BIOCHEMISTRY

FOURTH EDITION

Geoffrey L. Zubay

生物化学

第四版

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GEOFFREY ZUBAY

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生物化学

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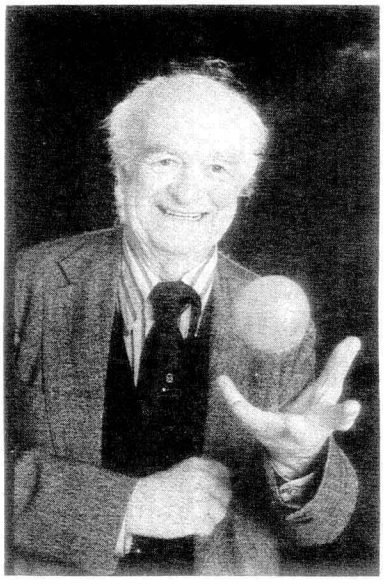

I wanted to dedicate this text to a pioneer in the field of biomolecular structure to emphasize the importance of this subject to our current understanding of biochemistry. If we look back over the twentieth century, there were many pioneers who played major roles in developing the methods and discovering the principles of biomolecular structure. Certainly, Linus Pauling stands out as one of the most colorful and possibly the greatest.

In the early part of his career, Pauling concerned himself with the structures of small molecules; this culminated in the publication of *The Nature of the Chemical Bond,* a book that was intensively used in the classroom and as a guide to researchers for more than a quarter of a century. Pauling's interest in small molecules was but a starting point. Together with R.B. Corey, Pauling studied the structures of amino acids and small peptides and applied the rules that came out of these studies to the enormously complex problems of protein structure. In the 1940s he and Corey proposed two conformations for polypeptide chains, the alpha helix and the beta sheet, which are the most common secondary structures found in most proteins.

In this picture we see Pauling juggling a fruit rich in vitamin C. He had high hopes that vitamin C in large doses might be beneficial to human health.

PREFACE

Biochemistry is a growing discipline, closely linked to other fields of study. As biochemistry has grown, so has the need to relate biochemical phenomena to cell biology, physiology, and genetics. We must familiarize the student with the relationship of biochemistry to these other disciplines without going too far afield. The goal of this edition of *Biochemistry* is like that of the previous three editions: to provide a comprehensive, up-to-date teaching text that will enlighten today's students and equip them to deal with tomorrow's problems in biochemical research and medicine. As a discipline in college courses, graduate schools, and medical schools, biochemistry is of ever-increasing importance. The demands for a uniformly authoritative text have never been greater. We have passed the time when this subject could be properly conveyed in a one-quarter or one-semester course to a time when two or three quarters or semesters are required.

The unique concept of our text in a field that is crowded with many texts is the *team-of-experts* approach. From the start of my textbook writing, I knew I could not cope with the vast literature on the subject. That is why I involved so many people in the effort of writing a textbook. This text is written by experts whose knowledge for their chapters comes from the primary scientific literature and their scientific experiences. All of the contributors to our text are researchers who have made their mark in specific areas of biochemistry; they are also teachers of the subject. Their contributed chapters are scrutinized and sometimes edited by me so that they fit into a coordinated whole. In fact, the amount of editing has been steadily diminishing with each edition as the contributing authors have become increasingly aware of the teaching goals of this text, the role that their contributions play, and the need for good pedagogy.

The long list of contributors to previous editions has made a lasting impression on this text that has helped us to mold it into its present form. I am sure you will recognize most of the names:

Daniel Atkinson	**James P. Ferris**	**P. C. Peterson**
Wayne Becker	**Irving Geis**	**Milton H. Saier, Jr.**
James W. Bodley	**Max Gottesman**	**F. Raymond Salemme**
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In addition to myself the contributors to the current edition include:

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Chapter 26
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Student Learning Aids

Chapter Opening Outline and Overview The chapter opening outline and overview were written to help students preview how the chapter is organized and the major concepts that are to be covered in the chapter.

Declarative Statement Headings Clear, informative headings help students to understand each topic.

Underlined Terms and Key Concepts Underlined important terms and key concepts are easy for students to locate.

Numbered Equations Important equations within a chapter are numbered so that students can easily locate and reference them.

Summary Tables Summary tables are designed to help students more easily understand and use important facts or characteristics presented for a specific topic.

Six Concept and Application Icons Throughout the text the student will find text sections flagged by six different graphic icons or images. These icons are intended to help the student to remember and mentally cross-reference the following concepts and applications:

Methods of Biochemical Analysis

Biomedical Applications

Regulatory Aspects of Biochemistry

Plant Biochemistry

Neurochemistry

Biochemistry of Cancer Cells

Boxed Readings Thought-provoking boxed readings on relevant topics are featured in various chapters.

Molecular Graphics and Illustration Program Molecular graphics images of key molecules enable students to "see" and interpret three-dimensional structures.

End-of-Chapter Enumerated Summary This concise summary of chapter concepts is designed to serve as a guide for chapter study.

End-of-Chapter Selected Readings Each chapter concludes with carefully selected references that contain further information on the topics covered in that chapter.

End-of-Chapter Problems These problems are designed to help students assess their understanding of the chapter's basic concepts. Brief solutions for the odd-numbered problems are found in the back of the book.

Appendix A: Some Major Discoveries in Biochemistry Summarizes major research discoveries from the past and present.

Appendix B: Answers to Odd-Numbered Problems Brief solutions are provided to help the students to determine whether they are on the right track.

Glossary Over 700 important biochemical terms are defined in this end-of-book glossary.

Index An easy-to-use, comprehensive index is provided.

Endsheets with Reference Material The endsheets of the text contain useful easily accessible reference material.

Organizational Changes in the Fourth Edition

Our efforts in this edition have focused on integrating new knowledge into an already extensive body of information. Changes have been made throughout the text, with major changes being confined to areas in which the most important advances have been made. In some cases, old references have been removed from the ends of chapters, and in most cases, appropriate new references have been included.

The contents of the different parts and chapters should be self-evident from the titles and section headings. Parts 1 and 3 and the chapters therein are organized in the same way as they were in the third edition. In the remaining parts of this edition, substantial changes in organization have been made. In the third edition, part 2 covered the structures and functions of most of the major components of the cell. In the fourth edition, part 2 focuses on protein structure and function, leaving the discussion of structure and function of the remaining components to be dealt with immediately before addressing their metabolism. In this way the structure and function will be fresh in the mind as one delves into the metabolism, a clear advantage for the student.

In parts 4 and 5 of the third edition we attempted to divide the metabolism into a discussion of the catabolism and the anabolism, respectively. These parts have been supplanted by parts 4, 5, and 6 in the fourth edition, in which the intermediary metabolism is considered first for carbohydrates (part 4), then for lipids (part 5), and finally for nitrogen-containing compounds (part 6). This arrangement is considered superior because it facilitates comparison of the similar and dissimilar features of the metabolism for opposing anabolic and catabolic pathways and a discussion of their regulation, which usually focuses on strategies that prevent opposing pathways from functioning simultaneously.

The strategy of presenting structures and functions adjacent to the related metabolism sections is carried over to part 7, in which the structures and functions of nucleic acids are considered just prior to a discussion of their metabolism.

Although we believe that many instructors of biochemistry will find these changes in organization to be superior for teaching purposes, we also recognize that there are others who prefer the organizational scheme followed in the third edition. In consideration of this, the relevant materials have been flexibly packaged so that the order of teaching need not follow the order in the text. For example, if the instructor wishes to consider most of the structures first before getting into the metabolism, then after a consideration of part 2 as it appears in the fourth edition, one can turn to chapter 13 for a discussion of the structures of sugars and energy storage polysaccharides, followed by chapter 19 for a discussion of the structure and function of biological membranes, perhaps chapter 20, which deals with membrane transport, and, finally, chapter 30 for a discussion of the structures of DNA and nucleoproteins.

Physiological biochemistry, which comprised part 7 in the third edition, has been eliminated in the fourth edition, and the chapters that it contained have been relocated to the most relevant sections of the text. Vision and neurotransmission have been moved to part 6, and immunobiology and carcinogenesis, along with a new chapter on AIDS and the HIV virus, have been moved to part 7, "Storage and Utilization of Genetic Information."

Detailed Content Changes of the Fourth Edition

Part 1, "An Overview of Biochemistry and Bioenergetics," contains changes only to chapter 1, with the addition of the new section entitled "The First Living Systems Were Acellular." This section contains a brief but authoritative account of the most significant prebiotic events that are believed to have led to the origin of life.

Part 2, "Protein Structure and Function," starts with a new chapter, "The Structure and Function of Water." This chapter pulls together information that was previously scattered in several early chapters and adds new information on the general nature of buffers and the physiologically important buffers containing either phosphate or carbonate. In chapter 4 some information on the determination of amino acid composition has been added. Material in chapter 5 on the three-dimensional structures of proteins has been substantially revised in the middle and final parts. In particular, the discussion of globular protein structures has been reorganized. The structural motif is introduced as the fundamental unit of tertiary structure. Then it is shown how domains are built from single motifs or combinations of motifs and so on. Sections on nuclear magnetic resonance and optical rotatory dispersion and circular dichroism have been added to the last part of chapter 5.

In chapter 6 the discussion of the way in which various factors negatively affect oxygen binding by hemoglobin has been elaborated upon. Thanks to new structural information on myosin (see the references), it has been possible to describe the actin–myosin cycle associated with muscular contraction in greater molecular detail (see figures 6.19, 6.20, and 6.21). In box 6A a comprehensive explanation of multiple binding and the Hill plot is given. In box 6B a detailed explanation of the inheritance pattern of genetic defects is presented that will be useful for the discussion of hemoglobin in this chapter and will continue to be useful at many points throughout the text. Chapter 7 is a new chapter in which the methods of characterization and purification of proteins are presented. In the third edition this discussion was tacked onto the previous chapter, which dealt with the functional diversity of proteins. Only minor changes have been made to the content of this chapter.

Part 3 begins with chapter 8, of which substantial portions of the middle sections have been rewritten in the interest of achieving greater clarity. Some complex equations have been eliminated without any substantial loss of substance. The section entitled "The Henri-Michaelis-Menten Treatment Assumes That the Enzyme-Substrate Complex Is in Equilibrium with Free Enzyme and Substrate" is new.

The changes in chapter 9 are probably the most important changes made in this text. This is due to a new development in the field of enzymology that invites a reconsideration of many enzyme mechanisms that have been proposed. The second main section of chapter 9, which is concerned with detailed mechanisms of enzyme catalysis, has been substantially revised. In two cases, trypsin and triose phosphate isomerase, the revised mechanisms have resulted from the realization that extra-strong hydrogen bonds are probably formed in the activated complexes. Extra-strong hydrogen bonds known as low-barrier hydrogen bonds were identified in the early 1970s, but their significance in the field of enzyme catalysis has come to light only recently, partly as a result of papers published by W. W. Cleland and Kreeway and Perry Frey and his co-workers (see references and box 9B). Revision of the proposed mechanism for RNase A action has resulted from a recent paper by Ron Breslow. Several new computer-generated fig-

ures have been added to aid in visualization of the overall enzyme structure and the active site (see figures 9.6, 9.7, 9.25, and 9.26). Box 9D discusses catalytic antibodies.

Chapter 10 contains the description of how the mechanism of action of calmodulin has been significantly amplified and updated as a result of new structural information. In chapter 11 the section on coenzyme A has been expanded. The role of ascorbic acids in maintaining the enzyme that catalyzes hydroxyproline formation in collagen is explained in a new short section. Finally, a new box 11A discusses aconitase as an example of an enzyme containing an iron–sulfur complex that is involved in something other than an oxidation–reduction reaction.

In chapter 12 a new section, "A Regulated Reaction Is Effective Only if It Is Exergonic," was added to give emphasis to a principle that was made clear earlier in the text. Although chapter 13 is a new chapter, the material in it is not new; it comes from the first part of chapter 6 in the third edition, which deals with the structures and functions of simple sugars and polysaccharides.

As seen in chapter 14, it is quite remarkable how new understandings of the ancient subject of carbohydrate metabolism keep appearing as we learn more and more about the enzymes that are involved. An expanded discussion of the hexokinases found in different tissues explains why glucose is normally absorbed by most tissues but not by the liver. The hexokinases in question are assembled from different isozymes. An expanded discussion of the different isozymal forms of the bifunctional enzyme that regulates the level of fructose-2,6-bisphosphate explains the different responses of liver and muscle tissue to the hormone epinephrine. The metabolism of the two most important dietary disaccharides is presented with particular reference to the problems they can produce when there are metabolic lesions. A new box 14A describes the history of events leading to the discovery of the glycolytic pathway. A new box 14B describes factors that influence the levels of the regulatory molecule glycerate-2,3-bisphosphate in erythrocytes. This subject is taken up here because the compound in question is also an intermediate in the glycolytic pathway. Chapter 15 contains only minor changes.

The headings in chapter 16 are similar to the ones in the comparable chapter (15) of the third edition. Despite this, many sections have undergone considerable revision. The proton translocation that is powered by electron transport is described as resulting from either redox loops or proton pumps. There are still considerable mysteries concerning how these processes work. Recent crystal structure studies of the F_1 subunit of the ATP-synthase have elevated our understanding of the mechanism for ATP synthesis.

In addition to many minor changes, new information is presented in chapter 17 on the operation of the antenna systems at the photocenters and the mechanism of oxygen evolution. Chapter 18 is derived from chapter 21 of the third edition. In addition, it includes a description of the relevant structures that were presented in chapter 6 of the third edition. Except for reorganizational changes, there have been no major additions or deletions within the contents of the chapter.

Chapter 19 on lipids and membranes, the beginning of part 5, has been completely rewritten to yield a more exciting and shorter presentation. Chapter 20 on mechanisms of membrane transport has been completely rewritten, relocated, and shortened. This subject was relocated because it was considered highly desirable to present the mechanisms of transport before getting too far into the metabolism section. Although the chapter has been considerably shortened, I do not feel that this has resulted in a serious loss of substance.

In chapter 21, only a few changes have been made to accommodate recent advances. In chapter 22, many small changes have been made in the coverage of biosynthesis of membrane lipids. These changes were made to update the material, but clarity of explanation was also addressed. Chapter 23 on cholesterol metabolism includes new information on the factors that control the rate of mevalonate synthesis; the molecular basis of the inherited disease abetalipoproteinemia in which patients have no chylomicrons, VLDLs, or LDLs in the bloodstream; a description of how cholesterol suppresses the synthesis of LDL receptors; and box 3A, a description of the isoprenylation of proteins.

Chapters 24 and 25 on amino acid metabolism are closely knit, as they were in the third edition. The material has been realigned to make it more accessible and to make it easier to use either chapter independently of the other. Chapter 24 deals with amino acid biosynthesis and nitrogen fixation in plants and microorganisms. Important changes in the regulation of the enzyme glutamine synthase have been added to chapter 24. Chapter 25 deals with amino acid metabolism in vertebrates. I suspect that if time is limited, chapter 25 will be favored because of the somewhat greater interest in this subject in most college courses. An appendix that discusses detailed aspects of many catabolic pathways has been added to chapter 25.

Chapter 26 on nucleotides has been considerably updated to accommodate the rapidly changing subject of inhibitors of nucleotide synthesis and their role in chemotherapy. In chapter 27 several sections have been substantially revised to bring them up to date. These sections are "General Aspects of Cell Signaling," "The Adenylate Cyclase Pathway Is Triggered by a Membrane-Bound Receptor," "Protein Phosphorylation Is the Most Common Way in Which Regulatory Proteins Respond to Hormonal Signals," "Variability in G Proteins Adds to the Variability of the Hormone-Triggered Response," "Guanylyl Cyclase Can Be Activated by a Gas," and "Growth Factors Are Proteins That Behave Like Hormones."

In chapter 28 on neurotransmission the section entitled "The Acetylcholine Receptor Is the Best-Understood Neurotransmitter" has been revised to bring it up to date. Two new sections have been added: "Synaptic Receptors Coupled to G Proteins Produce Slow Synaptic Responses" and "Synaptic Plasticity and Learning." Minor changes have been made in chapter 29 on vision to bring the subject up to date.

In chapter 30 a new section, "Helical Structures That Use Additional Kinds of Hydrogen Bonding," deals with the conformational variants formed by telomeres. Four new sections have been added to chapter 31: "Initiation of Chromosomal Replication in Eukaryotes," "The Mismatch Repair System Is Important for Maintaining Genetic Stability," "Some Transposable Genetic Elements Encode a Reverse Transcriptase," and "Bacterial Reverse

Transcriptase Catalyzes Synthesis of a DNA-RNA Molecule." Other sections ("SV40 Is Similar to Its Host in Mode of Replication," "Several Systems Exist for DNA Repair," and "Telomerase Facilitates Replication at the Ends of Eukaryotic Chromosomes") have been significantly modified. These additions reflect important advances in our understanding of chromosome replication in eukaryotic systems and DNA repair in both prokaryotic and eukaryotic systems.

For chapter 32 there has been an enormous amount of activity in this field but surprisingly few fundamental advances. This is particularly true in the field of application to practical problems (plenty of sizzle but no steak). Two new sections have been added: "Yeast Artificial Chromosomes (YACS) Are Used for Cloning Fragments as Large as 500 kb in Length" and "Will Nucleic Acids Become Useful Therapeutic Agents?"

In chapter 33, two new sections have been added: "Comparison of *E. coli* RNA Polymerase with DNA PolI and PolIII" and "RNA Editing Involves Changing of the Primary Sequence of a Nascent Transcript." Several existing sections have been updated. The most important updated section, "Messenger RNA Transcription by Polymerase II," has resulted from genetic and biochemical studies of yeast RNA polymerase. Many heretofore unrecognized proteins have been unequivocally recognized as key components of RNA polymerase II. The popular model for stepwise assembly of the RNA polymerase II–DNA complex must now share the limelight with a model in which the holoenzyme remains largely intact in its association–dissociation cycle at the promoter.

In chapter 34, three new sections have been added: "In Addition to the P Site and the A Site for Binding tRNAs, the Ribosome May Possess a Third Site, the E Site," "Protein Folding Is Mediated by Protein Chaperones," and "ATP Plays Multiple Roles in Protein Degradation." Ten sections have been updated: "Ribosomes Are the Site of Protein Synthesis," "The Code Is Highly Degenerate," "Each Synthase Recognizes a Specific Amino Acid and Specific Regions on Its Cognate tRNA," "Aminoacyl-tRNA Synthases Can Correct Acylation Errors," "Translation Begins with the Binding of mRNA to the Ribosome," "Three Elongation Reactions Are Repeated with the Incorporation of Each Amino Acid," "Two (or Three) GTPs Are Required for Each Step in Elongation," "Targeting and Posttranslational Modification of Proteins," "Proteins Are Targeted to Their Destination by Signal Sequences," and "Ubiquitin Tags Proteins for Proteolysis."

Three new sections have been added to chapter 35: "Helix-Turn-Helix Regulatory Proteins Are Symmetrical," "DNA–Protein Cocrystals Reveal Gross Features of the Complex," and "RNA Can Function as a Repressor." The first two of these new sections reflect the progress that has been made in structural studies of DNA regulatory protein complexes. The third relates to the increasing number of examples in which DNA functions as a transcription regulator.

Regarding chapter 36, enormous progress has been made in the area of gene-regulatory proteins in eukaryotes. This has resulted in several new sections and several modified sections in the central part of this chapter. In addition to this, the section entitled "DNA Methylation Is Correlated with Inactivated Chromatin" has been updated by the finding of a long-sought-for genetic correlate. A long-overdue section on how translation controls transcription in eukaryotes has been added. The chapter ends with a new section entitled "Early Development in *Drosophila* and Vertebrates Shows Striking Similarities."

Two new sections have been added to chapter 37. The first, "T-Cell Action Is Frequently Augmented by the Secretion of Hormonelike Proteins Called Interleukins," deals with the hormonelike proteins that bias the interactions between cells of the immune system. The second, "The Immune System in Action," describes three examples of how the immune system disposes of specific invaders by choosing the most appropriate weapons from its arsenal.

Four new sections have been added to chapter 38, and another four have been substantially revised to bring them up to date. These sections comprise most of the latter half of this chapter. The changes help to delineate the distinction between protooncogenes and tumor suppressor genes. In the new chapter 39 the causes and progression of the disease known as AIDS are discussed at an introductory level. Approaches for preventing the spread of AIDS and treating AIDS patients are also discussed.

Ancillary Materials

Student Study Guide and Solutions Manual
Written by Larry Loomis-Price, Johns Hopkins University, and Gwen E. Shafer, independent scientific consultant, this manual contains study information and self-quizzes. It can help students to better understand how to solve the problems in the text and to prepare for exams.

Instructor's Manual with Test Item File and Transparency Masters
This manual contains suggestions on how to use the text in different course situations and detailed, worked-out solutions for the even-numbered problems found in the text chapters. In addition, this manual offers several objective test questions for each chapter, which can be used to generate exams, along with 300 black-and-white transparency masters from the text.

Classroom Testing Software
This software is offered free upon request to adopters of the text. It provides a database of questions for preparing exams. No programming experience is necessary to use the software. Available in IBM and Macintosh formats.

Transparency Acetates
A set of 100 full-color transparencies is available free to adopters. These acetates feature key illustrations that can be used to enhance your classroom lectures. When these acetates are coupled with the 300 masters provided with the instructor's manual, each adopter has access to 400 figures and tables from the text to use in the lecture setting.

Slides
A set of 100 full-color projection slides derived from the transparency illustrations is available free to adopters.

Biochemistry Electronic Image Bank
These computerized image files are available free to adopters upon request. These files contain images from this text along with images from other Wm. C. Brown biochemistry titles. These electronic acetates can be clearly projected on large lecture hall screens by using an LCD projection system.

Biochemical Pathways Software
Created by Bill Sofer, this is an easy-to-use tutorial review software program for Macintosh that provides quizzes and memory exercises that test students' knowledge of glycolysis and the TCA cycle. Contact your bookstore or call Wm. C. Brown Publishers at 1-800-338-5578 to place an order or request more information on this software. (ISBN 25100)

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Brief Contents

CONTENTS