



# Principles of Biochemistry

ALBERT L. LEHNINGER

THE JOHNS HOPKINS UNIVERSITY

SCHOOL OF MEDICINE

WORTH PUBLISHERS, INC.

**Principles of Biochemistry**

Copyright © 1982 by Worth Publishers, Inc.

All rights reserved

Printed in the United States of America

Library of Congress Catalog Card No. 82-70015

ISBN: 0-87901-136-X

Third Printing, December 1984

Editors: Sally Anderson, June Fox

Production: Kenneth Ekkens

Illustrator: Shirley Baty

Picture Editor: Anne Feldman

Design: Malcolm Gear Designers

Typographer: Progressive Typographers, Inc.

Printing and Binding: Rand McNally and Company

Cover: Computer graphics representation of  
bovine trypsin inhibitor--trypsin complex  
(inhibitor surface in red, trypsin surface  
in green), courtesy of Robert Langridge

**Worth Publishers, Inc.**

444 Park Avenue South

New York, New York 10016

## Preface

*Principles of Biochemistry* is intended primarily for students taking their first course in biochemistry. It is a new book, not simply an updating of my earlier books, *Biochemistry* (1970, 1975) and *Short Course in Biochemistry* (1973). In setting out to prepare new editions of those books, I grew increasingly uneasy about my objectives. The first edition of *Biochemistry*, published in 1970, was primarily for an undergraduate audience, for those taking their first, perhaps their only, course in biochemistry. The second edition in 1975 grew by more than 20 percent. A third edition, with a proportional effort to include new biochemical advances, would become a volume of 1,500 pages. Such a book could of course play an important role in biochemical education, but it would not properly serve the undergraduate audience for whom I had written *Biochemistry* in the first place. *Principles of Biochemistry* is, then, a return to my original objective; it is, in a manner of speaking, the 1982 rebirth of the first edition of *Biochemistry*.

Size was not the only consideration. The time has come when a single biochemistry textbook cannot be all things to all students. A comprehensive book that describes the full panoply of today's biochemistry at a level that would satisfy the needs of graduate students would surely be found intimidating by most undergraduates in their first encounter with the field. Textbooks have a tendency, moreover, to acquire more complex structure and become more densely written in successive editions, with the result that they often lose the very clarity of exposition and organization that made their first editions successful. A fresh start seemed called for.

I once felt that biochemistry should be primarily a graduate subject, to be approached only after a thorough grounding in chemistry and biology. Today I have quite a different view. Biochemistry should be taught much earlier, since it has become the *lingua franca* of the life sciences and greatly illuminates subsequent study in any area of biology. And not only biology: An early course in biochemistry for students of chemistry or

physics provides challenging glimpses of how living organisms solve some of the most fundamental chemical and physical problems.

Considered more broadly, an undergraduate course in biochemistry also has a place in educating young people for a future in which there will be ever-greater concern for the health and well-being of mankind. The extraordinary advances in biochemical genetics and genetic engineering, together with their social implications, are already matters of wide public interest. The growing world population, with its increasing demands for food, raw materials, and energy, can even now be seen to impinge on the delicate ecological balances within the biosphere. Increasingly, society must make important decisions involving conflicts between biological principles and political, industrial, or ethical concerns. It can therefore be argued that a knowledge of biochemistry is useful for all well-informed citizens, whatever their calling—quite apart from the special intellectual excitement it offers to those who wish to explore and understand the molecular interactions that take place in living organisms.

*Principles of Biochemistry* is made up of four parts: biomolecules, bioenergetics and metabolism, aspects of human biochemistry, and the fundamentals of molecular genetics; it is written in the same style and language I used in *Biochemistry*. Throughout the book I have tried to emphasize the framework and the molecular logic of biochemistry rather than encyclopedic detail, always with full explanations and descriptions of fundamental processes.

The book opens with chapters on cell structure and on some rudiments of organic chemistry relevant to biomolecules; thus it can be useful to those with a minimal background in biology and organic chemistry. After considering the properties of water, the structure and biological functions of proteins are described in depth. Hemoglobin is examined in detail to show how amino acid sequence and primary structure determine conformation, and how conformation can influence cell structure and function. Enzymes and the regulation of enzyme activity are then treated in depth, with repeated emphasis on conformation illustrated by a “gallery” of enzyme structures. Chapters on vitamins and coenzymes, on carbohydrates, and on lipids and membranes complete Part I.

Part II deals with bioenergetics and cell metabolism—the “meat and potatoes” of biochemistry. A thorough grounding in cell bioenergetics is followed by detailed discussions of glycolysis, the citric acid cycle, electron transport, and oxidative phosphorylation. Chapters on the catabolism of fatty acids and amino acids follow, succeeded by chapters on biosynthetic pathways and photosynthesis. Regulation of metabolic pathways is discussed in detail.

Part III is devoted to human biochemistry. It includes chapters on organ relationships in metabolism, endocrine regulation, and human nutrition. To me, nutrition is not simply a



matter of knowing that a given vitamin serves as part of a given coenzyme. The science of nutrition is one of biochemistry's greatest contributions to human welfare, and I believe it deserves a more holistic treatment than it usually receives.

In Part IV I have provided an especially full treatment of the "cutting edges" of molecular genetics; these chapters take into account the rapid pace of new developments (through 1981), including the techniques of DNA cloning.

Throughout the book there are many interest-provoking items of related information, some historical in nature, many dealing with medicine and human health, still others touching on zoology and animal physiology, agriculture and food, environmental issues, and world nutritional problems. Occasionally, there are brief sections covering more difficult, quantitative, or interesting but optional information. This material may not be covered in all courses, so it is boxed for easy identification. Examples include the derivation of the Henderson-Hasselbalch equation, the RS system, how to tell a person's age through amino acid chemistry, and the sequencing of DNA.

There are almost 850 illustrations, tables, charts, and photographs in the book. Each chapter has a summary as well as a useful list of readings and references. There is a comprehensive glossary of over 400 biochemical terms at the end of the book.

Particularly noteworthy are the problems at the end of each chapter, over 350 altogether, most of them written by Paul van Eikeren of Harvey Mudd College. The problems are not merely numerical; they focus on biochemical reasoning and require thoughtful analysis. All of them, together with their answers in an appendix, have been thoroughly reviewed by experienced teachers of undergraduate biochemistry.

In presenting this new book, I again welcome suggestions and criticisms from teachers and students alike.

## Acknowledgments

I am very grateful to those who have helped me prepare this book. First, I must thank Paul van Eikeren for writing most of the problems in the book and the answers in the appendix. Carl Shonk of Central Michigan State University went over each problem and its solution with a fine-toothed comb and made many valuable suggestions to enhance their didactic value. I want also to thank Barbara Sollner-Webb of Johns Hopkins School of Medicine for providing the problems for the chapters on genetic biochemistry.

The entire text, both in drafts and final version, was reviewed in detail by Edward Harris of Texas A & M University, James Hageman of New Mexico State University, and Carl Shonk. Specific sections of the manuscript were also closely scrutinized by Norman Sansing, University of Georgia; James Bamberg, Colorado State University; Michael Dahmus, University of California, Davis; and Paul Englund and Barbara Sollner-Webb of the Johns Hopkins School of Medicine. Keith

Roberts of the John Innes Institute provided useful suggestions for illustrations in the early chapters. Geoffrey Martin carefully checked the accuracy of all the equations and structural formulas in the book, and Linda Hansford proofread the entire book and prepared the index. I must, however, take sole responsibility for errors of fact or emphasis.

I am especially grateful to Peggy Jane Ford, who not only typed the manuscript, several times over, but also marshaled my time and attention to the competing demands of teaching, research, administration, and book writing. I also wish to thank June Fox and particularly Sally Anderson of Worth Publishers, who edited and guided the book through production. Indeed, I wish to thank the entire staff of Worth Publishers for their understanding, encouragement, and practical help. An author could not ask for better cooperation in seeing his brainchild into print.

Finally, I must acknowledge with deep appreciation the indispensable aid and encouragement of my wife, who not only tolerated the occupational agonies that beset the long-distance writer, but also served as my keenest critic of style and language.

ALBERT L. LEHNINGER

Sparks, Maryland  
January 1982

# Contents in Brief

## PART I

### Biomolecules 1

1. Biochemistry: The Molecular Logic of Living Organisms 3
2. Cells 15
3. The Composition of Living Matter: Biomolecules 45
4. Water 67
5. Amino Acids and Peptides 95
6. Proteins: Covalent Structure and Biological Function 121
7. Fibrous Proteins 147
8. Globular Proteins: The Structure and Function of Hemoglobin 169
9. Enzymes 207
10. Vitamins and Trace Elements in the Function of Enzymes 249
11. Carbohydrates: Structure and Biological Function 277
12. Lipids and Membranes 303

## PART II

### Bioenergetics and Metabolism 331

13. A Survey of Metabolism 333
14. The ATP Cycle and Cell Bioenergetics 361
15. Glycolysis: A Central Pathway of Glucose Catabolism 397
16. The Citric Acid Cycle 435
17. Electron Transport, Oxidative Phosphorylation, and Regulation of ATP Production 467
18. The Oxidation of Fatty Acids in Animal Tissues 511
19. Oxidative Degradation of Amino Acids: The Urea Cycle 531

20. Biosynthesis of Carbohydrates in Animal Tissues 561

21. The Biosynthesis of Lipids 583

22. Biosynthesis of Amino Acids and Nucleotides 615

23. Photosynthesis 645

## PART III

### Some Aspects of Human Biochemistry 681

24. Digestion, Transport, and the Integration of Metabolism 683

25. Hormones 721

26. Human Nutrition 753

## PART IV

### Molecular Transmission of Genetic Information 791

27. DNA: The Structure of Chromosomes and Genes 793

28. Replication and Transcription of DNA 837

29. Protein Synthesis and Its Regulation 871

30. More about Genes: Repair, Mutation, Recombination, and Cloning 913

### APPENDIX A: Common Abbreviations in Biochemical Research Literature 946

### APPENDIX B: Unit Abbreviations, Prefixes, Constants, and Conversion Factors 948

### APPENDIX C: International Atomic Weights 949

### APPENDIX D: Logarithms 950

### APPENDIX E: Answers to Problems 952

### APPENDIX F: Glossary 969

### Illustration Acknowledgments 981

### Index 983



# Contents

## PART I

### Biomolecules 1

#### CHAPTER 1

##### Biochemistry: The Molecular Logic of Living Organisms 3

Living Matter Has Several Identifying Characteristics 3

Biochemistry Seeks to Understand the Living State 5

All Living Organisms Contain Organic Macromolecules Built According to a Common Plan 5

Living Organisms Exchange Energy and Matter 7

Enzymes, the Catalysts of Living Cells, Promote Sequences of Organized Chemical Reactions 8

Cells Transmit Energy in a Chemical Form 9

Cell Metabolism Is Constantly Regulated 10

Living Organisms Replicate Themselves Accurately 10

#### CHAPTER 2

##### Cells 15

All Cells Share Some Structural Features 15

Cells Must Have Very Small Dimensions 16

There Are Two Great Classes of Cells: Prokaryotes and Eukaryotes 17

The Prokaryotes Are the Simplest and Smallest Cells 18

*Escherichia coli* Is the Best-Known Prokaryotic Cell 20

Eukaryotic Cells Are Larger and More Complex than Prokaryotes 22

The Nucleus of Eukaryotes Is a Very Complex Structure 24

Mitochondria Are the Power Plants of Eukaryotic Cells 25

The Endoplasmic Reticulum Forms Channels through the Cytoplasm 27

Golgi Bodies Are Secretory Organelles 28

Lysosomes Are Packets of Hydrolyzing Enzymes 28

Peroxisomes Are Peroxide-Destroying Vesicles 29

Microfilaments Function in Contractile Processes of Cells 29

Microtubules Also Function in Cell Movements 30

Microfilaments, Microtubules, and the Microtrabecular Network Constitute the Cytoskeleton 30

Cilia and Flagella Give Cells Propulsive Power 31

The Cytoplasm Also Contains Granular Bodies 32

The Cytosol Is the Continuous Aqueous Phase of the Cytoplasm 33

The Cell Membrane Presents a Large Surface Area 33

The Surface of Many Animal Cells Also Contains "Antennae" 34

Eukaryotic Plant Cells Have Some Special Features 35

Viruses Are Supramolecular Parasites 37

Summary 39

References 40

Problems 41

#### CHAPTER 3

##### The Composition of Living Matter: Biomolecules 45

The Chemical Composition of Living Matter Differs from That of the Earth's Crust 45

Most Biomolecules Are Compounds of Carbon 46

Organic Biomolecules Have Specific Shapes and Dimensions	47
Functional Groups of Organic Biomolecules Determine Their Chemical Properties	50
Many Biomolecules Are Asymmetric	51
The Major Classes of Biomolecules in Cells Are Very Large Molecules	53
Macromolecules Are Constructed from Small Building-Block Molecules	55
The Building-Block Molecules Have Simple Structures	55
There Is a Hierarchy in Cell Structure	58
Biomolecules First Arose by Chemical Evolution	59
Chemical Evolution Can Be Simulated	61
Summary	62
References	63
Problems	64

## CHAPTER 4

### Water 67

The Unusual Physical Properties of Water Are Due to Hydrogen Bonding	67
Hydrogen Bonds Are Common in Biological Systems	69
Water Has Unusual Solvent Properties	70
Solutes Change the Properties of Water	71
The Equilibrium Point of Reversible Reactions Is Expressed by an Equilibrium Constant	73
The Ionization of Water Is Expressed by an Equilibrium Constant	74
The pH Scale Designates the $H^+$ and $OH^-$ Concentrations	76
Box 4-1 The ion product of water	77
Acids and Bases Reflect the Properties of Water	78
Weak Acids Have Characteristic Titration Curves	79
Buffers Are Mixtures of Weak Acids and Their Conjugate Bases	81
Phosphate and Bicarbonate Are Important Biological Buffers	83
Box 4-2 The Henderson-Hasselbalch equation	84
Box 4-3 How the bicarbonate buffer system of blood works	86
The Fitness of the Aqueous Environment for Living Organisms	87
Acid Rain Is Polluting Our Lakes and Streams	88
Summary	89
References	90
Problems	90

## CHAPTER 5

### Amino Acids and Peptides 95

Amino Acids Have Common Structural Features	95
Nearly All Amino Acids Have an Asymmetric Carbon Atom	96
Stereoisomers Are Named on the Basis of Their Absolute Configuration	97
The Optically Active Amino Acids of Proteins Are L Stereoisomers	98
Box 5-1 The RS system of designating optical isomers	99
Box 5-2 How to tell a person's age through amino acid chemistry	100
Amino Acids Can Be Classified on the Basis of Their R Groups	100
Eight Amino Acids Have Nonpolar R Groups	102
Seven Amino Acids Have Uncharged Polar R Groups	102
Two Amino Acids Have Negatively Charged (Acidic) R Groups	102
Three Amino Acids Have Positively Charged (Basic) R Groups	103
Some Proteins Also Contain "Special" Amino Acids	103
Amino Acids Are Ionized in Water Solutions	103
Amino Acids Can Act as Acids and as Bases	104
Amino Acids Have Characteristic Titration Curves	104
The Titration Curve Predicts the Electric Charge of Amino Acids	106
Amino Acids Differ in Their Acid-Base Properties	107
Their Acid-Base Properties Are the Basis for the Analysis of Amino Acids	108
Paper Electrophoresis Separates Amino Acids According to Electric Charge	108
Ion-Exchange Chromatography Is a More Useful Separation Process	109
Amino Acids Have Characteristic Chemical Reactions	110
Peptides Are Chains of Amino Acids	111
Peptides Can Be Separated on the Basis of Their Ionization Behavior	112
Peptides Have Characteristic Chemical Reactions	113
Some Peptides Have Intense Biological Activity	114
Summary	115
References	115
Problems	116

**CHAPTER 6****Proteins: Covalent Structure and Biological Function 121**

Box 6-1 How many amino acid sequences are possible? 122

Proteins Have Many Different Biological Functions 122

Proteins Can Also Be Classified According to Shape 124

Proteins Yield Their Amino Acids on Hydrolysis 124

Some Proteins Contain Chemical Groups Other Than Amino Acids 125

Proteins Are Very Large Molecules 126

Proteins Can Be Separated and Purified 127

The Amino Acid Sequence of Polypeptide Chains Can Be Determined 129

Insulin Was the First Protein to Be Sequenced 134

Many Other Proteins Have Been Sequenced Since 135

Homologous Proteins from Different Species Have Homologous Sequences 137

The Immune Response Can Detect Differences between Homologous Proteins 138

Proteins Undergo a Structural Change Called Denaturation 140

Summary 141

References 142

Problems 142

**CHAPTER 7****Fibrous Proteins 147**

Configuration and Conformation Have Different Meanings 147

Paradoxically, Native Proteins Appear to Have Only One or a Few Conformations 148

$\alpha$ -Keratins Are Fibrous Proteins Made by Epidermal Cells 149

X-Ray Analysis of Keratins Shows That They Have Repeating Structural Units 150

X-Ray Studies of Peptides Show the Peptide Bond to Be Rigid and Planar 150

In  $\alpha$ -Keratin the Polypeptide Chains Form an  $\alpha$  Helix 151

Some Amino Acids Are Not Compatible with the  $\alpha$  Helix 152

The  $\alpha$ -Keratins Are Rich in Amino Acids Compatible with  $\alpha$ -Helical Structures 153

In Native  $\alpha$ -Keratins  $\alpha$ -Helical Polypeptide Chains Are Supercoiled into Ropes 154

The Insolubility of  $\alpha$ -Keratins Is a Reflection of Their Nonpolar R Groups 154

$\beta$ -Keratins Contain a Different Conformation of Their Polypeptide Chain:  $\beta$  Structure 155

Permanent Waving Is Biochemical Engineering 156

Collagen and Elastin Are the Major Fibrous Proteins of Connective Tissues 157

Collagen Is the Most Abundant Protein in the Body 157

Collagen Has Both Familiar and Unusual Properties 158

The Polypeptides in Collagen Are Three-Stranded Helical Structures 159

The Structure of Elastin Confers Distinctive Properties on Elastic Tissue 160

What Fibrous Proteins Tell Us About Protein Structure 162

Other Types of Fibrillar or Filamentous Proteins Occur in Cells 162

Summary 163

References 164

Problems 165

**CHAPTER 8****Globular Proteins: The Structure and Function of Hemoglobin 169**

The Polypeptide Chain(s) of Globular Proteins Are Tightly Folded 169

X-Ray Analysis of Myoglobin Was the Breakthrough 170

Myoglobins from Different Species Have Similar Conformations 173

The Tertiary Structure of Each Type of Globular Protein Is Distinctive 173

Amino Acid Sequence Determines Tertiary Structure 177

Four Different Forces Stabilize the Tertiary Structure of Globular Proteins 178

The Rate of Folding of Polypeptide Chains Is Critical 179

Oligomeric Proteins Have Both Tertiary and Quaternary Structure 180

X-Ray Analysis Has Revealed the Complete Structure of Hemoglobin 181

Myoglobin and the  $\alpha$  and  $\beta$  Chains of Hemoglobin Have Nearly the Same Tertiary Structure 183

Quaternary Structures of Other Oligomeric Proteins Have Been Determined 184

Red Blood Cells Are Specialized to Carry Oxygen 185

Myoglobin and Hemoglobin Differ in Their Oxygen-Binding Curves	186
The Cooperative Binding of Oxygen Enhances the Efficiency of Hemoglobin as an Oxygen Carrier	187
Hemoglobin Also Transports $H^+$ and $CO_2$	188
Oxygenation of Hemoglobin Causes a Change in Its Three-Dimensional Conformation	190
Box 8-1 Diphosphoglycerate and the oxygen affinity of hemoglobin	192
Sickle-Cell Anemia Is a Molecular Disease of Hemoglobin	194
Sickle-Cell Hemoglobin Has an Altered Amino Acid Sequence	196
Sickling Is Caused by the Tendency of Hemoglobin S Molecules to Stick Together	198
Proteins Containing "Wrong" Amino Acids Are the Result of Gene Mutations	198
Can a Molecular Cure for Sickle Hemoglobin Be Found?	199
Summary	200
References	201
Problems	202

## CHAPTER 9

### Enzymes 207

Much of the History of Biochemistry Is the History of Enzyme Research	208
Enzymes Show All the Properties of Proteins	209
Enzymes Are Classified on the Basis of the Reactions They Catalyze	210
Enzymes Enhance the Rate of Chemical Reactions by Lowering Their Activation Energy	211
The Substrate Concentration Has a Profound Effect on the Rate of Enzyme-Catalyzed Reactions	212
There Is a Quantitative Relationship between the Substrate Concentration and the Rate of an Enzymatic Reaction	213
Box 9-1 The Michaelis-Menten equation	214
Each Enzyme Has a Characteristic $K_M$ for a Given Substrate	216
Box 9-2 Transformations of the Michaelis-Menten equation: The double-reciprocal plot	217
Many Enzymes Catalyze Reactions in Which There Are Two Substrates	217
Enzymes Have an Optimum pH	218
Enzymes Can Be Assayed Quantitatively	218
Enzymes Show Specificity toward Their Substrates	220
Enzymes Can Be Inhibited by Specific Chemical Agents	221

There Are Two Kinds of Reversible Inhibitors: Competitive and Noncompetitive	223
Noncompetitive Inhibition Is Also Reversible but Not by the Substrate	224
Box 9-3 Kinetic tests for distinguishing between competitive and noncompetitive inhibition	225
Several Factors Contribute to the Catalytic Efficiency of Enzymes	225
X-Ray Analysis Has Revealed Important Structural Features of Enzymes	226
Box 9-4 A gallery of enzyme structures revealed by x-ray diffraction analysis	228
Enzyme Systems Have a Pacemaker or Regulatory Enzyme	233
Allosteric Enzymes Are Regulated by Noncovalent Binding of Modulator Molecules	233
Allosteric Enzymes May Be Inhibited or Stimulated by Their Modulators	235
Allosteric Enzymes Deviate from Michaelis-Menten Behavior	235
Allosteric Enzymes Show Communication between Subunits	237
Some Enzymes Are Regulated by Reversible Covalent Modification	237
Box 9-5 The three-dimensional structure of the regulatory enzyme aspartate transcarbamoylase	238
Many Enzymes Occur in Multiple Forms	239
Enzymes May Be Catalytically Defective Due to Genetic Mutation	241
Summary	242
References	243
Problems	244

## CHAPTER 10

### Vitamins and Trace Elements in the Function of Enzymes 249

Vitamins Are Essential Organic Micronutrients	250
Vitamins Are Essential Components of Coenzymes and Enzyme Prosthetic Groups	250
Vitamins Can Be Grouped into Two Classes	251
Thiamine (Vitamin $B_1$ ) Functions in the Form of Thiamine Pyrophosphate	252
Riboflavin (Vitamin $B_2$ ) Is a Component of the Flavin Nucleotides	254
Nicotinamide Is the Active Group of the Coenzymes NAD and NADP	255
Pantothenic Acid Is a Component of Coenzyme A	256
Pyridoxine (Vitamin $B_6$ ) Is Important in Amino Acid Metabolism	258

Biotin Is the Active Component of Biocytin, the Prosthetic Group of Some Carboxylating Enzymes	259
Folic Acid Is the Precursor of the Coenzyme Tetrahydrofolic Acid	260
Vitamin B <sub>12</sub> Is the Precursor of Coenzyme B <sub>12</sub>	262
The Biochemical Function of Vitamin C (Ascorbic Acid) Is Not Known	264
The Fat-Soluble Vitamins Are Derivatives of Isoprene	264
Vitamin A Probably Has Several Functions	265
Vitamin D Is the Precursor of a Hormone	267
Vitamin E Protects Cell Membranes against Oxygen	268
Vitamin K Is a Component of a Carboxylating Enzyme	269
Many Inorganic Elements Are Required in Animal Nutrition	269
There Are Many Iron-Requiring Enzymes	270
Copper Also Functions in Some Oxidative Enzymes	271
Zinc Is Essential in the Action of Many Enzymes	271
Manganese Ions Are Required by Several Enzymes	271
Cobalt Is Part of Vitamin B <sub>12</sub>	272
Selenium Is Both an Essential Trace Element and a Poison	272
Other Trace Elements Are Known to Be Required by Some Enzymes	272
Summary	273
References	274
Problems	274

## CHAPTER 11

### Carbohydrates: Structure and Biological Function 277

There Are Three Classes of Carbohydrates, Based on the Number of Sugar Units	277
There Are Two Families of Monosaccharides: Aldoses and Ketoses	278
The Common Monosaccharides Have Several Asymmetric Centers	279
The Common Monosaccharides Occur in Ring Forms	281
Simple Monosaccharides Are Reducing Agents	284
Disaccharides Contain Two Monosaccharide Units	284
Polysaccharides Contain Many Monosaccharide Units	287

Some Polysaccharides Serve as a Storage Form of Cell Fuel	287
Cellulose Is the Most Abundant Structural Polysaccharide	289
Cell Walls Are Rich in Structural and Protective Polysaccharides	292
Glycoproteins Are Hybrid Molecules	294
Animal Cell Surfaces Contain Glycoproteins	295
Acid Mucopolysaccharides and Proteoglycans Are Important Components of Connective Tissue	296
Summary	297
References	298
Problems	299

## CHAPTER 12

### Lipids and Membranes 303

Fatty Acids Are Building-Block Components of Most Lipids	303
Triacylglycerols Are Fatty Acid Esters of Glycerol	306
Triacylglycerols Are Storage Lipids	308
Waxes Are Fatty Acid Esters of Long-Chain Alcohols	309
Phospholipids Are Major Components of Membrane Lipids	310
Sphingolipids Are Also Important Components of Membranes	312
Steroids Are Nonsaponifiable Lipids with Specialized Functions	315
Lipoproteins Blend the Properties of Lipids and Proteins	315
Polar Lipids Form Micelles, Monolayers, and Bilayers	317
The Major Components of Membranes Are Polar Lipids and Proteins	318
Box 12-1 Electron microscopy of membranes	320
Membranes Have a Fluid-Mosaic Structure	321
Membranes Have a Specific Sidedness or Asymmetry	322
Red-Blood-Cell Membranes Have Been Studied in Detail	322
Lectins Are Specific Proteins Capable of Binding to or Agglutinating Certain Cells	324
Membranes Have Very Complex Functions	325
Summary	326
References	327
Problems	328



## PART II

### Bioenergetics and Metabolism 331

#### CHAPTER 13

##### A Survey of Metabolism 333

Living Organisms Participate in the Cycling of Carbon and Oxygen 333

Nitrogen Is Cycled in the Biosphere 335

Metabolic Pathways Are Promoted by Sequential Enzyme Systems 337

Metabolism Consists of Catabolic (Degradative) Pathways and Anabolic (Biosynthetic) Pathways 337

Catabolic Pathways Converge to a Few End Products 338

Biosynthetic (Anabolic) Pathways Diverge to Yield Many Products 340

There Are Important Differences between Corresponding Catabolic and Anabolic Pathways 341

ATP Carries Energy from Catabolic to Anabolic Reactions 343

NADPH Carries Energy in the Form of Reducing Power 344

Cell Metabolism Is an Economical, Tightly Regulated Process 345

Metabolic Pathways Are Regulated at Three Levels 346

Secondary Metabolism 347

There Are Three Main Approaches to Identification of a Metabolic Sequence 348

Mutants of Organisms Allow Identification of Intermediate Steps in Metabolism 349

Isotopic Tracers Provide a Powerful Method of Studying Metabolism 351

Metabolic Pathways Are Compartmented in Cells 352

Summary 356

References 356

Problems 357

#### CHAPTER 14

##### The ATP Cycle and Cell Bioenergetics 361

The First and Second Laws of Thermodynamics 361

Box 14-1 The concept of entropy 364

Cells Require Free Energy 366

The Standard-Free-Energy Change of a Chemical Reaction Can Be Calculated 366

$\Delta G^\circ$  Has Characteristic Values for Different Chemical Reactions 368

There Is an Important Difference between  $\Delta G^\circ$  and  $\Delta G$  369

Standard-Free-Energy Values of Chemical Reactions Are Additive 370

ATP Is the Major Chemical Link between Energy-Yielding and Energy-Requiring Cell Activities 371

The Chemistry of ATP Is Well Known 373

ATP Has a Characteristic Standard Free Energy of Hydrolysis 374

Why Does ATP Have a Relatively High Standard Free Energy of Hydrolysis? 374

ATP Acts as a Common Intermediate in Phosphate-Transfer Reactions 376

Box 14-2 The free energy of hydrolysis of ATP in intact cells 377

Two Super High-Energy Phosphate Compounds Are Generated by Breakdown of Glucose to Lactate 378

Transfer of a Phosphate Group from ATP to an Acceptor Molecule Can Energize It 379

ATP Is Used to Energize Muscle Contraction 380

Phosphocreatine Is a Temporary Storage Form of High-Energy Phosphate Groups in Muscles 383

ATP Also Energizes Active Transport across Membranes 384

ATP Can Also Be Broken Down to AMP and Pyrophosphate 386

Box 14-3 ATP provides the energy for firefly bioluminescence 388

There Are Other Energy-Rich Nucleoside 5'-Triphosphates besides ATP 389

The ATP System Functions in a Dynamic Steady State 391

Summary 392

References 393

Problems 394

#### CHAPTER 15

##### Glycolysis: A Central Pathway of Glucose Catabolism 397

Glycolysis Is a Central Pathway in Most Organisms 397

ATP Formation Is Coupled to Glycolysis 399

Much Free Energy Remains in the Products of Glycolysis 400

Glycolysis Has Two Phases 400

Box 15-1 Anaerobic glycolysis, oxygen debt, alligators, and coelacanths 401

Glycolysis Takes Place via Phosphorylated Intermediates 403



The First Phase of Glycolysis Results in Cleavage of the Hexose Chain 403

The Second Phase of Glycolysis Is Energy-Conserving 408

"Feeder" Pathways Lead from Glycogen and Other Carbohydrates into the Central Glycolytic Pathway 414

Other Monosaccharides Can Enter the Glycolytic Sequence 417

Disaccharides Must First Be Hydrolyzed to Monosaccharides 419

The Entry of Glucose Residues into the Glycolytic Sequence Is Regulated 420

Hormones Ultimately Regulate the Interconversion of Phosphorylase *a* and *b* 422

The Glycolytic Sequence Itself Is Regulated at Two Major Points 423

How Are the Regulated Steps of Glycolysis Identified in Intact Cells? 425

Alcoholic Fermentation Differs from Glycolysis Only in Its Terminal Steps 426

Box 15-2 Brewing beer 428

Summary 428

References 429

Problems 430

## CHAPTER 16

The Citric Acid Cycle 435

Oxidation of Glucose to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  Releases Much More Energy than Glycolysis 437

Pyruvate Must First Be Oxidized to Acetyl-CoA and  $\text{CO}_2$  437

The Citric Acid Cycle Is a Circular Rather than a Linear Enzyme System 441

How Did the Idea of the Citric Acid Cycle Arise? 441

The Citric Acid Cycle Has Eight Steps 444

Summary of the Cycle 448

Why a Citric Acid Cycle? 448

Isotopic Tests of the Citric Acid Cycle 449

The Conversion of Pyruvate to Acetyl-CoA Is Regulated 449

Box 16-1 Is citric acid the first tricarboxylic acid formed in the cycle? 450

The Citric Acid Cycle Is Regulated 452

Citric Acid Cycle Intermediates Are Used for Other Metabolic Purposes and Can Be Replenished 453

The Glyoxylate Cycle Is a Modification of the Citric Acid Cycle 455

There Are Secondary Pathways of Glucose Catabolism: The Pentose Phosphate Pathway 456

The Secondary Pathway from Glucose to Glucuronic Acid and Ascorbic Acid 457

Summary 459

References 460

Problems 461

## CHAPTER 17

Electron Transport, Oxidative Phosphorylation, and Regulation of ATP Production 467

Electron Flow from Substrates to Oxygen Is the Source of ATP Energy 467

Electron Transport and Oxidative Phosphorylation Take Place in the Inner Mitochondrial Membrane 469

Electron-Transferring Reactions Are Oxidation-Reduction Reactions 470

Each Conjugate Redox Couple Has a Characteristic Standard Potential 472

Free-Energy Changes Accompany Electron Transfers 474

There Are Many Electron Carriers in the Electron-Transport Chain 476

The Pyridine Nucleotides Have a Collecting Function 476

NADH Dehydrogenase Accepts Electrons from NADH 478

Ubiquinone Is a Lipid-Soluble Quinone 479

The Cytochromes Are Electron-Carrying Heme Proteins 480

Incomplete Reduction of Oxygen Causes Cell Injury 481

The Electron Carriers Always Function in a Specific Sequence 482

Electron-Transport Energy Is Conserved by Oxidative Phosphorylation 484

The ATP-Synthesizing Enzyme Has Been Isolated and Reconstituted 484

How Is the Redox Energy of Electron Transport Delivered to ATP Synthetase? 487

The Chemiosmotic Hypothesis Postulates That a Proton Gradient Carries Energy from Electron Transport to ATP Synthesis 489

Electron-Transport Energy Is Useful for Other Purposes 491

Box 17-1 Many questions on the mechanism of oxidative phosphorylation remain to be answered 492

Bacteria and Chloroplasts Also Contain  $\text{H}^+$ -Transporting Electron-Transport Chains 493

The Inner Mitochondrial Membrane Contains Specific Transport Systems 495

Shuttle Systems Are Required for Oxidation of Extramitochondrial NADH 496

The Complete Oxidation of Glucose Leads to Synthesis of 38 ATPs 497

ATP Formation by Oxidative Phosphorylation Is Regulated by the Cell's Energy Needs 498

The Energy Charge Is Another Index of Cellular Energy Status 500

Glycolysis, the Citric Acid Cycle, and Oxidative Phosphorylation Have Interlocking and Concerted Regulatory Mechanisms 500

Cells Contain Other Oxygen-Using Enzymes 502

Summary 504

References 505

Problems 506

## CHAPTER 18

### The Oxidation of Fatty Acids in Animal Tissues 511

Fatty Acids Are Activated and Oxidized in Mitochondria 511

Fatty Acids Enter Mitochondria by a Three-Step Transport Process 512

Fatty Acids Are Oxidized in Two Stages 514

The First Stage in the Oxidation of Saturated Fatty Acids Has Four Steps 515

The First Stage of Fatty Acid Oxidation Yields Acetyl-CoA and ATP 518

In the Second Stage of Fatty Acid Oxidation Acetyl-CoA Is Oxidized via the Citric Acid Cycle 519

The Oxidation of Unsaturated Fatty Acids Requires Two Additional Enzymatic Steps 520

Oxidation of Fatty Acids with an Odd Number of Carbons 521

Hypoglycin, a Toxic Agent of Some Plants, Inhibits Fatty Acid Oxidation 523

Formation of Ketone Bodies in the Liver and Their Oxidation in Other Organs 524

Regulation of Fatty Acid Oxidation and Ketone-Body Formation 526

Summary 527

References 527

Problems 528

## CHAPTER 19

### Oxidative Degradation of Amino Acids: The Urea Cycle 531

Transfer of  $\alpha$ -Amino Groups Is Catalyzed by Transaminases 531

Ammonia Is Formed from Glutamate 534

Box 19-1 Transaminases and other enzymes in the blood are useful in medical diagnosis 535

The Carbon Skeletons of Amino Acids Are Degraded by 20 Different Pathways 536

Ten Amino Acids Yield Acetyl-CoA during Their Degradation 537

Phenylalanine Catabolism Is Genetically Defective in Some People 540

Box 19-2 The human, social, and economic costs of some genetic diseases 542

Five Amino Acids Are Converted into  $\alpha$ -Ketoglutarate 543

Three Amino Acids Are Converted into Succinyl-CoA 544

Phenylalanine and Tyrosine Yield Fumarate 544

The Oxaloacetate Pathway 544

Some Amino Acids Can Be Converted into Glucose and Some into Ketone Bodies 545

Ammonia Is Toxic to Animals 545

Glutamine Carries Ammonia from Many Peripheral Tissues to the Liver 546

Alanine Carries Ammonia from Muscles to the Liver 546

Excretion of Amino Nitrogen Is Another Biochemical Problem 548

Glutaminase Participates in Excretion of Ammonia 549

Urea Is Formed by the Urea Cycle 549

The Urea Cycle Has Several Complex Steps 550

The Energy Cost of Urea Synthesis 554

Genetic Defects in the Urea Cycle Lead to Excess Ammonia in the Blood 554

Birds, Snakes, and Lizards Excrete Uric Acid 555

Summary 556

References 557

Problems 557

## CHAPTER 20

### Biosynthesis of Carbohydrates in Animal Tissues 561

The Pathway of Gluconeogenesis Shares Seven Steps with the Pathway of Glycolysis 562

Conversion of Pyruvate into Phosphoenolpyruvate Requires a Bypass 564

The Second Bypass Reaction in Gluconeogenesis Is the Conversion of Fructose 1,6-Diphosphate into Fructose 6-Phosphate 565

Conversion of Glucose 6-Phosphate into Free Glucose Is the Third Bypass Reaction 566

Gluconeogenesis Is Costly 566

Gluconeogenesis and Glycolysis Are Regulated Reciprocally	567
Citric Acid Cycle Intermediates Are Also Precursors of Glucose	568
Most Amino Acids Are Glucogenic	568
Gluconeogenesis Takes Place during Recovery from Muscular Exercise	569
Gluconeogenesis Is an Especially Active Process in Ruminant Animals	569
Alcohol Consumption Inhibits Gluconeogenesis	570
"Futile Cycles" in Carbohydrate Metabolism	571
Biosynthesis of Glycogen Proceeds by a Pathway Different from That of Glycogen Breakdown	572
Glycogen Synthase and Glycogen Phosphorylase Are Reciprocally Regulated	574
Glycogen Metabolism Is Subject to Genetic Defects	576
Lactose Synthesis Is Regulated in a Unique Way	576
Summary	577
References	578
Problems	579

## CHAPTER 21

### The Biosynthesis of Lipids 583

The Biosynthesis of Fatty Acids Proceeds by a Distinctive Pathway	583
Malonyl-CoA Is Formed from Acetyl-CoA	585
The Fatty Acid Synthase System Has Seven Active Sites	587
The Sulfhydryl Groups of Fatty Acid Synthase Are First Charged with Acyl Groups	588
Addition of Each 2-Carbon Unit Requires Four Steps	589
Palmitic Acid Is the Precursor of Other Long-Chain Fatty Acids	594
Regulation of Fatty Acid Biosynthesis	595
The Biosynthesis of Triacylglycerols and Glycerol Phosphatides Begins with Common Precursors	595
Triacylglycerol Biosynthesis Is Regulated by Hormones	597
Triacylglycerols: Energy Sources in Some Hibernating Animals	598
Box 21-1 Another biological function of triacylglycerols	599
Biosynthesis of Phosphoglycerides Requires a Head Group	600
Phosphatidylcholine Is Made by Two Different Pathways	602
Polar Lipids Are Inserted into Cell Membranes	603

Lipid Metabolism Is Subject to Genetic Defects	604
There Are Many Lysosomal Diseases	606
Cholesterol and Other Steroids Are Also Made from 2-Carbon Precursors	607
Isopentenyl Pyrophosphate Is the Precursor of Many Other Lipid-Soluble Biomolecules	610
Summary	611
References	611
Problems	612

## CHAPTER 22

### Biosynthesis of Amino Acids and Nucleotides 615

Some Amino Acids Must Be Obtained from the Diet	615
Glutamate, Glutamine, and Proline Share a Common Biosynthetic Pathway	616
Alanine, Aspartate, and Asparagine Also Arise from Central Metabolites	618
Tyrosine Is Made from an Essential Amino Acid, Phenylalanine	618
Cysteine Is Made from Two Other Amino Acids, Methionine and Serine	618
Serine Is a Precursor of Glycine	620
Biosynthesis of the Essential Amino Acids	621
Amino Acid Biosynthesis Is under Allosteric Regulation	622
Amino Acid Biosynthesis Is Also Regulated by Changes in Enzyme Concentration	624
Glycine Is a Precursor of Porphyrins	625
Porphyrin Derivatives Accumulate in Some Genetic Disorders	626
Degradation of Heme Groups Yields Bile Pigments	627
Purine Nucleotides Are Made by a Complex Pathway	627
Purine Nucleotide Biosynthesis Is Regulated by Feedback Control	630
Pyrimidine Nucleotides Are Made from Aspartate and Ribose Phosphate	631
Regulation of Pyrimidine Nucleotide Biosynthesis	632
Ribonucleotides Are the Precursors of the Deoxyribonucleotides	632
Degradation of Purines Leads to Uric Acid in Human Beings	634
Purine Bases Are Recycled by a Salvage Pathway	634
Overproduction of Uric Acid Causes Gout	636
The Nitrogen Cycle	636
Not Many Organisms Can Fix Nitrogen	637