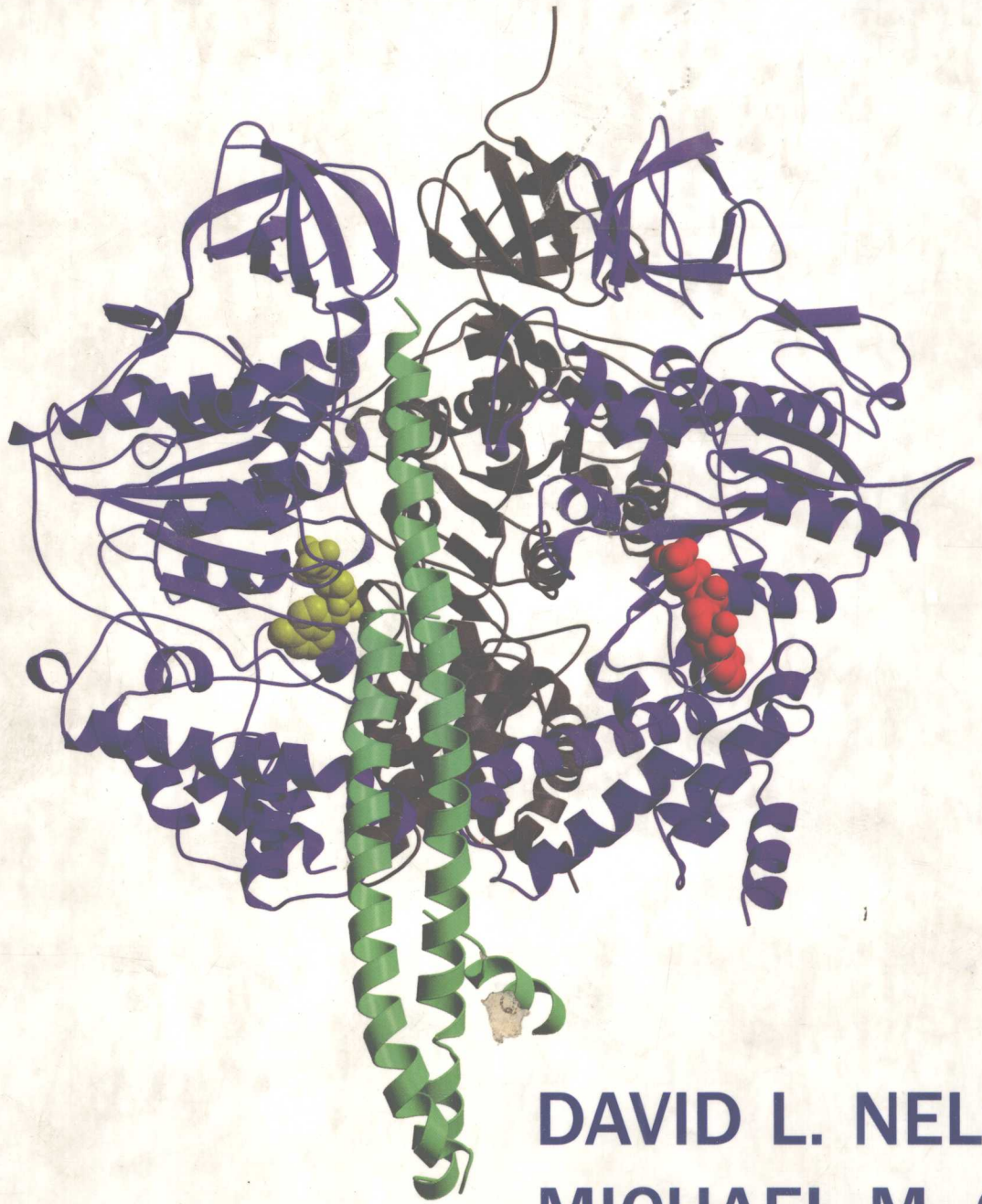
Lehninger
PRINCIPLES OF BIOCHEMISTRY
fourth edition



DAVID L. NELSON
MICHAEL M. COX

Lehninger
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DAVID L. NELSON
Professor of Biochemistry
University of Wisconsin–Madison

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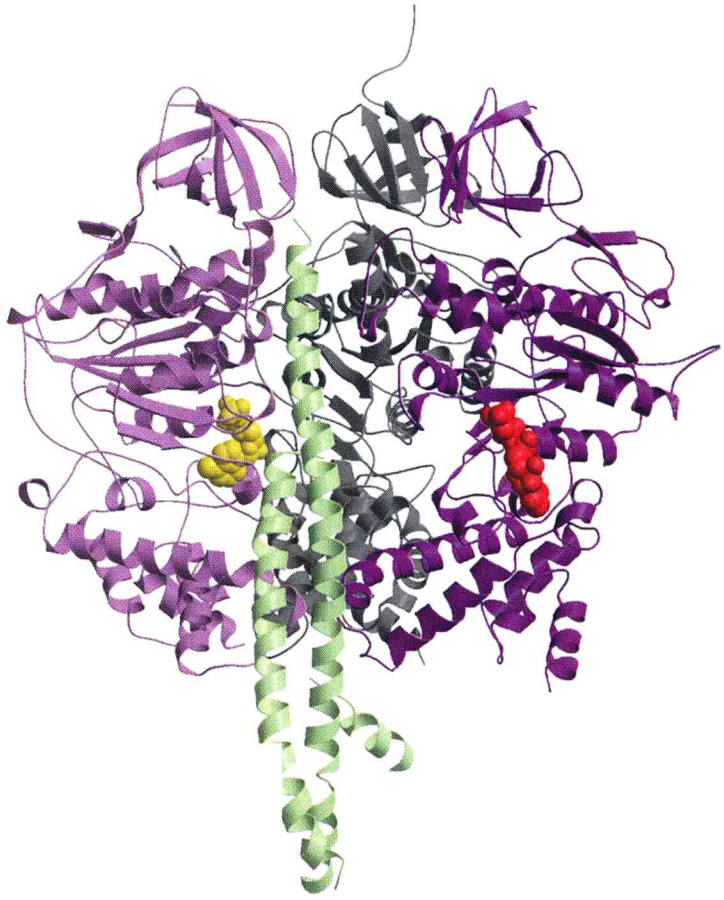

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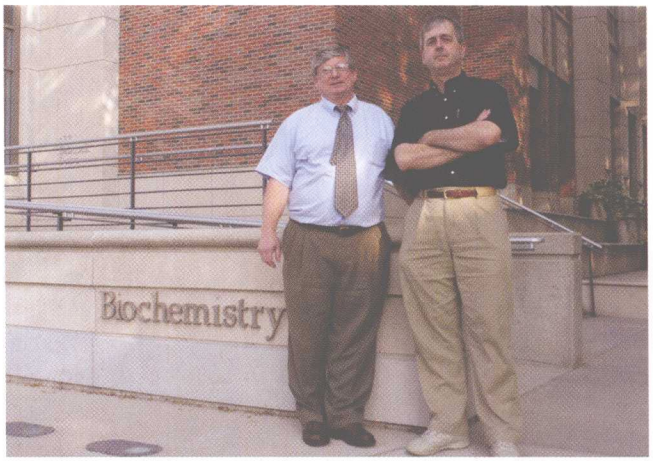


David L. Nelson (left) and Michael M. Cox

David L. Nelson, born in Fairmont, Minnesota, received his BS in Chemistry and Biology from St. Olaf College in 1964 and earned his PhD in Biochemistry at Stanford Medical School under Arthur Kornberg. He was a postdoctoral fellow at the Harvard Medical School with Eugene P. Kennedy, who was one of Albert 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.

Dave Nelson has a distinguished record as a lecturer and research supervisor. For 32 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. In 2002 he was appointed Director of the University of Wisconsin Center for Biology Education.

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. He moved to the University of Wisconsin–Madison in 1983, and 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. The work focused particularly on the RecA protein, designing purification and assay methods that are still in use, and illuminating the process of DNA branch migration. Exploration of the enzymes of genetic recombination has remained the central theme of his research.

Mike 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 RecA protein–mediated DNA strand exchange and the role of ATP in the RecA system. More recently, part of the research program has focused more generally on recombinational DNA repair processes in *E. coli* and *Deinococcus radiodurans*. For the past 20 years he has taught (with Dave Nelson) the survey of biochemistry to undergraduates 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. His hobbies include gardening, wine collecting, and assisting in the design of laboratory buildings.

PREFACE

Lehninger Principles of Biochemistry, Fourth Edition, is an introduction to our favorite subject—and our attempt to make it yours. In the four years since the publication of the third edition, both the pace and the scope of discovery in biochemistry have been breathtaking. We are learning not only what occurs within a cell but where and when it occurs, what determines location, and what controls timing. From the draft sequence of the human genome to elucidation of the high-resolution structure of the ribosome, major recent advances deepening our understanding of biochemistry fill the pages of this book.

While including these exciting new developments, we have also tried to remain focused on our mission: to communicate to students the fundamentals of biochemistry in a way that reflects the field as it is understood today. As always, our efforts to integrate new discoveries are balanced by our efforts to improve the accuracy and pedagogy of the core material of the field.

Coverage of Major Recent Advances in Biochemistry

Every chapter has been thoroughly revised and updated. Some of the major recent advances incorporated into the Fourth Edition include:

- A revised mechanism for the enzyme lysozyme (Chapter 6)
- Functions of heparan sulfates in extracellular matrix (Chapter 7)
- The human genome (Chapter 9)
- The structure and roles of membrane rafts and caveolae (Chapter 11)

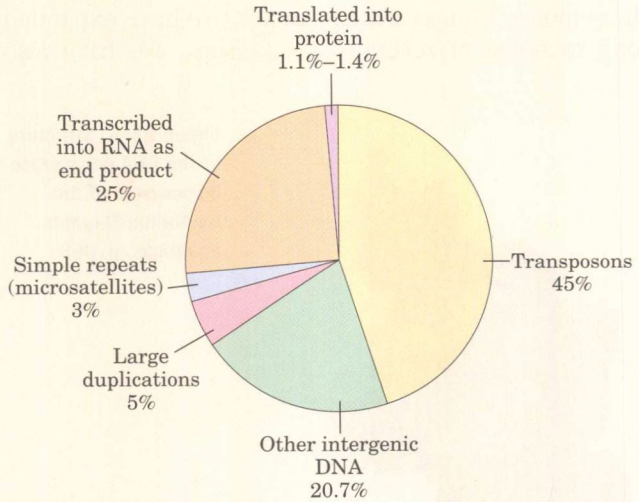


Figure 9–19 Snapshot of the human genome. p. 324

- The structure and function of ABC transporters (Chapter 11)
- Assembly of signaling complexes by the interaction of protein domains with phosphoserine and phosphotyrosine residues in partner proteins (Chapter 12)
- A two-component signaling system in bacteria and plants (Chapter 12)
- Receptorlike protein kinases in plant signaling (Chapter 12)
- Nonclassical actions of steroid hormones at plasma membrane receptors (Chapter 12)
- New developments in metabolic regulation and in the structure of enzymes and enzyme complexes, and new examples of human diseases that result from defective metabolism (throughout Part II)
- Inorganic polyphosphate metabolism (Chapter 13)
- Mechanisms by which metabolism of carbohydrates and fats is integrated in mammalian tissues (Chapters 14, 16, 17, and 23)
- Prevention of ATP hydrolysis by ATP synthase inhibitory protein during ischemia (Chapter 19)
- The role of mitochondria in apoptosis and oxidative stress (Chapter 19)
- The glycine decarboxylase complex and photorespiration (Chapter 20)
- A proposed lipid primer in cellulose synthesis (Chapter 20)
- A proposed new mechanism for starch synthesis from its reducing end (Chapter 20)
- The pathway for glyceroneogenesis, discussed in the context of its role in type II diabetes (Chapter 21)
- Hormonal regulation of body weight and the medical problems posed by the current epidemic of obesity in industrialized countries (Chapter 23)
- The role of cohesins and condensins in chromosome structure (Chapter 24)
- Coordination of multiple replication forks in replication factories (Chapter 25)
- New information on the mechanism and structure of bacterial RNA polymerase (Chapter 26)
- The high-resolution structure of the bacterial ribosome (Chapter 27)
- RNA interference (Chapter 28)

New Methodologies

As scientists and as teachers, we are interested in new technology not just for its own sake but for what

it can teach us—how it can provide us with clues to the biochemical mysteries around us. The following list includes just a few of the new experimental methodologies and their applications that are introduced or expanded in this edition:

- **High throughput methodologies** for determining protein structure, which have revealed many new structures that give us insight into the function of proteins and their interactions with each other and with ligands/substrates (Chapter 5)
- An introduction to modern **genomics** and **proteomics** (Chapter 9)
- Improvements in **DNA microarrays** that allow the detailed and comprehensive study of changes in gene expression caused by hormones and drugs and by mutations that lead to defects in function, including human diseases (Chapter 9)
- Visualization at the level of subcellular organelles of proteins fused genetically with green fluorescent protein (**GFP**) (Chapters 9, 12), providing information on cellular location and function
- **Atomic force microscopy,** used to visualize protein complexes and membrane surfaces (Chapter 11)
- Use of **fluorescence** for following the movement of a single lipid molecule in the plasma membrane (Chapter 11)
- Fluorescence resonance energy transfer (**FRET**), used to measure transient changes in second messenger or protein kinase activity in living cells (Chapter 12)
- Improved methods for **purifying and crystallizing membrane proteins,** which have provided a wealth of information about the details of such processes as oxidative phosphorylation and photophosphorylation (Chapter 19)
- RNA interference (**RNAi**), used to manipulate specific gene products in living cells, and the technology for creating knockout mice; these methods provide windows into the function of specific gene products in a whole organism. One strain of knockout mice has opened up a large field of research aimed at understanding the control of body weight—a subject of great interest, given the increasing incidence of obesity and its many medical consequences (Chapter 28).

More Molecular Graphics

Our understanding of molecular structure has advanced significantly in the past few years, as has the interest on the part of students and instructors in working with this new structural information. As in the last edition, all the molecular structures you will find here are unique to this book, the result of close collaboration with our colleague Jean-Yves Sgro, biophysicist and master of molecular graphics. Jean-Yves has produced more than 70 new images for this edition. We have also added the Protein Data Bank identification code (PDB ID) to the legend of every figure where a structure appears. Students can use the PDB ID to access data about the molecule from the Protein Data Bank website and follow links to a variety of other resources. Structures new to this edition include:

- Aquaporin and voltage-gated K^+ channels—structures revealed by 2003 Nobel Prize–winning research (Chapter 11)
- The lactose permease of *E. coli* (Chapter 11)
- Extraordinary views of photosystem II and the cytochrome b_6f complex (Chapter 19)
- Bacterial RNA polymerase (Chapter 26)
- Multiple images of the bacterial ribosome in all its detail (Chapter 27)

Redesigned and Expanded Treatment of Enzyme Reaction Mechanisms

In response to instructor feedback, we have expanded our coverage of reaction mechanisms. We have also

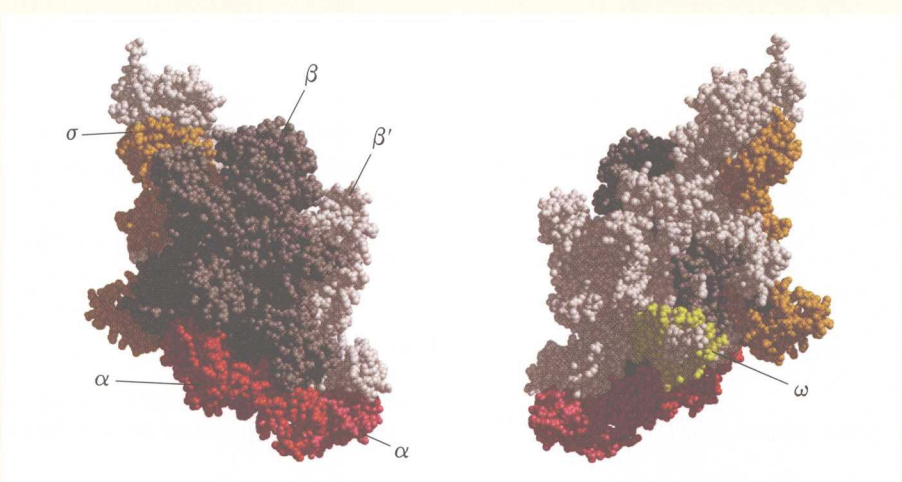


Figure 26–4 Structure of the RNA polymerase holoenzyme of the bacterium *Thermus aquaticus*. **p. 999**

worked to address the concern that students often enter biochemistry without a solid grasp of how to read reaction mechanisms. So, new in this edition:

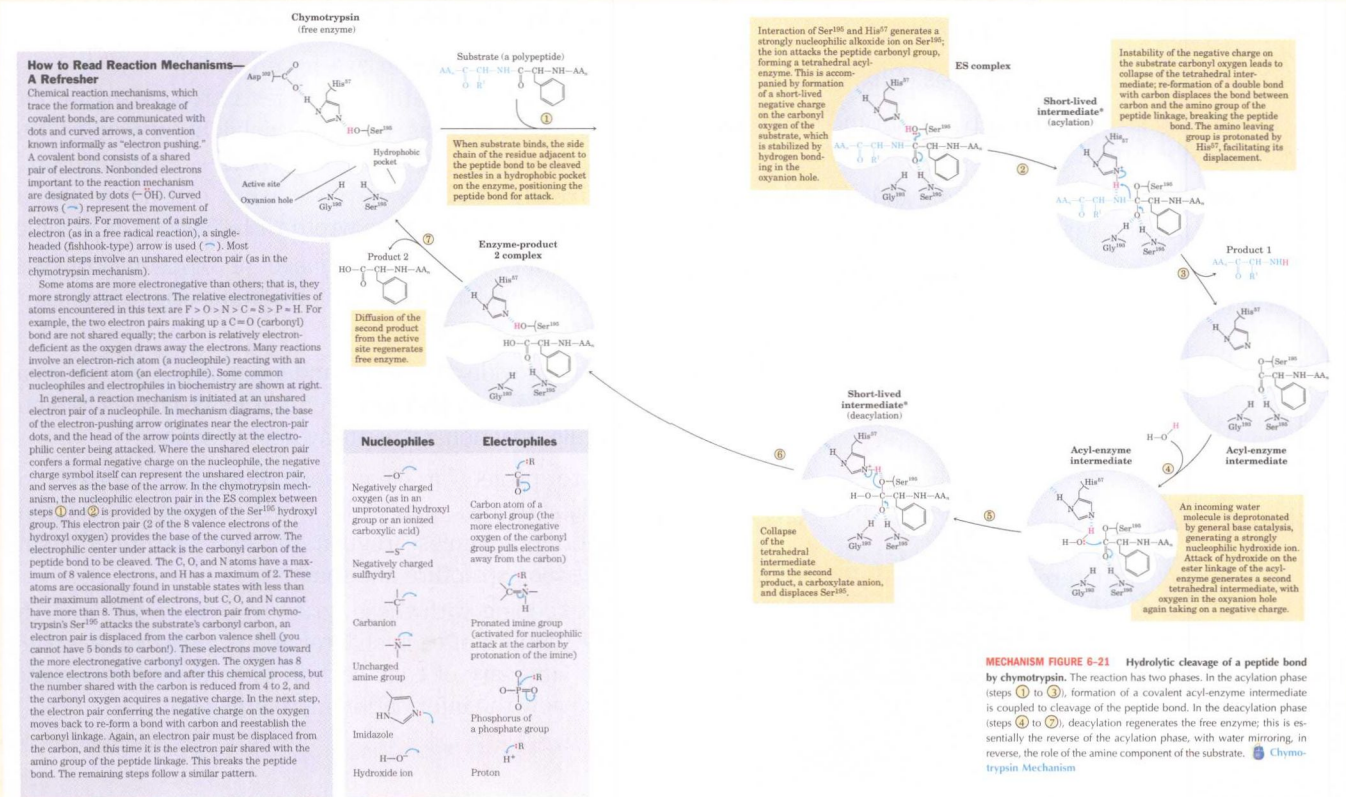
- An expansive, two-page figure on the mechanism of chymotrypsin (the first reaction mechanism treated in the book), which serves as the framework for an illuminating discussion of how to read and extract information from mechanism diagrams (Fig. 6–21). Conventions are presented and explained.
- Building on the information communicated in the chymotrypsin figure, we've designed new **Mechanism Figures** that walk students through complex mechanisms step by step.
- Many new mechanisms; every major coenzyme is represented, with a discussion of its characteristic chemical role. Additional mechanisms highlight key classes of metabolic transformations and illuminate the chemical logic of reaction sequences in pathways.

Detailed Mechanisms in the Fourth Edition

Alcohol dehydrogenase (Chapter 14) NEW
Aminoacyl-tRNA synthetase (Chapter 27)
Bacterial topoisomerase (Chapter 24) NEW
Chymotrypsin (Chapter 6) SIGNIFICANTLY REVISED
Citrate synthase (Chapter 16) NEW
Class I aldolase (Chapter 14) NEW
Coenzyme B_{12} reactions (Chapter 17)
DNA photolyase (Chapter 25) SIGNIFICANTLY REVISED
DNA polymerases (Chapter 25) SIGNIFICANTLY REVISED
Enolase (Chapter 6)
Fatty acyl–CoA synthetase (Chapter 17)
Glutamine amidotransferases (Chapter 22) NEW
Glyceraldehyde 3-phosphate dehydrogenase (Chapter 14) SIGNIFICANTLY REVISED
Isocitrate dehydrogenase (Chapter 16) NEW
Lysozyme (Chapter 6) NEW
Phosphohexose isomerase (Chapter 14) NEW
Pyridoxal phosphate (PLP) reactions (Chapter 18) NEW
Pyruvate carboxylase (Chapter 16) NEW
Ribonucleotide reductase (Chapter 22) SIGNIFICANTLY REVISED
RNA polymerase (Chapter 26) SIGNIFICANTLY REVISED
Rubisco (Chapter 20) SIGNIFICANTLY REVISED
Thiamine pyrophosphate (TPP) reactions (Chapters 14, 16)
Thymidylate synthase (Chapter 22)
Tryptophan synthase (Chapter 22)
Urea production: origin of amino groups (multiple reactions) (Chapter 18) NEW

Many more mechanisms are provided in abbreviated form.

Mechanism Figure 6–21 Hydrolytic cleavage of a peptide bond by chymotrypsin. pp. 216–217



MECHANISM FIGURE 6–21 Hydrolytic cleavage of a peptide bond by chymotrypsin. The reaction has two phases. In the acylation phase (steps ① to ③), formation of a covalent acyl-enzyme intermediate is coupled to cleavage of the peptide bond. In the deacylation phase (steps ④ to ⑦), deacylation regenerates the free enzyme; this is essentially the reverse of the acylation phase, with water mirroring, in reverse, the role of the amine component of the substrate. Chymotrypsin Mechanism

More Medically Relevant Examples

This icon is used throughout the book to denote material of special medical interest.

We have added many new and fascinating examples relating biochemistry to medicine to help students see the relevance of biochemistry to their lives. Some of the medical examples we have added in this edition:

- Scurvy (Chapter 4)
- Carbon monoxide poisoning (Chapter 5)
- Role of ABC transporters in multidrug resistance (Chapter 11)
- Adverse physiological consequences of defective ion channels (Chapter 11)
- Defect in the PTEN gene that causes tumors (Chapter 12)
- Treatment of erectile dysfunction with sildenafil (Viagra) (Chapter 12)
- Lactose intolerance (Chapter 14)
- Role of the pentose phosphate pathway in prevention of oxidative damage (Chapter 14)
- Exacerbation of Wernicke-Korsakoff syndrome by a defect in transketolase (Chapter 14)
- Glycogen storage diseases (Chapter 15)
- Disease caused by genetic defects in fatty acyl–CoA dehydrogenases (Chapter 17)
- Zellweger syndrome and X-linked adrenoleukodystrophy (Chapter 17)
- Refsum's disease (Chapter 17)
- Kidney stones (Chapter 18)
- Diabetes and glyceroneogenesis (Chapter 21)
- Heme as the source of bile pigments and its colorful metabolism in bruising (Chapter 22)
- Obesity as a medical problem, and the hormonal regulation of body weight (Chapter 23)
- Adiponectin and insulin resistance in mice (Chapter 23)
- RNAi and its potential uses in medicine (Chapter 28)

Updated Organization

While the overall structure of *Lehninger Principles of Biochemistry* remains consistent with previous editions, we have made a few key changes in the organization of the fourth edition, in consultation with many teachers and students.

- Earlier placement of the thoroughly revised chapter on **DNA-based information technologies** (Chapter 9). This includes recent advances in genomics and proteomics and introduces the human and other genomes. Providing this material early in the text allows us to refer to important findings from molecular genetics throughout subsequent chapters.
- **Glycolysis and gluconeogenesis** presented in a single chapter (Chapter 14); the parallels between these pathways are thus more easily seen.
- A new chapter on the **regulation of metabolism** (Chapter 15). Using the pathways of glycolysis, gluconeogenesis, glycogenolysis, and glycogenesis to illustrate general principles, we discuss the various mechanisms by which cells and organisms regulate their metabolic affairs. We also introduce the principles of **metabolic control analysis,** a powerful way to determine which enzymes limit the flux through a pathway, and say goodbye to the concept of a single limiting step.
- Reorganization of the introductory material previously presented in three chapters and its condensation into one chapter, in which we describe the cellular, chemical, physical, genetic, and evolutionary **foundations of biochemistry** (Chapter 1). For students who would benefit from more background information on biology and chemistry, third edition Chapters 1 to 3 are available on the book's website, www.whfreeman.com/lehninger.

Focus on Fundamental Principles

As in the third edition, we have carefully selected new material that illustrates or clarifies a broader theme. Our major objective has been to highlight principles that rationalize and systematize large bodies of information.

To help students navigate what can seem like an ocean of information, we wrote with these 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; and
- to project a clear and repeated emphasis on major themes, especially those relating to evolution, thermodynamics, regulation, and the relationship between structure and function.

In keeping with these goals, we have numbered the major sections of each chapter and provided an overview and a summary of each section to help students master and review the information more efficiently.

Supplements

Instructor's Resource CD-ROM with Test Bank; 0-7167-5953-5

To help instructors create their own websites and orchestrate dynamic lectures, the two-disc IRCD contains:

- **Animated enzyme mechanisms,** which show key mechanisms step-by-step, in Flash format
- **Living Graphs,** which bring to life important equations from the text by allowing the user to see the graphic result of changing the parameters
- ***Test Bank,*** organized by chapter in both PDF files and editable Word files
- **All the figures** and tables from the text in JPEG and PowerPoint formats, **optimized for projection** with enhanced colors, higher resolution, and enlarged fonts for easy reading in the lecture hall

Overhead Transparency Set; 0-7167-5956-X

The full-color transparency set contains 150 key illustrations from the text that have been **optimized** with enlarged labels, bolder lines, and more vivid colors that project more clearly for lecture hall presentation.

Printed *Test Bank*, Fourth Edition, by Terry Platt and Eugene Barber (University of Rochester Medical Center) and David L. Nelson and Brook Chase Soltvedt (University of Wisconsin–Madison); 0-7167-5952-7

The new *Test Bank* contains many new multiple-choice and short-answer problems and solutions—approximately 50 problems and solutions per chapter. Each problem is keyed to the corresponding chapter of the text and rated by level of difficulty. The *Test Bank* is also available on the IRCD, organized by chapter, as PDF and editable Word files.

Website at www.whfreeman.com/lehninger

Created with both instructors and students in mind, the website features:

- **All the figures** and tables from the book **optimized for projection,** available in PowerPoint and JPEG format; also available on the IRCD
- **Animated enzyme mechanisms,** showing key mechanisms step-by-step, in Flash format
- **Living Graphs,** dynamically illustrating equations and graphed material featured in the text

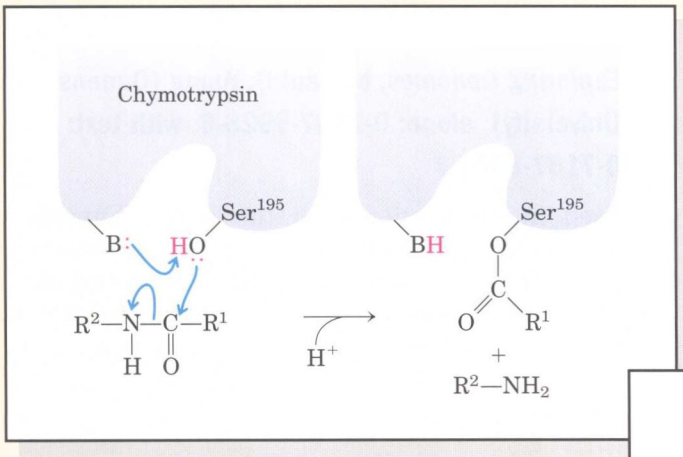
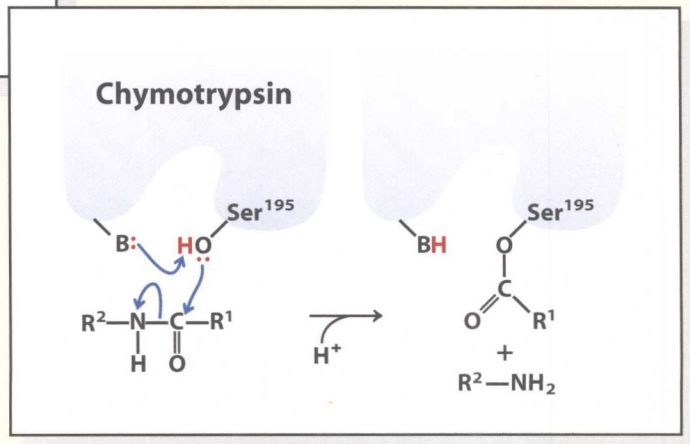


Figure 6–10 Covalent and general acid-base catalysis. p. 202

Figure 6–10 Optimized for projection



- **Biochemistry in 3D molecular structure tutorials,** self-paced interactive tutorials based on the Chemscape Chime molecular visualization browser plug-in; allow students to explore the basic and advanced topics covered in the textbook
- **Online quizzing** for each chapter, a new way for students to review material and prepare for exams
- **Flashcards** on key terms from the text
- Bonus material from *Lehninger Principles of Biochemistry,* Third Edition, fundamental Chapters 1, 2, and 3, which instructors find useful for students requiring a basis for the study of biochemistry

Throughout the text, this icon alerts the reader to a website connection

The Absolute, Ultimate Guide to Lehninger Principles of Biochemistry, Fourth Edition, Study Guide and Solutions Manual, by Marcy Osgood (University of New Mexico School of Medicine) and Karen Ocorr (University of California, San Diego); 0-7167-5955-1

The Absolute, Ultimate Guide combines an innovative study guide with a reliable solutions manual in one convenient volume. Thoroughly class-tested, it includes for each chapter:

- **Major Concepts:** a roadmap through the chapter
- **What to Review:** questions that recap key points from previous chapters
- **Discussion Questions:** provided for each section; designed for individual review, study groups, or classroom discussions
- **A Self-Test:** "Do you know the terms?"; crossword puzzles; multiple-choice, fact-driven questions; and questions that ask students to apply their new knowledge in new directions—plus answers!
- **Biochemistry on the Internet problems:** provided for many chapters, to encourage students to use the Web to solve problems
- **Complete and Detailed Solutions:** solutions for all end-of-chapter problems

A poster-size **Cellular Metabolic Map** is packaged with the Guide, on which students can draw the reactions and pathways of metabolism in their proper cellular compartments. To order the Cell Map separately, use ISBN 0-7167-9950-2.

Lecture Notebook; 0-7167-5954-3

For students who find that they are too busy copying drawings to keep up with the lecture, the *Notebook* is an indispensable classroom companion, offering

- **Illustrations** in the order in which they appear in the textbook, with plenty of room to take notes
- **Essential reaction equations** and **mathematical equations** with identifying labels
- Complete **pathway diagrams** and **individual reaction diagrams** for all metabolic pathways in the book
- **References** that key the material in the text to the book's website.
- **Three-hole-punched, perforated pages** so that students can reorganize pages in any order necessary to follow instructor's lectures, and can insert instructor handouts

Exploring Genomes, by Paul G. Young (Queens University); alone: 0-7167-9928-6; with text: 0-7167-8995-7

Used in conjunction with the online tutorials at www.whfreeman.com/young, *Exploring Genomes* guides students through live searches and analyses on the most commonly used National Center for Biotechnology Information (NCBI) databases.

Acknowledgments

Our writing has been supported by many people whose advice and encouragement were critical throughout the years of revision, and we are indebted to all of them. At W. H. Freeman and Company, the organization of the project was overseen by Kate Ahr and Sara Tenney and developed by Morgan Ryan. Kate, Sara, and Morgan were part of our immediate production team. Their creative input and constructive challenges inspired many of the improvements in this edition. The final manuscript benefited from the superb copyediting of Linda Strange (who has been involved in the writing of every edition—this is number 6—of Lehninger's biochemistry texts!). Our project editor, Jane O'Neill, has kept us all on track if not always on schedule, showing inordinate patience. Our indexer, Ellen Brennan, has compiled a great index on a very tight schedule. We thank our production coordinator, Paul Rohloff, for helping us to produce the book on time. In Madison, we relied heavily on Brook Soltvedt for her invaluable editorial and organizational input, involving every phase of the project. Brook helped the two authors find a similar voice and avoid redundancies, while keeping the countless pieces of the project moving. Shelley Lusetti read and expertly critiqued the page proofs for every chapter. It was a great privilege to work with so talented and energetic a production team, and they have all had much to do with the quality of the book before you.

The new art for this edition includes work from Fine Line Illustrations, coordinated by Shawn Churchman. 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. We thank Rae Grant and Blake Logan for the beautiful work they have done on the design for the book. Paul Lacy worked magic getting the chapters to lay out in the new two-column format. We have already noted the invaluable contribution of Jean-Yves Sgro, who prepared all the molecular graphics. The photographs used in this edition were carefully tracked down by Vikii Wong. Melanie Mays and Nick Tymoczko arranged for the many reviewers of the text and, with Jeff Ciprioni, coordinated the development of the supplemental materials—the website, *Test Bank, Lecture Notebook,* overhead transparencies, PowerPoint files, and *Absolute, Ultimate Guide.* Marcy Osgood of the University of New Mexico School of Medicine and Karen Ocorr of the University of California, San Diego, made helpful comments on the textbook manuscript as they revised their study guide for this edition. Five of the boxes in the book were written by Lou Pech of Carroll College.

One of the special advantages we have had is our access to the extraordinary community of researchers at the University of Wisconsin–Madison. More often than not, the expertise we needed to tie down a loose end or develop a new topic was right at hand. Our colleagues provided us with timely data, critiqued sections of the text, helped us develop figures, answered our questions, and helped in innumerable other ways. Space precludes a detailing of every contribution, but we are especially grateful to the following colleagues at the University of Wisconsin–Madison:

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The book has benefited enormously from the combined wisdom and experience of countless reviewers. Every

chapter was critiqued at one stage or another by biochemists with interests and expertise in both the chapter topic and biochemical education. These formal reviews helped shape this new edition in many ways. For their indispensable advice and criticism, we thank them.

Fourth Edition Text Reviewers

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