

Case 3: Pediatric gastroenteritis, 329

Case 4: Galactosemia, 331

Case 5: Von Gierke's disease, 332

Case 6: Diabetes mellitus, 333

Case 7: Type IV glycogen storage disease—enzyme therapy, 334

Case 8: Hereditary fructose intolerance, 334

Case 9: Factitious hypoglycemia, 335

#### 8 LIPID METABOLISM, 336

Classification of lipids, 336

Fatty acids, 337

Fatty acid derivatives, 343

Liposomes, 347

Analytic methods in lipid chemistry, 348

Saponification, 348

Thin-layer chromatography (TLC), 348

Gas-liquid chromatography (GLC), 349

Digestion and absorption of dietary fat, 349

Emulsification of dietary lipids, 349

Hydrolytic enzymes, 350

Absorption and reesterification, 350

Secretion and utilization of dietary triglycerides, 351

Medium-chain triglycerides, 352

Lipid transport, 353

Lipoproteins, 353

Lipoprotein lipase, 356

Lipoprotein separations, 356

Proteolipids, 357

Free fatty acids (FFA), 357

Integration of lipid transport, 357

Hyperlipoproteinemias, 357

Adipose tissue, 359

Fatty acid oxidation, 360

Acyl CoA synthetase, 361

Acylcarnitine formation, 362

 $\beta$ -Oxidation sequence, 362

Other types of fatty acid oxidation, 365

Energy yield of fatty acid oxidation, 365

Regulation of substrate utilization, 365

Ketone body oxidation, 366

Fatty acid synthesis, 367

Source of acetyl CoA, 367

Carboxylation of acetyl CoA, 368

Fatty acid synthetase, 368

Regulation of de novo biosynthesis, 371

Differences between synthesis and oxidation, 372

Chain elongation, 372

Desaturation, 372

Phosphoglyceride metabolism, 374

Complete (de novo) synthesis, 374

Partial synthesis, 376

Phosphoglyceride degradation, 378

Surfactant, 378

Phospholipid exchange proteins, 378

Alkyl ether and plasmalogen metabolism, 378

Sphingolipid metabolism, 379

Sphingolipid degradation, 379

Glyceride metabolism, 380

Lipases, 380

Clinical examples, 381

Case 1: Endogenous hypertriglyceridemia (type IV hyperlipoproteinemia), 381

Case 2: Hyperchylomicronemia (type I hyperlipoproteinemia), 383

Case 3: Glucosylceramide lipidosis (Gaucher's disease), 385

Case 4: Carnitine deficiency, 386

Case 5: Obesity, 387

Case 6: Steatorrhea, 387

Case 7: Angina pectoris, 387

Case 8: Lipogranulomatosis (Farber's disease), 388

Case 9: Type III hyperlipoproteinemia, 388

Case 10: Milk for infant feeding, 389

Case 11: Enzyme replacement therapy, 389

Case 12: Dietary fat and cancer, 390

## 9 AMINO ACID METABOLISM, 392

Dietary protein requirements, 392

Digestion of proteins, 394

Absorption of amino acids and peptides, 395

y-Glutamyl cycle, 396

Genetic abnormalities of the y-glutamyl cycle, 397

Glutathione in detoxification, 398

Biosynthesis of nonessential amino acids, 398

Metabolism supporting amino acid biosynthesis, 399

Biosynthesis of amino acids from dietary essential amino acids, 403

Summary of the biosynthesis of amino acids, 405

#### xvi Contents

Amino acid catabolism, 406

Fate of nitrogen atoms, 406

Fate of carbon atoms, 410

Amino acids as precursors of metabolites, 419

Amine synthesis, 419

Clinical examples, 427

Case 1: Amino acid metabolism in starvation, 427

Case 2: Glomerulonephritis, 430

Case 3: Hartnup disease, 432

Case 4: Inherited hemolytic anemia, 434

Case 5: Hereditary hyperammonemia, 435

Case 6: Methylmalonic acidemia, 435

Case 7: Glutathionuria, 436

Case 8: Homocystinuria, 437

Case 9: Isovaleric acidemia, 437

Case 10: Tyrosinemia, 437

## 10 STEROL AND STEROID METABOLISM, 439

Steroid chemistry, 439

Sterols, 440

Cell membranes, 441

Fluid mosaic model of membrane structure, 444

Cholesterol in plasma lipoproteins, 446

Dietary cholesterol, 447

Absorption, 447

Digestion, 447

Excretion, 447

Bile acids, 448

Synthesis of the primary bile acids, 449

Metabolism, 451

Secondary bile acids, 451

Enterohepatic circulation, 451

Cholelithiasis, 452

Cholesterol metabolism, 453

Ester formation, 453

Ester hydrolysis, 454

Biosynthesis, 454

Mevalonate shunt, 458

Ketone body synthesis, 459

Regulation of cholesterol synthesis, 460

Regulation of cholesterol levels in humans, 462

Steroid hormones, 463

Chemistry, 463

Biosynthesis, 466

Hydroxylation reactions, 470

Transport in plasma, 470

Metabolism, 470

Conjugation and excretion, 472

Clinical examples, 474

Case 1: β-Sitosterolemia, 474

Case 2: Spinocerebellar degeneration, 475

Case 3: Hypercholesterolemia and atherosclerosis, 477

Case 4: Hypercholesterolemia, 480

Case 5: Selective hypoaldosteronism, 482

- Case 6: Lecithin-cholesterol acyltransferase deficiency, 482
- Case 7: Chronic adrenal cortical insufficiency, 482
- Case 8: Gallstones, 483
- Case 9: Type IIa hyperlipoproteinemia, 484
- Case 10: Cerebrotendinous xanthomatosis, 484
- Case 11: Duchenne muscular dystrophy. 484
- Case 12: Dietary therapy of hypercholesterolemia, 485

## 11 NUCLEIC ACIDS AND NUCLEOTIDES, 487

Nucleic acids, 487

Nomenclature and hydrolysis products, 488

Cellular location of DNA, 490

Cellular location of RNA, 492

Structure, 492

Digestion of dietary nucleic acids, 496

Biosynthesis of purine and pyrimidine nucleotides, 497

Folic acid functions, 497

Purine nucleotide synthesis, 501

Pyrimidine nucleotide synthesis, 504

Purine and pyrimidine analogues, 506

Deoxyribonucleotide synthesis, 507

Thymidylate synthesis, 508

Biosynthesis of nucleotide-containing coenzymes, 509

Catabolism of nucleotides, 511

Purines, 511

Pyrimidines, 512

Clinical examples, 513

Case 1: Gout, 513

Case 2: Tropical sprue, 518

Case 3: Defect in synthesis of B<sub>12</sub> coenzymes, 521

Case 4: Orotic aciduria, 523

Case 5: Excessive purine synthesis in gout, 524

Case 6: Lesch-Nyhan syndrome, 524

Case 7: Adenosine deaminase deficiency, 525

Case 8: Chemotherapy in treatment of breast cancer, 526

Case 9: Methotrexate treatment of adenocarcinoma, 526

Case 10: Folate deficiency in alcoholism, 527

Case 11: Purine nucleoside phosphorylase deficiency, 527

Case 12: Adenine phosphoribosyltransferase deficiency, 528

### 12 NUCLEIC ACID AND PROTEIN BIOSYNTHESIS. 530

Functional roles of DNA, 530

Genetic material, 530

The "central dogma," 531

DNA synthesis, 532

Molecular basis of mutation, 537

Sequence analysis of DNA, 540

RNA synthesis: expression of the genetic material, 542

Operons and control of RNA synthesis, 545

Transfer and ribosomal RNA synthesis, 546

Protein biosynthesis, 549

Aminoacyl-tRNA synthetases, 550

Ribosome: site of protein synthesis, 551

#### xviii Contents

Polyribosome, 552

Initiation of protein synthesis, 552

Messenger RNA binding to ribosomes, 554

Protein chain elongation, 555

Termination of protein synthesis, 556

Posttranslational processing of secretory proteins, 556

Antibiotics and protein synthesis, 556

Genetic code, 557

Synthesis of specific proteins, 559

Immunoglobulins, 559

Virus replication, 560

Genetic analysis of human disease, 561

Cytogenetic diseases, 562

Clinical examples, 563

Case 1: Acute leukemia, 563

Case 2:  $\beta$ -Thalassemia, 566

Case 3: Xeroderma pigmentosum, 568

Case 4: Systemic lupus erythematosus, 569

Case 5: Duchenne type muscular dystrophy, 570

Case 6: Diphtheria, 571

Case 7: Tetracycline-induced hypoplasia of the teeth, 572

Case 8: Transmission of herpes simplex virus, 572

Case 9: Blastic chronic myelogenous leukemia, 572

#### 13 HORMONAL REGULATION OF METABOLISM, 574

Nature of hormones, 574

Definition of a hormone, 574

Endocrine glands, 575

Neurotransmitters, 575

Regulation of hormone secretion, 576

Target tissue, 577

Prohormone, 577

Mechanisms of hormone action, 578

Adenylate cyclase mechanism, 578

Guanylate cyclase and cGMP, 581

Induction of protein synthesis, 582

Hypothalamic regulatory hormones, 583

Chemistry, 585

Adenohypophyseal hormones, 586

Neurohypophyseal hormones, 588

Thyroid hormones, 589

Parathyroid hormone, calcitonin, and vitamin D, 591

Pancreatic hormones, 594

Adrenal hormones, 597

"Corticosteroid hormones, 599

Sex hormones, 601

Enteric hormones, 603

Hormone-related secretions, 604

Clinical examples, 614

Case 1: Hyperparathyroidism, 614

Case 2: Insulinoma, 615

Case 3: Hyperthyroidism, 616

Case 4: Cushing's syndrome, 617

Case 5: Psoriasis, 619

Case 6: Bronchial asthma, 620

Case 7: Zollinger-Ellison syndrome, 620

Case 8: Pituitary insufficiency, 621

Case 9: Follicle-stimulating hormone deficiency, 621

Case 10: Phosphate depletion syndrome, 622

Case 11: Leprechaunism, 622

Case 12: Thyroid storm, 622

#### 14 COMPREHENSIVE CASE ANALYSIS, 624

Blood coagulation: an integrated enzymatic cascade mechanism, 624

Case 1: Thrombophlebitis, anticoagulants, and hemorrhage, 625

Integration of metabolic pathways, 630

Case 2: Acute starvation—gluconeogenesis, lipid mobilization, ketosis, and acidosis, 630

Pancreatitis: a multienzyme, multisystem disease, 634

Case 3: Acute pancreatitis, 634

Osteogenesis imperfecta: a connective tissue disease, 639

Case 4: Osteogenesis imperfecta, 639 Central nervous system diseases, 643

Case 5: Refsum's disease, 644

Cystinosis: an error in an amino acid transport system, 645

Case 6: Cystinuria and cystine stones, 646

Chronic alcoholism: a metabolic disease, 649

Case 7: Cirrhosis, 649

Hemochromatosis: a disease of iron metabolism, 654

Case 8: Hemochromatosis, 654

Clinical examples for further analysis, 658

Case 9: Pheochromocytoma, 658

Case 10: Primary aldosteronism, 659

Case 11: Acromegaly, 659

Case 12: Obesity, 659

Case 13: Anorexia nervosa, 660

Case 14: Vitamin D-resistant rickets, 660

Case 15: Multiple myeloma, 661

Case 16: Diabetic ketoacidosis, 662

Case 17: Protein-losing gastroenteropathy, 663

Case 18: Wilson's disease, 663

Case 19: Primary biliary cirrhosis, 664

Case 20: Renal tubular acidosis, 664

#### Abbreviations, 665

#### Appendixes

- A Recommended daily dietary allowances designed for maintenance of goo nutrition of practically all healthy people in the United States, 670
- **B** International classification of enzymes, 672
- C Four-place logarithms, 674
- D Laboratory values, 676
- E Clinical biochemistry standardization, the Système Internationale, 678