• Lehninger
• Nelson
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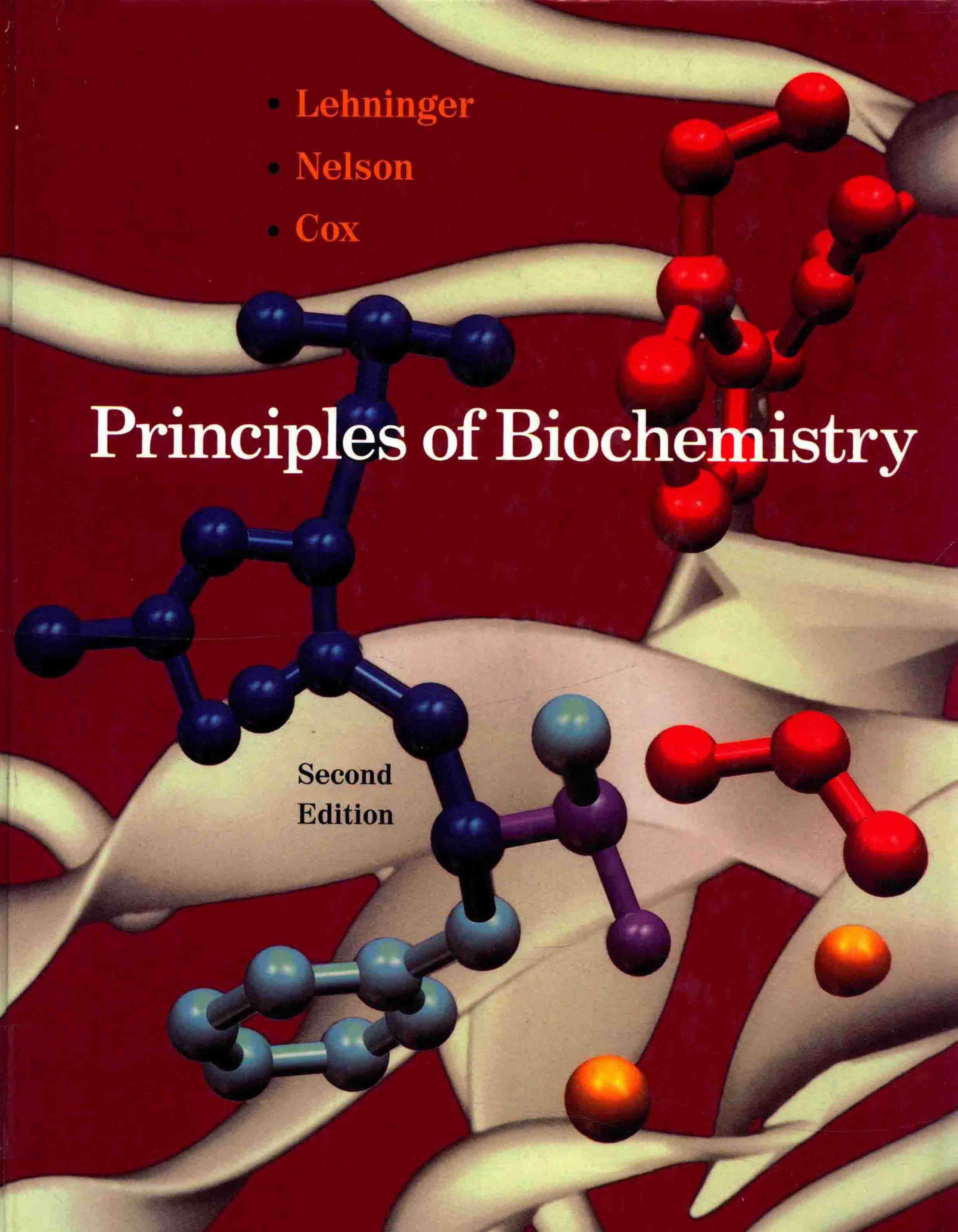
Principles of Biochemistry

Second Edition



SECOND EDITION

Principles of Biochemistry

with an Extended Discussion of Oxygen-Binding Proteins

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Cover: The active site of the proteolytic enzyme chymotrypsin, showing the substrate (blue and purple) and the amino acid residues (red and orange) critical to catalysis. Determination of the detailed reaction mechanism of this enzyme (described on pp. 223–226) helped to establish the general principles of enzyme action.

Frontispiece: A view of tobacco ribulose-1,5-bisphosphate carboxylase (rubisco). This enzyme is central to photosynthetic carbon dioxide fixation; it is the most abundant enzyme in the biosphere. Different subunits are shown in blues and grays. Important active site residues are shown in red. Sulfates bound at the active site (an artifact of the crystallization procedure) are shown in yellow.

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Preface

This revision of Lehninger's *Principles of Biochemistry* was conceived late in 1987, as we (Nelson and Cox) were reluctantly concluding that the first edition of *Principles* would soon be out of date for the introductory biochemistry course we teach at the University of Wisconsin–Madison. Our long and productive experience with this text and its predecessors (the first and second editions of *Biochemistry*), the positive appraisals of our students, and our belief that none of the other available texts complemented our course and teaching philosophy quite so well, provided the inspiration for the book now in your hands.

Principles of Biochemistry, Second Edition, is an introduction to our favorite subject—and our attempt to make it yours. It has been designed for one- and two-semester courses for undergraduates majoring in biochemistry and related disciplines, as well as for graduate students who require a broad introduction to biochemistry. It is also suitable for courses at medical, dental, veterinary, pharmacy, and other professional schools. The book will be used most successfully by students who have completed two years of college-level chemistry, including organic chemistry, and have received at least an introduction to biology. While some background in physics and physical chemistry would be useful, all relevant principles are introduced in a manner that should make them accessible to most students.

Although more than a decade has passed since Albert Lehninger wrote the first edition of *Principles of Biochemistry,* our goals in revising it have remained true to the original. A look at the Contents will confirm that Lehninger's ground-breaking organization, in which a discussion of biomolecules is followed by metabolism and then information pathways, has been retained; we believe it is still pedagogically sound. At every other level, however, this second edition is a re-creation, rather than a revision, of the original text. Every chapter has been comprehensively overhauled, not just by adding and deleting information, but by completely reorganizing its presentation and content, and in some cases its relationship to other chapters. More than half of the chapters were written wholly or nearly from scratch.

The need for fundamental changes arose from the advance of biochemical knowledge and the continued emergence of basic principles. Recent advances have profoundly influenced the manner in which biochemistry can and should be taught. A decade ago, for example, only a few well-studied proteins were available to illustrate the principles of protein structure and function; now hundreds vie for attention.

We have resisted the temptation to allow the book to become encyclopedic, focusing instead on subjects appropriate to its ambitious title. The decision to include or delete a topic was generally based on the degree to which it illustrated or clarified a broader theme. Our major objective has been to highlight principles that rationalize and systematize large bodies of information.

Although these principles are often surprisingly simple, the body of information and experimental advances that must be understood to appreciate them can be daunting. Biochemistry first and foremost seeks to explain biology in chemical terms.

We wrote with the following goals in mind:

- to introduce the language of biochemistry, with careful explanations of the meaning, origin, and significance of terms;
- to provide a balanced understanding of the physical, chemical, and biological context in which each biomolecule, reaction, or pathway operates (here, for instance, you will not only read that ATP is a cell's energy currency, but you will also find out what chemical properties make ATP—rather than pyrophosphate, say—suitable for this function);
- to project a clear and repeated emphasis on major themes, especially those relating to evolution, thermodynamics, regulation, and the relationship between structure and function;
- to explain and to place in context the most important techniques that have brought us to our current understanding of biochemistry; and
- to sustain the student's interest by developing topics in a logical and stepwise manner; taking every opportunity to point out connections between processes; identifying gaps in our knowledge that promise to challenge future generations of scientists; supplying the historical context of selected major discoveries, when such context is useful; and highlighting the implications of biochemical advances for society.

The information in *Principles of Biochemistry,* Second Edition, is still presented in four parts, but the organization, content, and function of each have undergone substantial changes from the previous edition. Themes that unify groups of chapters are introduced in the opening text for each part and reinforced in individual chapters. The organization within and across chapters will help students to maintain the focus on major themes and essential information and so will enhance their understanding.

Part I represents an acknowledgment of the broad range of backgrounds that students bring to their study of biochemistry. Many years of teaching have convinced us of the value of introducing certain fundamental concepts, even for those students who have already been exposed to them. Students will find these chapters useful for filling gaps in their understanding of biology and chemistry, and for consolidating information that they have never fully assimilated. Part I introduces the central concepts of bioenergetics and thermodynamics—in the first stages of an incremental build-up in the student's understanding and appreciation of the cellular transformations of energy and matter. The structure and evolution of cells and organelles are described; in later chapters frequent reference is made to this material. A simplified overview of nucleic acids and information pathways is also provided in Part I so that key concepts can be used to support the discussion of protein structure and function.

In **Part II** we describe each major class of biomolecule, with the focus in each chapter on a detailed description of molecular properties. A special effort has been made to gather information of practical significance into easily accessible reference tables. This material is not simply a list of molecules to memorize; biomolecules are beautiful and the principles underlying their structures and functions are fundamental to everything else in biochemistry. Thermodynamics and the critical role of water and noncovalent interactions in the structure and function of macromolecules provide unifying themes that are developed gradually throughout Part II. Computer-generated images of biomolecules, with clear didactic rather than aesthetic functions, play a prominent role in these chapters.

Although derived from Chapters 5 to 12 of the previous edition and still presented in eight chapters, Part II has undergone major changes. The separate chapters on fibrous proteins and vitamins are gone. Fibrous proteins take their rightful place in the coverage of three-dimensional protein structure in Chapter 7. Extensive changes have been made to the presentation of protein structure and enzymatic catalysis in Chapters 7 and 8. The discussion of allosteric mechanisms in Chapter 8 is illustrated with allosteric enzymes, not hemoglobin. But for teachers who prefer to use myoglobin and hemoglobin to illustrate allosteric regulation, we have included an extended discussion, "Protein Function as Illustrated by Oxygen-Binding Proteins," found just before Appendix A on page S-1. Vitamins and cofactors are individually integrated wherever their biochemical functions are first introduced. Two new chapters have been added, one dealing with membrane structure and function including transport (Chapter 10) and the other with nucleotides and nucleic acids (Chapter 12). By presenting membranes and transport in Part II, we are able to integrate the role of transmembrane ion gradients, membrane-bound enzymes, and cellular compartmentation into the discussion of metabolism in Part III. The placement of the chapter on nucleotides and nucleic acids at the end of Part II permits a thorough treatment of the subject, drawing on principles of macromolecular structure and carbohydrate chemistry introduced in Chapters 7 and 11. The discussion of nucleotide chemistry in Chapter 12 also provides a critical foundation for several aspects of thermodynamics and metabolism that are elaborated upon in Part III.

Part III covers bioenergetics and intermediary metabolism. Thermodynamics takes center stage as Chapter 13 builds on the development of this theme woven through Parts I and II. This chapter also introduces oxidation and reduction reactions, permitting quantitative descriptions of redox changes in metabolic pathways.

Catabolic processes are grouped together in Chapters 14 to 18, and the biosynthetic pathways are grouped in Chapters 19 to 21. Although this organization necessarily separates the coverage of some related reactions, it facilitates the parallel presentation of many more related processes (such as the similar types of reactions and intertwined pathways that link amino acid biosynthesis to nucleotide biosynthesis). Most important, it maintains a focus on the larger metabolic patterns and themes. This fundamental organization was Lehninger's own, a natural outgrowth of his perspective on bioenergetics and the integration of metabolism.

The light-dependent and light-independent reactions of photosynthesis, treated together in a single chapter in the first edition, are now divided between two adjacent chapters. Photophosphorylation is presented along with oxidative phosphorylation in Chapter 18, which has been extensively revised to emphasize the fundamental mechanistic similarity between the two processes. Photosynthetic carbon fixation is presented in Chapter 19, where it finds a logical home within a larger discussion of carbohydrate biosynthesis. The first-edition chapter on human nutrition is gone; relevant material and updated examples have been integrated into the remaining chapters. Part III culminates in Chapter 22 on the integration of metabolism and an overview of regulation, including the biochemical basis of hormone action. This largely new chapter includes some material from the chapters entitled "Hormones" and "Digestion, Transport, and the Integration of Metabolism" in the first edition; much new information has been added on the mechanism of hormone action, on the role of protein phosphorylation in regulation, and on oncogenes as defective regulatory proteins.

Major enzymatic cofactors and classes of biochemical reactions are described where they are first encountered. Selected examples of reaction mechanisms are provided to help convey the chemical rationale of each pathway. The division of labor between organs and cellular organelles is carefully traced so that these elegant schemes and their importance to life can be readily appreciated. Differences in pathways utilized by different classes of organisms are regularly examined; examples relevant to vertebrates (and particularly to human medicine) are balanced by the addition of more complete descriptions of processes in plants and microorganisms. These features are complemented by the careful application of color in pathway diagrams; colors used for certain classes of processes are standardized throughout Part III.

Part IV consists of six chapters devoted to information pathways. Here, very little has been retained from the first edition. Part IV is not designed as an encyclopedic survey of molecular biology, but as a thorough introduction to the *biochemistry* underlying the conversion of information contained in DNA to cellular macromolecules. The theme of thermodynamics recurs throughout Part IV, with emphasis on the special requirements encountered in the synthesis of a macromolecule containing information.

Chapter 23 covers higher-order structure in DNA, building on material in Chapter 12. The next three chapters cover all important aspects of the synthesis, modification, and degradation of DNA, RNA, and proteins. Regulation of gene expression is presented in Chapter 27, emphasizing principles and patterns that have a firm biochemical foundation. Each of these chapters covers the key advances to date in both prokaryotic and eukaryotic biochemistry. Combining the two is somewhat nontraditional, but advances in biochemistry have consistently demonstrated that fundamental principles are universal. The few significant biochemical distinctions between prokaryotes and eukaryotes are more readily recognized and appreciated within a parallel discussion.

The book concludes with a discussion of recombinant DNA technology (Chapter 28). The biochemical foundation of the technology is emphasized, as well as its impact on biochemical advances and on society as a whole. This chapter is designed as a portal through which the student can move to more advanced courses in many areas of biochemistry, molecular biology, and cell biology.

An understanding of modern biochemistry is impossible without an introduction to the experimental methods that made possible each major advance. Descriptions of many of these important techniques are woven into the presentations of the concepts and principles they have revealed. A complete listing of the experimental methods described in the book can be found in the index, under "Techniques."

Within each chapter, many new tables have been added. Boxed essays enhance and extend the text material by providing historical information, descriptions of methods, relevant stories and examples, in-depth discussions of related topics, and some material that is simply interesting. Each chapter concludes with a summary of important points, an up-to-date list of suggested readings, and a set of problems. The over 300 problems include many that require the student to work with and interpret original data.

The end-papers now feature a number of useful tables summarizing information that must be referred to often. The improved appendices include an extensive list of abbreviations found in the biochemical literature and solutions to the end-of-chapter problems, many of which include detailed explanations. The glossary has been revised and expanded to provide definitions of nearly 750 important terms.

The text is complemented by a new art program, providing over 900 figures in full color. These illustrations elucidate and extend the text, substituting meticulously crafted images for the proverbial thousand words. Over 100 computer-generated images illustrate biomolecules ranging from simple metabolites to large protein complexes. In all of these illustrations, whether drawn by hand or by computer, great care has been taken to devise and consistently apply color and styling codes that enhance clarity. Photographs of some of the pioneers of biochemistry have been included to give flesh and blood to the chemistry.

The relevance of biochemistry to society has never been greater; the impact of biotechnology on advances in medicine, agriculture, environmental sciences, forensic science, and a host of other fields has profound implications for our future. As scientists increasingly advance the capability to alter life itself, we emphatically reiterate Albert Lehninger's argument that a knowledge of biochemistry is useful for all well-informed citizens, whatever their callings—quite apart from the very real intellectual excitement it offers.

The two new authors are longtime colleagues at the University of Wisconsin–Madison who have collaborated in the teaching of undergraduate biochemistry for over a decade. Lehninger's textbooks have played a formative role not only in our teaching, but also in our own educations. Our interests and areas of expertise (Nelson: in intermediary metabolism and its regulation, comparative biochemistry, cell biology, and evolution; Cox: in enzyme mechanisms, macromolecular structure and topology, and molecular biology at the enzymatic level) complement each other, as well as the expertise in metabolism and bioenergetics that Lehninger brought to the first edition. While each of us bore primary responsibility for the revision of half the chapters, each chapter bears the marks of the close consultation that has characterized the planning and execution of this book.

In presenting this new edition of *Principles of Biochemistry,* we welcome your criticisms, suggestions, and comments of all kinds.

Acknowledgments

Our writing has been supported by many people in a project that evolved into an international effort. Their advice and encouragement were critical throughout these five years, and we are indebted to all of them for their contributions to this book and for the education they have given us in textbook development.

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The outstanding production staff at Worth Publishers gave new meaning to the phrase "grace under pressure." The critical and demanding role of project editor was very capably executed by Elizabeth Geller. In supporting roles, Alison Brower facilitated communication in this far-flung enterprise, and Maja Lorkovic augmented the proofreading of galleys and page proofs. Anne Vinnicombe's active support and participation also played a vital role in the project's success. The overall book design was conceived by Malcolm Grear Designers, the beautiful page layouts were the work of George Touloumes and Pat Lawson, and the entire production process was supervised by Sarah Segal.

The extraordinary art program was conceived and overseen by Susan Tilberry and her associates in Washington, DC. Sue personally supervised and collaborated with every artist who contributed to the book, ensuring pedagogic unity in the art program, as well as aesthetic and stylistic continuity. Some of Sue's concepts were rendered by Laura Pardi Duprey in New York using computer graphics. Contributions to this enterprise were also made by Alan Landau in New York. We have been impressed and gratified to witness the process by which our often indecipherable scribbles have been transformed into the elegant figures that grace this book.

Virtually all of the computer-generated images of biomolecules were custom designed by the authors and executed under their supervision by Alisa Zapp in Madison. Alisa's mastery of modern graphics workstations made the generation of these images both a pleasure and an educational experience for the authors. The molecular graphics effort was greatly aided by several colleagues at Madison; the Silicon Graphics system was generously loaned to us by Ron Raines, and Andrzej Krezel and Ivan Rayment provided valuable advice and assistance. The molecular images were generated using the MidasPlus software package from the University of California, San Francisco, where Alisa received training and guidance from Julie Newdoll. Laura Vanderploeg photographed the images. In generating these images, we are indebted not only to the many researchers who deposited coordinates in the Brookhaven and Cambridge databases, but also to numerous scientists who freely shared coordinates for macromolecular structures very recently generated, and in some cases before their publication elsewhere.

Sean Carroll contributed valuable material and ideas on the biochemistry of development for Chapter 27.

A number of the end-of-chapter problems were derived in whole or in part from the excellent *Guide to Lehninger's Principles of Biochemistry with Solutions to Problems*, written by Paul van Eikeren. Two of the problems in Chapter 19 were contributed by Roger Persell of Hunter College.

Sarah Green entered the entire first edition into a word processor to provide a starting point. The manuscript was subsequently retyped many times by Karen Davis. Kerri Phillips typed the appendices. Scarlett Presley checked and corrected the suggested readings and many other details. The photographs used in this edition were tracked down by Stuart Kenter.

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they helped guide to completion. We, of course, assume full responsibility for errors of fact or emphasis.

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Madison, Wisconsin
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David L. Nelson
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To our teachers:

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About the Authors

David L. Nelson, born in Fairmont, Minnesota, received his BS in Chemistry and Biology from St. Olaf College in 1964. He earned his PhD in Biochemistry at Stanford Medical School under Arthur Kornberg, and was a postdoctoral fellow at the Harvard Medical School with Eugene P. Kennedy, who was one of Lehninger's first graduate students. Nelson went to the University of Wisconsin–Madison in 1971 and became a full professor of biochemistry in 1982.

Nelson's thesis research at Stanford was on the intermediary metabolism of sporulating and germinating bacteria. At Harvard he studied the energetics, genetics, and biochemistry of ion transport in *E. coli*. At Wisconsin his research has focused on the signal transductions that regulate ciliary motion and exocytosis in the protozoan *Paramecium*. The enzymes of signal transductions, including a variety of protein kinases, are primary targets of study. His research group uses enzyme purification, immunological techniques, electron microscopy, genetics, molecular biology, and electrophysiology to study these processes.

Dr. Nelson has a distinguished record as a lecturer and research supervisor. For 20 years he has taught an intensive survey of biochemistry for advanced biochemistry undergraduates and graduate students in the life sciences (using Lehninger's *Biochemistry* and *Principles of Biochemistry* for much of that time). He has also taught a survey of biochemistry for nursing students, a graduate course on membrane structure and function, and a graduate seminar on membranes and sensory transductions. He has sponsored numerous PhD, MS, and undergraduate honors theses, and has received awards for his outstanding teaching, including the Dreyfus Teacher–Scholar Award and the Atwood Distinguished Professorship. In 1991–1992 he was a visiting professor of chemistry and biology at Spelman College.

Michael M. Cox was born in Wilmington, Delaware. In his first biochemistry course, Lehninger's *Biochemistry* was a major influence in refocusing his fascination with biology and inspiring him to pursue a career in biochemistry. After graduating from the University of Delaware in 1974, Cox went to Brandeis University to do his doctoral work with William Jencks, and then to Stanford in 1979 for postdoctoral study with I. Robert Lehman, moving to the University of Wisconsin–Madison in 1983. He became a full professor of biochemistry in 1992.

His doctoral research was on general acid and base catalysis as a model for enzyme-catalyzed reactions. At Stanford, Cox began work on the enzymes involved in genetic recombination, designing still-used purification and assay methods, illuminating the process of DNA branch migration, and cloning the gene for a site-specific recombinase from yeast. Exploration of the enzymes of genetic recombination has remained the central theme of his research.

Dr. Cox has coordinated a large and active research team at Wisconsin, investigating the enzymology, topology, and energetics of genetic recombination. A primary focus has been the mechanism of DNA strand exchange and the role of ATP in the RecA system. The research team has also concentrated on the FLP recombinase of yeast and the process it controls, and is developing chromosomal targeting systems based on the FLP recombinase. For the past 8 years he has taught (with Dave Nelson) the survey of biochemistry and has lectured in graduate courses on DNA structure and topology, protein–DNA interactions, and the biochemistry of recombination. He has received awards for both his teaching and his research, including the Dreyfus Teacher–Scholar Award and the 1989 Eli Lilly Award in Biological Chemistry.

Contents in Brief