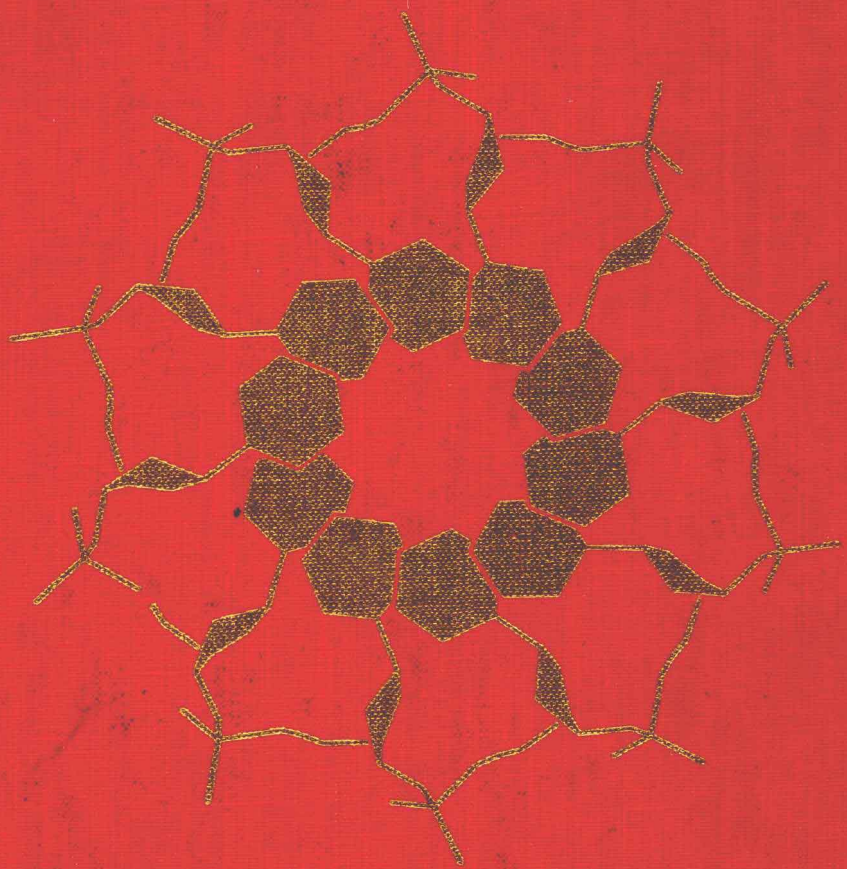
Biochemistry

FOURTH EDITION



Lubert Stryer

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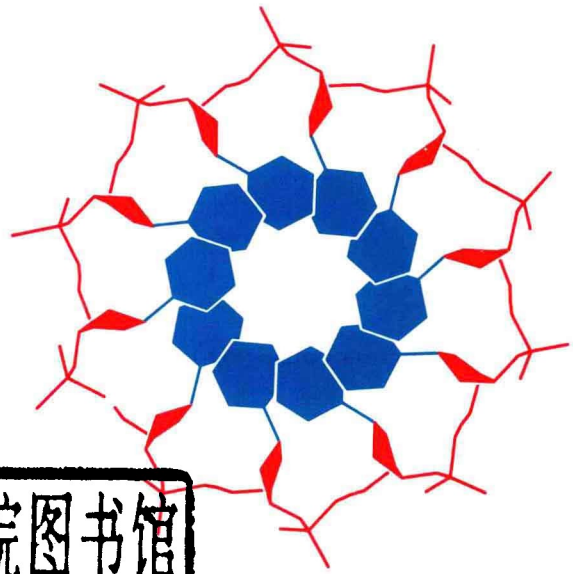

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STANFORD UNIVERSITY

W. H. Freeman and Company
New York

Library of Congress Cataloging-in-Publication Data

Stryer, Lubert.
Biochemistry/Lubert Stryer.—4th ed.
Includes index.
ISBN 0-7167-2009-4
1. Biochemistry. I. Title.
QP514.2.S66 1995
574.19'2—dc20 94-22832

Printed in the United States of America

Sixth printing, 1999

To my teachers

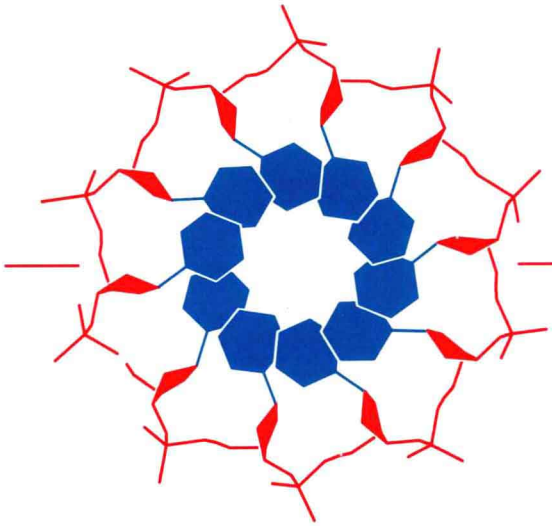
Paul F. Brandwein

Daniel L. Harris

Douglas E. Smith

Elkan R. Blout

Edward M. Purcell



Biochemistry

I Molecular Design of Life

II Proteins: Conformation, Dynamics, and Function

III Metabolic Energy: Generation and Storage

IV Biosynthesis of Building Blocks

V Genes: Replication and Expression

Preface

This is a wonderful time in biochemistry. Recombinant DNA technology, protein chemistry, and structural biology have come together to reveal the molecular mechanisms of fundamental biological processes. Many of our dreams of only a few years ago have been fulfilled. One of the fruits of this continuing harvest is a deeper understanding of protein form and function. We now see that proteins are highly sophisticated molecular machines that process energy, matter, and information. Their beautiful molecular ballet is coming into view. Indeed, we can even see the steps taken by a single molecular motor and the flow of ions through a single membrane channel.

These profound advances compel a change in how biochemistry is taught. I have expanded Part II, Proteins: Conformation, Dynamics, and Function, to bring our new understanding of proteins into the core of biochemistry. Membrane channels and pumps, signal transduction cascades, antibodies and T-cell receptors, and molecular motors are now presented in Part II rather than in a separate section at the end of the book. The proteins considered in these chapters reveal much about fundamental processes such as free-energy conversion, signal amplification, and molecular recognition. An understanding of proteins as energy-transforming and information-processing devices enriches the study of metabolism. Oxidative phosphorylation and photosynthesis, for example, are more readily understood and appreciated if the proton-pumping mechanism of bacteriorhodopsin is considered first. Likewise, the hormonal control of metabolism is easier to comprehend if G-protein and tyrosine-kinase cascades are presented first. Another noteworthy change is the new chapter on protein folding and design, an exciting area of inquiry that has broad import.

In 1962, the structures of only two proteins—myoglobin and hemoglobin—were known at atomic resolution. I was fortunate to see them at close range while I was a postdoctoral fellow at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. Max Perutz, John Kendrew, and the young crystallographers in the laboratory instilled in me a deep appreciation of molecular architecture and its importance in understanding the molecular basis of life. Now, three decades later, we see the fruition of structural biology. X-ray crystallography, joined by electron crystallography and nuclear magnetic resonance spectroscopy, have revealed the structures of hundreds of proteins. This wealth of structural information has illuminated and enriched our understanding of how proteins function as enzymes, transporters, motors, signal transducers, and gene regulators. Recurring structural modules have come into view, bringing insight into how proteins evolved. Structural

biology has also contributed greatly to our understanding of how genetic information is replicated and expressed. DNA is now seen as a highly dynamic molecule that can twist, bend, and breathe. The structures of many complexes of DNA and RNA with polymerases, synthetases, transcriptional regulators, and other cognate proteins have been immensely informative. They are presented in depth in Part V, Genes: Replication and Expression. Throughout this edition, as in previous ones, I have sought to vividly depict the beautiful relations between molecular architecture and biological function, inspired by the experiences of my scientific childhood.

I am grateful to Elva Diaz, Richard Gumport, Roger Koeppe, Carl Rhodes, and John Tymoczko for their critical and perceptive review of the entire manuscript, and to Alexander Glazer for his sustained support and wise counsel. Clint Ballou, Ronald Bentley, Stuart Edelstein, Roger Koeppe II, Brian Law, Peter Rubenstein, Alan Sachs, Ihor Skrypka, Ronald Somerville, Mary Waltner, and Derrick Williamson provided valuable comments on major parts of this book. I have also gained much from the advice provided by Robert Baldwin, Jeremy Berg, Nicholas Cozzarelli, Marilyn Farquhar, Michel Goldberg, Peter Kim, Daniel Koshland, Jr., Richard Mathies, David McKay, George Palade, Peter Parham, Suzanne Pfeffer, Alexander Rich, Timothy Ryan, Robert Shulman, Paul Sigler, James Spudich, Thomas Steitz, Nigel Unwin, Max Vasquez, John Wagner, and William Weis. Joanne Tisch carefully scrutinized the proofs and helped in many other ways with the preparation of this edition, as with the last.

I wish to thank Richard Gumport, Ana Jonas, Richard Mintel, Carl Rhodes, and Roger Koeppe for having written a *Student Companion* to this work. This valuable study guide is an outgrowth of their devotion to teaching and the advancement of biochemical knowledge.

The flowering of structural biology has been accompanied and reinforced by rapid advances in molecular graphics. This edition contains hundreds of new drawings of biomolecules that were generated using a host of powerful tools for visualizing molecular architecture. I am indebted to Michael Levitt for introducing me to *MacImdad,* his interactive graphics program for personal computers, and for providing advice on molecular structure and graphics. Most of the new space-filling models shown in this edition were drawn using *MIDAS,* a program developed by Thomas Ferrin and Conrad Huang. Ball-and-stick models and schematic representations were drawn primarily with *MOLSCRIPT,* a program written by Per Kraulis. I have also benefited from *GRASP,* a program devised by Anthony Nicholls. David Hinds, Kevin Flaherty, and Peter David guided me through UNIX and helped me in many ways with both software and hardware on my Silicon Graphics IRIS computer. I am grateful to Paul Haeberli for making it possible to capture in print the striking molecular images seen on the IRIS screen. I have made extensive use of the Protein Data Bank, a rich and highly accessible repository of structural information maintained by Brookhaven National Laboratory. Many crystallographers shared with me the atomic coordinates of their recently solved structures.

Sonia DiVittorio played a key role in developing this edition and in guiding the preparation of new art. Her sensitive appreciation of biochemistry and dedication to excellence in publishing have made their mark. I am grateful to her for her outstanding contributions. Bill O'Neal, Jr., thoughtfully edited the manuscript, which gained much from his care-

ful scrutiny. I am also indebted to Tomo Narashima and Ian Worpole for many fine drawings. Bill Page was the illustration coordinator. John Hatzakis provided an esthetic design, and Stan Hatzakis crafted each page with a fine eye for integrating word and picture. Georgia Lee Hadler expertly guided the flow and convergence of manuscript and thousands of pages of text and art proof. Julia DeRosa ably coordinated a challenging production process. Nancy Brooks provided valuable assistance at crucial times. Her command of the classics enlivened and enriched the preparation of this edition.

The twelve foreign-language editions of this book—Chinese, French, German, Greek, Italian, Japanese, Korean, Polish, Portuguese, Russian, Serbo-Croatian, and Spanish—have given me special pleasure. I am indebted to the translators for their devoted and scholarly contributions. They have made this book accessible to students in many lands and have fostered the universality of biochemistry. I have greatly enjoyed my contact with students and faculty around the world and look forward to continuing this stimulating and rewarding dialogue.

I was invited several years ago by a medical student newsletter to contribute to an issue entitled "Why Teach?" I responded by recounting my earliest recollection of school. During World War II, in the midst of uncertainty and strife, I attended a primary school in Shanghai that was taught by two Danish ladies in their small apartment. Their educational strategy was simple and highly effective: each student both taught and learned. I learned multiplication from a youngster who had mastered it only a week earlier, and in turn, I taught subtraction to a less advanced peer. Teaching remains my best way of learning. I also teach because the sharing of knowledge is joyful. Kindred souls are joined by the inseparable acts of teaching and learning.

Twenty-three years have passed since I embarked on the intellectual journey of writing a textbook of biochemistry. Each edition has been demanding in a different way. I am deeply grateful to my wife, Andrea, for her sustained support of this endeavor from its inception. Her wisdom has made all the difference. I have been nurtured too by our enlarging family. Two wonderful daughters have joined us—Daniel's wife, Stacy, and Michael's wife, Barri. The birth of our granddaughter Leah a few weeks ago has been an added blessing.

Lubert Stryer

NOVEMBER 1994

Prefaces

PREFACE TO THE THIRD EDITION

Biochemistry has been profoundly transformed by recombinant DNA technology. The genome is now an open book—any passage can be read. The cloning and sequencing of millions of bases of DNA have greatly enriched our understanding of genes and proteins. Indeed, recombinant DNA technology has led to the integration of molecular genetics and protein chemistry. The intricate interplay of genotype and phenotype is now being unraveled at the molecular level. One of the fruits of this harvest is insight into how the genome is organized and its expression is controlled. The molecular circuitry of growth and development is coming into view. The reading of the genome is also providing a wealth of amino acid sequence information that illuminates the entire protein landscape. Scarce proteins can be produced in abundance by transfected cells. Moreover, precisely designed novel proteins can be generated by site-specific mutagenesis to elucidate how proteins fold, catalyze reactions, transduce signals, transport ions, and interconvert different forms of free energy.

Our understanding of molecular evolution also has been greatly enriched by the recombinant DNA revolution. Families and superfamilies of proteins have come into view. Theme and variation at the level of proteins are vivid expressions of the underlying processes of gene duplication and divergence. The genes of complex proteins display the coming together in evolution of exons encoding functional modules. The many recurring structural and mechanistic motifs seen throughout nature testify to the fundamental unity of all forms of life. The discovery of catalytic RNA enables us to envision an RNA world early in the evolution of life, prior to the appearance of DNA and protein. The ubiquity of ribonucleotides in metabolism and the central roles played by them are reflections of their ancient origins—of the early RNA world, when RNA served both as gene and enzyme.

These remarkable advances compel a major change in the way biochemistry is taught. I have altered the architecture of this book to provide a new framework for the exposition of fundamental themes and principles of biochemistry. The book begins with a new part, entitled Molecular Design of Life, that provides an overview of the central molecules of life—DNA, RNA, and proteins—and their interplay. Recombinant DNA technology and other experimental methods for exploring proteins and genes are also presented in this part. This introduction prepares the reader for the detailed consideration of protein structure and function that follows. The teaching of metabolism is likewise enriched by this new organization. The other major structural changes are the addition of a chapter on carbohydrates and one on protein targeting. Many sections of

the book have been extensively revised and hundreds of new illustrations have been added. I have tried to preserve the unity of biochemistry as an intellectual discipline. My goal has been to make this powerful language comprehensible and to share its beautiful imagery.

I am grateful to Alexander Glazer, Daniel Koshland, Jr., and Alexander Rich for having encouraged me to write this edition. I would not have embarked on this endeavor had it not been for their warm support and good counsel.

The planning of this edition unexpectedly took place in terrain quite different from Yale, Stanford, and Aspen, where the first two editions took form. In December 1985, my family and I went to Nepal to trek in the Everest region. After two rewarding days in Kathmandu, we were on the verge of boarding the plane to Lukla, only to be turned back with the disappointing news that the landing strip was closed because of snow. We then headed for the Annapurna region in four-wheel-drive vehicles but had to return a day later because the road vanished in the heavy rain. The inaccessibility of the high Himalayas led to an abrupt change of itinerary. We flew to Bangkok and arrived in 95-degree heat, carrying our parkas and arctic sleeping bags. Instead of hiking at 12,000 feet, we found ourselves at a hotel pool at sea level. This dislocation led to a totally unforeseen benefit. I was able to unhurriedly reflect on the remarkable development of biochemistry since I wrote my last edition. I had the leisure to think and dream and plan this book. Best of all, I was able to share my thoughts with my son Daniel, who was then a senior majoring in human biology, and gain from his insights.

Alexander Glazer, Richard Gumport, Roger Koeppe, James Rawn, Carl Rhodes, and Peter Rubenstein read the entire manuscript. I have benefited greatly from their scholarly and perceptive criticism. Steve Block, Daniel Branton, Simone Brutlag, Carolyn Cohen, Jeffrey Critchfield, Peter Cullis, Russell Doolittle, Marilyn Farquhar, Robert Fletterick, Robert Fox, Michel Goldberg, Jack Griffith, James Hageman, Stephen Harrison, Brian Holl, Leroy Hood, Horace Jackson, Gunther Kohlhaw, Arthur Kornberg, Roger Kornberg, Stephen Kron, Michael Levitt, Bo Malmström, Lynne Mercer, Albert Mildvan, Jeremy Nathans, Christopher Newgard, Marion O'Leary, George Palade, Peter Parham, Frederic Richards, Ed Rock, Gottfried Schatz, Gray Scrimgeour, Paul Sigler, Jeffrey Sklar, James Spudich, Thomas Steitz, Nigel Unwin, Ronald Vale, William Wickner, and Robley Williams also gave valuable advice and help.

The contributors of many striking and informative illustrations are acknowledged in the figure legends. I am also indebted to crystallographers who have deposited the atomic coordinates of their solved structures in the Protein Data Bank, a valuable resource maintained by Brookhaven National Laboratory. Many new figures depicting molecular structure were generated on our departmental molecular graphics computer facility. David Austen and William Hurja helped me use this excellent system.

I was able to concentrate on the writing of this book because my office was in the capable hands of Joanne Tisch. She played a critical role in preparing the manuscript and reading the proofs. Her sensitivity, intelligence, and good spirits lightened my load. The Medline bibliographic retrieval system of the National Library of Medicine greatly facilitated my search of the literature. The staff of the Lane Medical Library and Falconer Biology Library of Stanford University were most helpful in locating books and references.

Andrew Kudlacik edited this manuscript with a fine sense of style and meaning. Mike Suh skillfully integrated word and picture in the design of each page. Susan Moran kept a watchful and discerning eye over many

thousands of pages of manuscript, figures, and proofs. I also wish to thank Tom Cardamone and Shirley Baty for many outstanding drawings.

I am grateful to my family for their sustained support of this endeavor, which was more arduous than anticipated. My sons, Michael and Daniel, now embarked on their own careers, cheered me from afar. My wife, Andrea, provided criticism, advice, and encouragement in just the right proportions. I have been nurtured, too, by many who have reached out to express their warmth and interest in continuing this dialogue of biochemistry. I feel very fortunate and privileged to partake in this process at such a wonderful time.

December 1987

PREFACE TO THE SECOND EDITION

The pace of discovery in biochemistry has been exceptionally rapid during the past several years. This progress has greatly enriched our understanding of the molecular basis of life and has opened many new areas of inquiry. The sequencing of DNA, the construction and cloning of new combinations of genes, the elucidation of metabolic control mechanisms, and the unraveling of membrane transport and transduction processes are some of the highlights of recent research. One of my aims in this edition has been to weave new knowledge into the fabric of the text. I have sought to enhance the book's teaching effectiveness by centering the exposition of new material on common themes wherever feasible and by citing recurring motifs. I have also tried to convey a sense of the intellectual power and beauty of the discipline of biochemistry.

I am indebted to Thomas Emery, Henry Epstein, Alexander Glazer, Roger Kornberg, Robert Martin, and Jeffrey Sklar for their counsel, criticism, and encouragement in the preparation of this edition. Robert Baldwin, Charles Cantor, Richard Caprioli, David Eisenberg, Alan Fersht, Robert Fletterick, Herbert Friedmann, Horace Jackson, Richard Keynes, Sung-Hou Kim, Aaron Klug, Arthur Kornberg, Daniel Koshland, Jr., Samuel Latt, Vincent Marchesi, David Nelson, Garth Nicolson, Vernon Oi, Robert Renthal, Carl Rhodes, Frederic Richards, James Rothman, Peter Sargent, Howard Schachman, Joachim Seelig, Eric Shooter, Elizabeth Simons, James Spudich, Theodore Steck, Thomas Steitz, Judit C.-P. Stenn, Robert Trelstad, Christopher Walsh, Simon Whitney, and Bernhard Witkop also gave valuable advice.

Patricia Mittelstadt edited both editions of this text. I deeply appreciate her critical and sustained contributions. I am indebted to Donna Salmon for her outstanding drawings. David Clayton, David Dressler, John Heuser, Lynne Mercer, Kenneth Miller, George Palade, Nigel Unwin, and Robley Williams generously provided many fine electron micrographs. Betty Hogan typed the manuscript and played an indispensable role in its preparation. Cary Leiden and Karen Marzotto carefully read the proofs. I also wish to thank Michael Graves for his excellent photographic work.

My wife, Andrea, and my sons, Michael and Daniel, have cheerfully allowed this text to become a member of the family. I am deeply grateful to them for their patience and buoyancy. Andrea provided much advice on style and design, as she did for the first edition.

I have been heartened by the many letters that I have received from readers of the first edition. Their comments and criticisms have enlightened, stimulated, and encouraged me. I look forward to a continuing dialogue with readers in the years ahead.

August 1980

PREFACE TO THE FIRST EDITION

This book is an outgrowth of my teaching of biochemistry to undergraduates, graduate students, and medical students at Yale and Stanford. My aim is to provide an introduction to the principles of biochemistry that gives the reader a command of its concepts and language. I also seek to give an appreciation of the process of discovery in biochemistry. My exposition of the principles of biochemistry is organized around several major themes:

1. Conformation—exemplified by the relationship between the three-dimensional structure of proteins and their biological activity

2. Generation and storage of metabolic energy

3. Biosynthesis of macromolecular precursors

4. Information—storage, transmission, and expression of genetic information

5. Molecular physiology—interaction of information, conformation, and metabolism in physiological processes

The elucidation of the three-dimensional structure of proteins, nucleic acids, and other biomolecules has contributed much in recent years to our understanding of the molecular basis of life. I have emphasized this aspect of biochemistry by making extensive use of molecular models to give a vivid picture of architecture and dynamics at the molecular level. Another stimulating and heartening aspect of contemporary biochemistry is its increasing interaction with medicine. I have presented many examples of this interplay. Discussions of molecular diseases such as sickle-cell anemia and of the mechanism of action of drugs such as penicillin enrich the teaching of biochemistry. Finally I have tried to define several challenging areas of inquiry in biochemistry today, such as the molecular basis of excitability.

In writing this book, I have benefited greatly from the advice, criticism, and encouragement of many colleagues and students. Leroy Hood, Arthur Kornberg, Jeffrey Sklar, and William Wood gave me invaluable counsel on its overall structure. Richard Caprioli, David Cole, Alexander Glazer, Robert Lehman, and Peter Lengyel read much of the manuscript and made many very helpful suggestions. I am indebted to Frederic Richards for sharing his thoughts on macromolecular conformation and for extensive advice on how to depict three-dimensional structures. Deric Bownds, Thomas Broker, Jack Griffith, Hugh Huxley, and George Palade made available to me many striking electron micrographs. I am also very thankful for the advice and criticism that were given at various times in the preparation of this book by Richard Dickerson, David Eisenberg,

Moises Eisenberg, Henry Epstein, Joseph Fruton, Michel Goldberg, James Grisolia, Richard Henderson, Harvey Himel, David Hogness, Dale Kaiser, Samuel Latt, Susan Lowey, Vincent Marchesi, Peter Moore, Allan Oseroff, Jordan Pober, Edward Reich, Russell Ross, Mark Smith, James Spudich, Joan Steitz, Thomas Steitz, and Alan Waggoner.

I am grateful to the Commonwealth Fund for a grant that enabled me to initiate the writing of this book. The interest and support of Robert Glaser, Terrance Keenan, and Quigg Newton came at a critical time. One of my aims in writing this book has been to achieve a close integration of word and picture and to illustrate chemical transformations and three-dimensional structures vividly. I am especially grateful to Donna Salmon, John Foster, and Jean Foster for their work on the drawings, diagrams, and graphs. Many individuals at Yale helped to bring this project to fruition. I particularly wish to thank Margaret Banton and Sharen Westin for typing the manuscript, William Pollard for photographing space-filling models, and Martha Scarf for generating the computer drawings of molecular structures on which many of the illustrations in this book are based. John Harrison and his staff at the Kline Science Library helped in many ways.

Much of this book was written in Aspen. I wish to thank the Aspen Center of Physics and the Given Institute of Pathobiology for their kind hospitality during several summers. I have warm memories of many stimulating discussions about biochemistry and molecular aspects of medicine that took place in the lovely garden of the Given Institute and while hiking in the surrounding wilderness areas. The concerts in Aspen were another source of delight, especially after an intensive day of writing.

I am deeply grateful to my wife, Andrea, and to my children, Michael and Daniel, for their encouragement, patience, and good spirit during the writing of this book. They have truly shared in its gestation, which was much longer than expected. Andrea offered advice on style and design and also called my attention to the remark of the thirteenth-century Chinese scholar Tai T'ung (*The Six Scripts: Principles of Chinese Writing*): "Were I to await perfection, my book would never be finished."

I welcome comments and criticisms from readers.

October 1974

Biochemistry

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